



Clinical trial results:

A Multicenter, Open-Label, Long-Term Safety Extension of Phase II Studies ABE4869g and ABE4955g in Patients with Mild to Moderate Alzheimer's Disease

Summary

EudraCT number	2012-003242-33
Trial protocol	GB DE ES
Global end of trial date	08 February 2017

Results information

Result version number	v1 (current)
This version publication date	16 February 2018
First version publication date	16 February 2018

Trial information

Trial identification

Sponsor protocol code	GN28525
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01723826
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	08 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess long-term safety and tolerability of crenezumab administered subcutaneously (SC) every 2 weeks (q2w) or intravenously (IV) every 4 weeks (q4w), in eligible subjects with Alzheimer's disease who participated in Study ABE4869g or ABE4955g and had completed the Week 73 study visit, including brain magnetic resonance imaging (MRI).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Canada: 69
Country: Number of subjects enrolled	United States: 206
Worldwide total number of subjects	360
EEA total number of subjects	85

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)	53
From 65 to 84 years	306
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 360 subjects were enrolled at 83 sites across 6 countries.

Pre-assignment

Screening details:

Subjects who completed either Phase II Study NCT01343966 or NCT01397578 and had Mini-Mental State Examination (MMSE) score of 10 or more at the time of screening were included. A total of 360/396 subjects were enrolled and included in Safety-Evaluable Population (Assigned Treatment); 47 in Group A, 67 in Group B, 101 in Group C and 145 in Group D.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Subjects who received placebo subcutaneously (SC) on their parent study followed by Crenezumab (Cren) SC, then Cren intravenously (IV), on Study NCT01723826.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo to crenezumab 300 milligrams (mg) subcutaneously (SC) every two weeks (q2w).

Investigational medicinal product name	Crenezumab IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were randomized to receive crenezumab 15 milligrams per kilogram (mg/kg) intravenously (IV) every four weeks (q4w).

Investigational medicinal product name	Crenezumab SC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were randomized to receive crenezumab 300 milligrams (mg) subcutaneously (SC) every two weeks (q2w). Following the implementation of Protocol amendment, all subjects were transferred into the intravenously (IV) dosing arm and received crenezumab 15 milligrams per kilogram (mg/kg) every four weeks (q4w), starting 2-4 weeks after the last SC dose.

Arm title	Group B
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Arm description:

Subjects who received placebo intravenously (IV) on their parent study followed by Crenezumab (Cren)

IV on Study NCT01723826.

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

Dosage and administration details:

Matching placebo to crenezumab 15 milligrams per kilogram (mg/kg) intravenously (IV) every four weeks (q4w).

Investigational medicinal product name	Crenezumab IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were randomized to receive crenezumab 15 milligrams per kilogram (mg/kg) intravenously (IV) every four weeks (q4w).

Arm title	Group C
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Arm description:

Subjects who received Crenezumab (Cren) subcutaneously (SC) on their parent study followed by Cren SC, then Cren intravenously (IV), on Study NCT01723826.

Arm type	Experimental
Investigational medicinal product name	Crenezumab SC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were randomized to receive crenezumab 300 milligrams (mg) subcutaneously (SC) every two weeks (q2w). Following the implementation of Protocol amendment, all subjects were transferred into the intravenously (IV) dosing arm and received crenezumab 15 milligrams per kilogram (mg/kg) every four weeks (q4w), starting 2-4 weeks after the last SC dose.

Investigational medicinal product name	Crenezumab IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were randomized to receive crenezumab 15 milligrams per kilogram (mg/kg) intravenously (IV) every four weeks (q4w).

Arm title	Group D
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Arm description:

Subjects who received Crenezumab (Cren) intravenously (IV) on their parent study followed by Cren IV on Study NCT01723826.

Arm type	Experimental
Investigational medicinal product name	Crenezumab IV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were randomized to receive crenezumab 15 milligrams per kilogram (mg/kg) intravenously (IV) every four weeks (q4w).

Number of subjects in period 1	Group A	Group B	Group C
Started	47	67	101
Completed	20	28	44
Not completed	27	39	57
Physician decision	1	3	4
Death	-	3	2
Adverse event	5	1	5
Non-compliance with study drug	-	1	-
Non-compliance	-	1	3
Lost to follow-up	1	3	1
Reason not specified	8	8	12
Protocol deviation	1	1	3
Withdrawal by subject	11	18	27

Number of subjects in period 1	Group D
Started	145
Completed	58
Not completed	87
Physician decision	11
Death	2
Adverse event	6
Non-compliance with study drug	-
Non-compliance	3
Lost to follow-up	1
Reason not specified	14
Protocol deviation	2
Withdrawal by subject	48

Baseline characteristics

Reporting groups

Reporting group title	Group A
Reporting group description: Subjects who received placebo subcutaneously (SC) on their parent study followed by Crenezumab (Cren) SC, then Cren intravenously (IV), on Study NCT01723826.	
Reporting group title	Group B
Reporting group description: Subjects who received placebo intravenously (IV) on their parent study followed by Crenezumab (Cren) IV on Study NCT01723826.	
Reporting group title	Group C
Reporting group description: Subjects who received Crenezumab (Cren) subcutaneously (SC) on their parent study followed by Cren SC, then Cren intravenously (IV), on Study NCT01723826.	
Reporting group title	Group D
Reporting group description: Subjects who received Crenezumab (Cren) intravenously (IV) on their parent study followed by Cren IV on Study NCT01723826.	

Reporting group values	Group A	Group B	Group C
Number of subjects	47	67	101
Age Categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	70.9	71.9	72.3
standard deviation	± 7.4	± 7.5	± 7.2
Gender Categorical Units: Subjects			
Female	26	38	58
Male	21	29	43

Reporting group values	Group D	Total	
Number of subjects	145	360	
Age Categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	72.2		
standard deviation	± 6.6	-	
Gender Categorical Units: Subjects			
Female	77	199	
Male	68	161	

End points

End points reporting groups

Reporting group title	Group A
Reporting group description: Subjects who received placebo subcutaneously (SC) on their parent study followed by Crenezumab (Cren) SC, then Cren intravenously (IV), on Study NCT01723826.	
Reporting group title	Group B
Reporting group description: Subjects who received placebo intravenously (IV) on their parent study followed by Crenezumab (Cren) IV on Study NCT01723826.	
Reporting group title	Group C
Reporting group description: Subjects who received Crenezumab (Cren) subcutaneously (SC) on their parent study followed by Cren SC, then Cren intravenously (IV), on Study NCT01723826.	
Reporting group title	Group D
Reporting group description: Subjects who received Crenezumab (Cren) intravenously (IV) on their parent study followed by Cren IV on Study NCT01723826.	
Subject analysis set title	PCP PL SC OLE CREN SC to IV
Subject analysis set type	Safety analysis
Subject analysis set description: Subject Analysis Set represents the population who received the treatment and were used for safety analysis. Here, PCP= Placebo-controlled portion; PL= Placebo; SC= Subcutaneous; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.	
Subject analysis set title	PCP PL IV OLE CREN IV
Subject analysis set type	Safety analysis
Subject analysis set description: Subject Analysis Set represents the population who received the treatment and were used for safety analysis. Here, PCP= Placebo-controlled portion; PL= Placebo; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.	
Subject analysis set title	PCP CREN SC OLE CREN SC to IV
Subject analysis set type	Safety analysis
Subject analysis set description: Subject Analysis Set represents the population who received the treatment and were used for safety analysis. Here, PCP= Placebo-controlled portion; PL= Placebo; SC= Subcutaneous; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.	
Subject analysis set title	PCP CREN IV OLE CREN IV
Subject analysis set type	Safety analysis
Subject analysis set description: Subject Analysis Set represents the population who received the treatment and were used for safety analysis. Here, PCP= Placebo-controlled portion; PL= Placebo; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.	

Primary: Percentage of Subjects with Adverse Events (AE)

End point title	Percentage of Subjects with Adverse Events (AE) ^[1]
End point description: An AE was defined as any untoward medical occurrence in a subject administered a pharmaceutical product which does not necessarily have a causal relationship with the treatment. Safety Analysis population included all subjects who received at least one dose of study drug.	
End point type	Primary
End point timeframe: Up to 50 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	PCP PL SC OLE CREN SC to IV	PCP PL IV OLE CREN IV	PCP CREN SC OLE CREN SC to IV	PCP CREN IV OLE CREN IV
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	63	101	149
Units: percentage of subjects				
number (not applicable)	89.4	90.5	96.0	87.9

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects by Nature of Adverse Events

End point title	Percentage of Subjects by Nature of Adverse Events ^[2]
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End point description:

A serious adverse event is any AE that meets any of the following criteria: fatal, life threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, congenital anomaly/birth defect in a neonate/infant. Non-Serious Adverse events of special interest for this study include the following: cerebral vascular edema, Superficial siderosis of central nervous system, cerebral micro-hemorrhages or macro-hemorrhages, pneumonia, liver injury. Safety Analysis population included all subjects who received at least one dose of study drug.

End point type	Primary
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End point timeframe:

Up to 50 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	PCP PL SC OLE CREN SC to IV	PCP PL IV OLE CREN IV	PCP CREN SC OLE CREN SC to IV	PCP CREN IV OLE CREN IV
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	63	101	149
Units: percentage of subjects				
number (not applicable)				
Serious Adverse Events (SAE)	19.1	22.2	21.8	23.5
Non-Serious Adverse Events (Non-SAE)	87.2	88.9	94.1	87.2

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects by Severity of Adverse Events

End point title	Percentage of Subjects by Severity of Adverse Events ^[3]
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End point description:

End point type	Primary
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End point timeframe:

Up to 50 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	PCP PL SC OLE CREN SC to IV	PCP PL IV OLE CREN IV	PCP CREN SC OLE CREN SC to IV	PCP CREN IV OLE CREN IV
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	63	101	149
Units: percentage of subjects				
number (not applicable)				
Grade 1	19.1	34.9	29.7	22.1
Grade 2	44.7	31.7	43.6	40.3
Grade 3	12.8	17.5	16.8	19.5
Grade 4	8.5	1.6	3.0	1.3
Grade 5	4.3	4.8	3.0	4.7

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Human Anti-Therapeutic Antibody (ATA) Formation

End point title	Percentage of Subjects with Human Anti-Therapeutic Antibody (ATA) Formation ^[4]
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End point description:

Anti-therapeutic antibodies (ATA), a measurement to explore the potential relationship of immunogenicity response with pharmacokinetics, safety and efficacy. Percentage of participants at post-baseline with positive results for ATA against crenezumab are reported. Safety Analysis population included all subjects who received at least one dose of study drug.

End point type	Primary
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End point timeframe:

Pre-dose (Day-14), predose at Week 25, 49, 97, Follow-up Week 8 (Week 153) and 12 (Week 157)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	PCP PL SC OLE CREN SC to IV	PCP PL IV OLE CREN IV	PCP CREN SC OLE CREN SC to IV	PCP CREN IV OLE CREN IV
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	63	101	149
Units: percentage of subjects				
number (not applicable)	9.1	3.4	9.1	0.7

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Amyloid-Related Imaging Abnormalities-Edema/Effusions (ARIA-E)

End point title	Percentage of Subjects with Amyloid-Related Imaging Abnormalities-Edema/Effusions (ARIA-E) ^[5]
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End point description:

Alzheimer's disease (AD) is associated with amyloid-related imaging abnormalities (ARIA). The occurrence of imaging abnormalities believed to represent cerebral vasogenic edema, has been reported in association with the investigational use of compounds that are intended to treat Alzheimer's disease by reducing Aβ in the brain. Here, the percentage of subjects with symptomatic and asymptomatic ARIA-E were reported. Safety Analysis population included all subjects who received at least one dose of study drug.

End point type	Primary
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End point timeframe:

Baseline, Weeks 23, 47, 71, 97, 121 and 153

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	PCP PL SC OLE CREN SC to IV	PCP PL IV OLE CREN IV	PCP CREN SC OLE CREN SC to IV	PCP CREN IV OLE CREN IV
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	63	101	149
Units: percentage of subjects				
number (not applicable)				
Symptomatic	0	0	0	0
Asymptomatic	0	0	0	0.7

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Amyloid-Related Imaging Abnormalities-Hemorrhage (ARIA-H)

End point title	Percentage of Subjects with Amyloid-Related Imaging Abnormalities-Hemorrhage (ARIA-H) ^[6]
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End point description:

Alzheimer's disease (AD) is associated with amyloid-related imaging abnormalities (ARIA). Cerebral micro-hemorrhages (microbleeds [MBs]) are radiologically defined as small dot-like foci of signal loss observed on MRI sequences sensitive for paramagnetic tissue properties. The occurrence of MBs has also been identified as an adverse event in anti-amyloid vaccination trials, and together with superficial siderosis, they have been termed "amyloid-related imaging abnormalities-hemorrhage (ARIA-H)". Safety

Analysis population included all subjects who received at least one dose of study drug.

End point type	Primary
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End point timeframe:

Baseline, Weeks 23, 47, 71, 97, 121 and 153

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was planned to be reported.

End point values	PCP PL SC OLE CREN SC to IV	PCP PL IV OLE CREN IV	PCP CREN SC OLE CREN SC to IV	PCP CREN IV OLE CREN IV
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	63	101	149
Units: percentage of subjects				
number (not applicable)				
Superficial Siderosis	2.1	0	3.0	0.7
New Micro-hemorrhage	6.4	9.5	4.0	6.0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 50 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	PCP PL SC OLE CREN SC to IV
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Reporting group description:

Subject Analysis Set represents the population who received the treatment and were used for all safety analyses. Here, PCP= Placebo-controlled portion; PL= Placebo; SC= Subcutaneous; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.

Reporting group title	PCP PL IV OLE CREN IV
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Reporting group description:

Subject Analysis Set represents the population who received the treatment and were used for all safety analyses. Here, PCP= Placebo-controlled portion; PL= Placebo; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.

Reporting group title	PCP CREN SC OLE CREN SC to IV
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Reporting group description:

Subject Analysis Set represents the population who received the treatment and were used for all safety analyses. Here, PCP= Placebo-controlled portion; PL= Placebo; SC= Subcutaneous; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.

Reporting group title	PCP CREN IV OLE CREN IV
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Reporting group description:

Subject Analysis Set represents the population who received the treatment and were used for all safety analyses. Here, PCP= Placebo-controlled portion; PL= Placebo; OLE= Open-label extension; CREN= Crenezumab; IV= Intravenous.

Serious adverse events	PCP PL SC OLE CREN SC to IV	PCP PL IV OLE CREN IV	PCP CREN SC OLE CREN SC to IV
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 47 (19.15%)	14 / 63 (22.22%)	22 / 101 (21.78%)
number of deaths (all causes)	2	3	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Colon cancer			

subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal adenocarcinoma			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastatic neoplasm			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Prostate cancer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exsanguination			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Hypotension			

subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
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 hernia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
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, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
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 granuloma			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachypnoea			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Aggression			
subjects affected / exposed	1 / 47 (2.13%)	0 / 63 (0.00%)	0 / 101 (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
Agitation			
subjects affected / exposed	1 / 47 (2.13%)	1 / 63 (1.59%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Disorientation			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			

subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 63 (0.00%)	0 / 101 (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
Device failure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Femoral neck fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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

Femur fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Fracture displacement			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured sacrum			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 47 (2.13%)	1 / 63 (1.59%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	2 / 47 (4.26%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Wrist fracture			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 47 (2.13%)	0 / 63 (0.00%)	0 / 101 (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 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinus tachycardia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
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			
Basilar artery stenosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
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 / 47 (0.00%)	2 / 63 (3.17%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dementia alzheimer's type			
subjects affected / exposed	2 / 47 (4.26%)	2 / 63 (3.17%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Dementia with lewy bodies			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Ischaemic stroke			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			

subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Syncope			
subjects affected / exposed	0 / 47 (0.00%)	2 / 63 (3.17%)	3 / 101 (2.97%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 47 (2.13%)	0 / 63 (0.00%)	0 / 101 (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
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 47 (2.13%)	0 / 63 (0.00%)	0 / 101 (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 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute prerenal failure			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Osteoarthritis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 63 (0.00%)	0 / 101 (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
Diverticulitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Influenza			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	1 / 101 (0.99%)
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 bacterial			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia escherichia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	1 / 101 (0.99%)
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 tract infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	2 / 101 (1.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 63 (1.59%)	0 / 101 (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
Metabolism and nutrition disorders			
Adult failure to thrive			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 47 (0.00%)	0 / 63 (0.00%)	0 / 101 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	PCP CREN IV OLE CREN IV		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 149 (23.49%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			

subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal adenocarcinoma			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastatic neoplasm			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Exsanguination			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypertension			

subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Phlebitis			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gait disturbance			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Incarcerated hernia			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Acute respiratory failure			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary granuloma			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachypnoea			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aggression			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Agitation			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disorientation			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental status changes			

subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device failure			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical vertebral fracture			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Femoral neck fracture				
subjects affected / exposed	0 / 149 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 149 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture displacement				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fractured sacrum				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	0 / 149 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				

subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			

subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Sinus tachycardia			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Basilar artery stenosis			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dementia			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dementia alzheimer's type			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dementia with lewy bodies			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			

subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	0 / 149 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolic encephalopathy				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				

subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			

subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	3 / 149 (2.01%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Pneumonia bacterial				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia escherichia				
subjects affected / exposed	0 / 149 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	0 / 149 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural infection				
subjects affected / exposed	0 / 149 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Adult failure to thrive			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dehydration			
subjects affected / exposed	3 / 149 (2.01%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PCP PL SC OLE CREN SC to IV	PCP PL IV OLE CREN IV	PCP CREN SC OLE CREN SC to IV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 47 (78.72%)	51 / 63 (80.95%)	80 / 101 (79.21%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	3 / 47 (6.38%)	1 / 63 (1.59%)	2 / 101 (1.98%)
occurrences (all)	8	1	2
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 47 (6.38%)	2 / 63 (3.17%)	2 / 101 (1.98%)
occurrences (all)	3	2	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 47 (4.26%)	0 / 63 (0.00%)	8 / 101 (7.92%)
occurrences (all)	2	0	8
Injection site erythema			
subjects affected / exposed	2 / 47 (4.26%)	1 / 63 (1.59%)	8 / 101 (7.92%)
occurrences (all)	13	1	10
Injection site extravasation			
subjects affected / exposed	3 / 47 (6.38%)	1 / 63 (1.59%)	3 / 101 (2.97%)
occurrences (all)	5	1	7
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 47 (10.64%)	3 / 63 (4.76%)	8 / 101 (7.92%)
occurrences (all)	11	3	9
Psychiatric disorders			
Agitation			
subjects affected / exposed	9 / 47 (19.15%)	4 / 63 (6.35%)	13 / 101 (12.87%)
occurrences (all)	9	4	20
Anxiety			
subjects affected / exposed	1 / 47 (2.13%)	4 / 63 (6.35%)	8 / 101 (7.92%)
occurrences (all)	1	4	9
Depression			
subjects affected / exposed	3 / 47 (6.38%)	8 / 63 (12.70%)	5 / 101 (4.95%)
occurrences (all)	3	9	5
Insomnia			

subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 6	1 / 63 (1.59%) 1	8 / 101 (7.92%) 10
Delusion subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	1 / 63 (1.59%) 1	7 / 101 (6.93%) 7
Confusional state subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	1 / 63 (1.59%) 1	3 / 101 (2.97%) 4
Investigations Weight decreased subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 4	2 / 63 (3.17%) 2	8 / 101 (7.92%) 11
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	7 / 47 (14.89%) 10	8 / 63 (12.70%) 11	26 / 101 (25.74%) 42
Laceration subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	2 / 63 (3.17%) 3	10 / 101 (9.90%) 11
Contusion subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 6	2 / 63 (3.17%) 2	6 / 101 (5.94%) 8
Skin abrasion subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	4 / 63 (6.35%) 4	5 / 101 (4.95%) 5
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 2	5 / 63 (7.94%) 5	11 / 101 (10.89%) 14
Cerebral microhaemorrhage subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	4 / 63 (6.35%) 5	3 / 101 (2.97%) 3
Headache subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	2 / 63 (3.17%) 2	8 / 101 (7.92%) 10
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	6 / 47 (12.77%) 7	3 / 63 (4.76%) 3	11 / 101 (10.89%) 12
Vomiting subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	3 / 63 (4.76%) 5	5 / 101 (4.95%) 6
Constipation subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	4 / 63 (6.35%) 4	3 / 101 (2.97%) 3
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 7	5 / 63 (7.94%) 5	2 / 101 (1.98%) 2
Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 4	0 / 63 (0.00%) 0	5 / 101 (4.95%) 6
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 4	5 / 63 (7.94%) 6	8 / 101 (7.92%) 10
Back pain subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	4 / 63 (6.35%) 5	7 / 101 (6.93%) 7
Muscle spasms subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	0 / 63 (0.00%) 0	4 / 101 (3.96%) 6
Tendonitis subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	2 / 63 (3.17%) 2	1 / 101 (0.99%) 1
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	7 / 47 (14.89%) 8	9 / 63 (14.29%) 13	16 / 101 (15.84%) 23
Viral upper respiratory tract infection			

subjects affected / exposed	5 / 47 (10.64%)	11 / 63 (17.46%)	10 / 101 (9.90%)
occurrences (all)	7	14	11
Upper respiratory tract infection			
subjects affected / exposed	6 / 47 (12.77%)	5 / 63 (7.94%)	15 / 101 (14.85%)
occurrences (all)	7	5	20
Bronchitis			
subjects affected / exposed	2 / 47 (4.26%)	2 / 63 (3.17%)	4 / 101 (3.96%)
occurrences (all)	2	2	5

Non-serious adverse events	PCP CREN IV OLE CREN IV		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 149 (65.10%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 149 (2.01%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 149 (2.68%)		
occurrences (all)	4		
Injection site erythema			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences (all)	2		
Injection site extravasation			
subjects affected / exposed	4 / 149 (2.68%)		
occurrences (all)	16		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 149 (7.38%)		
occurrences (all)	13		
Psychiatric disorders			

Agitation subjects affected / exposed occurrences (all)	13 / 149 (8.72%) 14		
Anxiety subjects affected / exposed occurrences (all)	15 / 149 (10.07%) 16		
Depression subjects affected / exposed occurrences (all)	7 / 149 (4.70%) 7		
Insomnia subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 9		
Delusion subjects affected / exposed occurrences (all)	4 / 149 (2.68%) 6		
Confusional state subjects affected / exposed occurrences (all)	3 / 149 (2.01%) 4		
Investigations Weight decreased subjects affected / exposed occurrences (all)	7 / 149 (4.70%) 7		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	18 / 149 (12.08%) 28		
Laceration subjects affected / exposed occurrences (all)	7 / 149 (4.70%) 7		
Contusion subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 10		
Skin abrasion subjects affected / exposed occurrences (all)	3 / 149 (2.01%) 5		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	10 / 149 (6.71%) 11		
Cerebral microhaemorrhage subjects affected / exposed occurrences (all)	6 / 149 (4.03%) 7		
Headache subjects affected / exposed occurrences (all)	3 / 149 (2.01%) 4		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	14 / 149 (9.40%) 23		
Vomiting subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 11		
Constipation subjects affected / exposed occurrences (all)	5 / 149 (3.36%) 5		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	6 / 149 (4.03%) 7		
Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 8		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 10		
Back pain subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 8		
Muscle spasms			

subjects affected / exposed	1 / 149 (0.67%)		
occurrences (all)	2		
Tendonitis			
subjects affected / exposed	0 / 149 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	18 / 149 (12.08%)		
occurrences (all)	34		
Viral upper respiratory tract infection			
subjects affected / exposed	13 / 149 (8.72%)		
occurrences (all)	13		
Upper respiratory tract infection			
subjects affected / exposed	13 / 149 (8.72%)		
occurrences (all)	15		
Bronchitis			
subjects affected / exposed	9 / 149 (6.04%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2012	1. Language was added to ensure subjects were followed for at least 90 days from their last dose of study drug, if they discontinue prematurely. 2. The Week 2 visit was removed in order to decrease visit burden for subjects and caregivers. 3. A baseline Columbia Suicide Severity Rating Scale (C-SSRS) measurement was added at Day 1.
23 August 2013	1. Included and excluded concomitant medications at screening and throughout the duration of the study were clarified. 2. Mini-Mental State Examination (MMSE) score required at enrollment was modified from greater than equal to 12 to greater than equal to 10. 3. Additional details regarding calculation and administration of the IV dose were provided.
19 August 2014	1. Clinical study information on the closed studies NCT01397578 and NCT01343966 was provided. 2. Human clinical pharmacology and immunogenicity information was updated. 3. The SC dosing regimen was eliminated. Subjects previously receiving crenezumab 300 mg SC q2w now received crenezumab 15 mg/kg IV q4w, starting 2-4 weeks after the last SC dose. 4. An additional protocol-defined adverse event of special interest (AESI) was added to comply with internal Roche/Genentech pharmacovigilance policy, in line with Module VI of Guideline on good pharmacovigilance practices: suspected transmission of an infectious agent by the study drug, suggestive of a quality defect, with contamination of the concerned medicinal product. 5. An additional protocol-defined AESI was added to comply with internal Roche/Genentech pharmacovigilance policy to monitor for Hy's Law deviations of liver function. 6. An additional protocol-defined AESI for pneumonia was added. 7. Subjects were allowed to switch from a marketed treatment for Alzheimer's disease to a treatment at an equivalent dose if the marketed treatment for Alzheimer's disease is no longer available, either commercially or through the subject's insurance formulary. 8. Clarification was added for reporting persistent or recurrent adverse events.
28 August 2014	1. Visit at Weeks 23, 47, 71, and 93 that were inadvertently omitted from the Protocol's Study Flowcharts were included.
22 November 2014	1. Clinical pharmacokinetics (PK) assessments were updated to include an elimination half-life estimate based on a population PK analysis of pooled PK data. 2. Based on the updated crenezumab half-life of 24.6 days, and updated Roche safety reporting policy, adverse events and pregnancy reporting periods were changed from 90 days to 8 weeks. It was also clarified that male subjects with partners with reproductive potential should use contraception for at least 8 weeks after the last dose of study drug. 3. The two safety follow-up visits have been consolidated into one safety follow-up visit occurring 8 weeks after the last administration of study drug. This change was made based on the safety profile to date of crenezumab and the above-mentioned updated Roche safety reporting policy. 4. The Open-Label Extension (OLE) treatment period was expanded by 52 weeks. Subjects could receive 13 additional doses (at Weeks 97, 101, 105, 109, 113, 117, 121, 125, 129, 133, 137, 141, and 145). For subjects who entered this additional OLE treatment period, safety follow-up visits occurred at Week 153. Subjects who had already discontinued treatment (either because of early treatment discontinuation or because they have already had their Week 93 dosing visit) could enter the additional OLE treatment period if they had not discontinued treatment for safety reasons. Subjects who have completed Study GN28525 or discontinued from Study GN28525 were not eligible to receive additional treatment. 5. Because the feeder studies NCT01343966 and NCT01397578 were completed and unblinded, it was specified that the Internal Safety Monitoring Committee would be disbanded, and periodic review of safety data would be conducted by the Sponsor project team.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported