



Clinical trial results:

An open label, multicenter, single arm study of pasireotide LAR in patients with rare tumors of neuroendocrine origin

Summary

EudraCT number	2008-007348-32
Trial protocol	FR DE IT ES
Global end of trial date	10 June 2015

Results information

Result version number	v2 (current)
This version publication date	24 August 2016
First version publication date	26 June 2016
Version creation reason	<ul style="list-style-type: none">• Correction of full data set no changes made

Trial information

Trial identification

Sponsor protocol code	CSOM230D2203
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00958841
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	10 June 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the efficacy of pasireotide long-acting release (LAR) in pancreatic neuroendocrine tumors (PNETs: insulinoma, gastrinoma, VIPoma, and glucagonoma) based on disease specific primary biochemical tumor markers.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	118
EEA total number of subjects	53

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)	103
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

For all other individual indications, the numbers of patients in the efficacy analyzable sets were less than 6 and therefore no responder analyses were carried out for these indications.

Pre-assignment

Screening details:

Each consenting patient, having confirmed diagnosis of PNETs (insulinoma, gastrinoma, VIPoma, and glucagonoma), received pasireotide LAR at 60 mg approximately once every 28 days for 6 months during the core treatment period and up to 48 months treatment during the extension phase.

Period 1

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

Arms

Arm title	pasireotide LAR 60mg
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Arm description:

All patients received pasireotide LAR at 60 mg approximately once every 28 days for 6 months during the core treatment period and additional treatment cycles up to a total of 48 months during the extension phase. Patients included patients with pancreatic neuroendocrine tumors (PNETs), pituitary NETs (PiNETs), Ectopic ACTH-secreting tumor (EAS) & Nelson's syndrome.

Arm type	Experimental
Investigational medicinal product name	pasireotide
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Pasireotide LAR was supplied in vials with 20 mg or 40 mg powder and 2 mL vehicle was supplied in ampoules for reconstitution.

Number of subjects in period 1	pasireotide LAR 60mg
Started	118
Completed Month 6 (M6)	90
Entered in Extension	63
Completed	22
Not completed	96
Abnormal laboratory value(s)	1
Consent withdrawn by subject	1
Adverse event, non-fatal	8
New cancer therapy	5
Unsatisfactory therapeutic effect	22

Administrative problems	1
Completed M6/did not enter extension	27
Discontinued prior to M*	28
Abnormal test procedure result(s)	3

Baseline characteristics

Reporting groups

Reporting group title	pasireotide LAR 60mg
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Reporting group description:

All patients received pasireotide LAR at 60 mg approximately once every 28 days for 6 months during the core treatment period and additional treatment cycles up to a total of 48 months during the extension phase. Patients included patients with pancreatic neuroendocrine tumors (PNETs), pituitary NETs (PiNETs), Ectopic ACTH-secreting tumor (EAS) & Nelson's syndrome.

Reporting group values	pasireotide LAR 60mg	Total	
Number of subjects	118	118	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	103	103	
From 65-84 years	15	15	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	45.9		
standard deviation	± 14.56	-	
Gender, Male/Female			
Units: Participants			
Female	68	68	
Male	50	50	

End points

End points reporting groups

Reporting group title	pasireotide LAR 60mg
Reporting group description: All patients received pasireotide LAR at 60 mg approximately once every 28 days for 6 months during the core treatment period and additional treatment cycles up to a total of 48 months during the extension phase. Patients included patients with pancreatic neuroendocrine tumors (PNETs), pituitary NETs (PiNETs), Ectopic ACTH-secreting tumor (EAS) & Nelson's syndrome.	
Subject analysis set title	Gastrinoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: One of the 10 types of PNETs analyzed	
Subject analysis set title	VIpoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: One of the 10 types of PNETs analyzed.	
Subject analysis set title	Glucagonoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: One of the 10 types of PNETs analyzed.	
Subject analysis set title	Prolactinoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: One of the 10 types of PNETs analyzed.	
Subject analysis set title	Nelson's syndrome
Subject analysis set type	Full analysis
Subject analysis set description: based on disease specific primary biochemical tumor markers. Patients received pasireotide LAR at 60 mg approximately once every 28 days for 6 months during the core treatment period and additional treatment cycles up to a total of 48 months during the extension phase.	
Subject analysis set title	All PNETs (gastrinoma)
Subject analysis set type	Full analysis
Subject analysis set description: One of the 10 types of PNETs analyzed	
Subject analysis set title	All PiNETs (prolactinoma)
Subject analysis set type	Full analysis
Subject analysis set description: One of the 10 types of PiNETs analyzed	

Primary: Percentage of responders at Month 6 - pooled pancreatic NETs (PNETs)

End point title	Percentage of responders at Month 6 - pooled pancreatic NETs (PNETs) ^[1]
End point description: Primary efficacy endpoint was defined as the percentage of responders at Month 6 (M6) among pooled PNET patients (insulinoma, gastrinoma, VIPoma, and glucagonoma). A responder was defined as a patient who either attained normalization or had a greater than 50% reduction from baseline of the level of the primary biochemical tumor marker at M6. 4 insulinoma pts were excluded from analysis because of unavailability of normal ranges for the associated primary biochemical tumor marker (insulin-to-glucose ratio). 1 patient with VIPoma with a normal baseline was also excluded. So only 20 of 25 pts with PNET were included in the assessment of the primary endpoint, which was less than the planned sample size of 34. Therefore, the primary objective could not be assessed with sufficient power. Pts with missing M6 assessment were considered as non-responders. Responder analyses reported only for indications with minimum of 6 patients. No statistical analysis was planned for this primary outcome.	

End point type	Primary
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End point timeframe:

6 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 summary analysis provided.

End point values	Gastrinoma	Vipoma	Glucagonoma	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	2	5	
Units: percentage of participants				
number (not applicable)	46.2	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of responders at Month 6 - individual NETs

End point title	Percentage of responders at Month 6 - individual NETs
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End point description:

Percentage of responders for each of the 10 NET indications considered in the study. Responder analyses were performed for an indication only if there were at least 6 patients in the efficacy analyzable set. For all other individual indications, the numbers of patients in the efficacy analyzable sets were less than 6 and therefore no responder analyses were carried out for these indications.

End point type	Secondary
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End point timeframe:

6 months

End point values	Gastrinoma	Prolactinoma	Nelson's syndrome	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	37	14	
Units: percentage of participants				
number (not applicable)	46.2	21.6	50	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of responders with probability of success at Month 6 - individual NETs

End point title	Percentage of responders with probability of success at Month 6 - individual NETs
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End point description:

Percentage of responders for each of the 10 NET indications considered in the study. Responder analyses were performed for an indication only if there were at least 6 patients in the efficacy analyzable set. For all other individual indications, the numbers of patients in the efficacy analyzable sets were less than 6 and therefore no responder analyses were carried out for these indications. The probability of success was a chance that the true responder rate was greater than 15%) for the indications gastrinoma, prolactinoma, and Nelson's syndrome.

End point type Secondary

End point timeframe:

6 months

End point values	Gastrinoma	Prolactinoma	Nelson's syndrome	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	37	14	
Units: Percentage of participants				
number (not applicable)	46.2	21.6	50	

Statistical analyses

No statistical analyses for this end point

Secondary: PNETs: Number of patients attaining normalization or a more than 50% reduction in primary biochemical tumor marker

End point title PNETs: Number of patients attaining normalization or a more than 50% reduction in primary biochemical tumor marker

End point description:

Specific primary biochemical tumor markers were used to assess the efficacy of pasireotide in PNETs. A Month 6 responder was defined as the patients who either attained normalization or greater than 50% reduction from baseline in the level of the primary biochemical tumor marker at Month 6. One gastrinoma patient had a missing primary tumor marker value at Month 6, but had a Month 5 assessment done on Day 141, which fell within the allowed window period for Month 6.

End point type Secondary

End point timeframe:

Baseline, month 6

End point values	All PNETS (gastrinoma)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: Participants				
Baseline	8			
Month 6	5			

Statistical analyses

No statistical analyses for this end point

Secondary: PiNETs: Number of patients attaining normalization or a more than 50% reduction in primary biochemical tumor marker

End point title	PiNETs: Number of patients attaining normalization or a more than 50% reduction in primary biochemical tumor marker
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End point description:

Specific primary biochemical tumor markers were used to assess the efficacy of pasireotide in PNETs. A Month 6 responder was defined as the patients who either attained normalization or greater than 50% reduction from baseline in the level of the primary biochemical tumor marker at Month 6.

End point type	Secondary
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End point timeframe:

Baseline, month 6

End point values	All PiNETS (prolactinoma)			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: Participants				
Baseline	7			
Month 6	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Nelson's syndrome: Number of patients attaining normalization or a more than 50% reduction in primary biochemical tumor marker

End point title	Nelson's syndrome: Number of patients attaining normalization or a more than 50% reduction in primary biochemical tumor marker
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End point description:

Six patients with Nelson's syndrome met the responder's criteria of attaining normalization or a reduction of more than 50% in primary tumor marker at Month 6.

End point type	Secondary
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End point timeframe:

Baseline, month 6

End point values	Nelson's syndrome			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Participants				
Baseline	6			
Month 6	17			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Pancreatic neuroendocrine tumors
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Reporting group description:

Pancreatic neuroendocrine tumors

Reporting group title	Pituitary neuroendocrine tumors
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Reporting group description:

Pituitary neuroendocrine tumors

Reporting group title	Ectopic ACTH-secreting tumors
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Reporting group description:

Ectopic ACTH-secreting tumors

Reporting group title	Nelson s syndrome
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Reporting group description:

Nelson s syndrome

Serious adverse events	Pancreatic neuroendocrine tumors	Pituitary neuroendocrine tumors	Ectopic ACTH-secreting tumors
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 25 (40.00%)	8 / 72 (11.11%)	5 / 7 (71.43%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (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
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (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			
Flushing			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Hypotension			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Thrombosis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
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 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Drug ineffective			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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

Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Pleural effusion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Pulmonary embolism			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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 aspiration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (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
Injury, poisoning and procedural complications			
Excoriation			

subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Incisional hernia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Multiple injuries			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Joint dislocation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Road traffic accident			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Congenital, familial and genetic disorders			
Haemophilia A without inhibitors			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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			
Bradycardia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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 failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Prinzmetal angina			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Tricuspid valve incompetence			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (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
Hepatic encephalopathy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Dizziness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Hypoaesthesia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Hypoglycaemic coma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Syncope			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Pancytopenia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Vision blurred			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Ascites			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Abdominal pain lower			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Diarrhoea			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Nausea			
subjects affected / exposed	2 / 25 (8.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Oesophageal ulcer			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Umbilical hernia			

subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Vomiting			
subjects affected / exposed	2 / 25 (8.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (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
Cholestasis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Hypopituitarism			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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

Adrenocortical insufficiency acute subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Flank pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Back pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 72 (0.00%)	0 / 7 (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
Musculoskeletal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Foot deformity			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Rhabdomyolysis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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

Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Sepsis syndrome			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Staphylococcal infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Diabetes mellitus			
subjects affected / exposed	1 / 25 (4.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	2 / 25 (8.00%)	3 / 72 (4.17%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	2 / 2	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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
Hypoglycaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (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
Hyponatraemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (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	Nelson s syndrome		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 14 (64.29%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Flushing			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Thrombosis			
subjects affected / exposed	1 / 14 (7.14%)		
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	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Drug ineffective			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypothermia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Incisional hernia			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple injuries			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Haemophilia A without inhibitors			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prinzmetal angina			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Tricuspid valve incompetence subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain oedema subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemic coma subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Syncope subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Coagulopathy			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vision blurred			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain lower			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal ulcer			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypopituitarism			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Foot deformity			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Neutropenic sepsis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis syndrome			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			

subjects affected / exposed	2 / 14 (14.29%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pancreatic neuroendocrine tumors	Pituitary neuroendocrine tumors	Ectopic ACTH-secreting tumors
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 25 (92.00%)	71 / 72 (98.61%)	7 / 7 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Malignant neoplasm progression			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Tumour pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Vascular disorders			

Flushing			
subjects affected / exposed	3 / 25 (12.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Hot flush			
subjects affected / exposed	0 / 25 (0.00%)	2 / 72 (2.78%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 25 (0.00%)	5 / 72 (6.94%)	0 / 7 (0.00%)
occurrences (all)	0	6	0
Poor venous access			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Phlebitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 25 (16.00%)	10 / 72 (13.89%)	0 / 7 (0.00%)
occurrences (all)	5	12	0
Chest discomfort			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	1 / 25 (4.00%)	1 / 72 (1.39%)	1 / 7 (14.29%)
occurrences (all)	2	1	1
Drug withdrawal syndrome			

subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypothermia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	3 / 25 (12.00%)	10 / 72 (13.89%)	1 / 7 (14.29%)
occurrences (all)	4	17	1
Injection site erythema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	1 / 25 (4.00%)	8 / 72 (11.11%)	0 / 7 (0.00%)
occurrences (all)	2	8	0
Injection site pruritus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Local swelling			
subjects affected / exposed	2 / 25 (8.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Injection site urticaria			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	1 / 25 (4.00%)	4 / 72 (5.56%)	0 / 7 (0.00%)
occurrences (all)	1	5	0
Oedema peripheral			
subjects affected / exposed	5 / 25 (20.00%)	1 / 72 (1.39%)	1 / 7 (14.29%)
occurrences (all)	11	1	1
Thirst			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	2 / 25 (8.00%)	4 / 72 (5.56%)	1 / 7 (14.29%)
occurrences (all)	5	4	1
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Reproductive system and breast disorders			
Endometrial hyperplasia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Amenorrhoea subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Hypomenorrhoea subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Menorrhagia subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 3	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	1 / 7 (14.29%) 1
Respiratory, thoracic and mediastinal disorders			
Dysphonia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 6	7 / 72 (9.72%) 10	1 / 7 (14.29%) 1
Emphysema subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	5 / 72 (6.94%) 6	0 / 7 (0.00%) 0
Respiratory disorder			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Pleurisy subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 72 (0.00%) 0	1 / 7 (14.29%) 2
Respiratory tract congestion subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2	1 / 72 (1.39%) 1	0 / 7 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 72 (1.39%) 1	0 / 7 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 4	7 / 72 (9.72%) 8	0 / 7 (0.00%) 0
Irritability subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	2 / 72 (2.78%) 2	0 / 7 (0.00%) 0
Panic attack subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	1 / 7 (14.29%) 2
Investigations Activated partial thromboplastin time prolonged			

subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 25 (4.00%)	3 / 72 (4.17%)	0 / 7 (0.00%)
occurrences (all)	1	3	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 25 (0.00%)	3 / 72 (4.17%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Blood corticotrophin increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood glucagon decreased			
subjects affected / exposed	0 / 25 (0.00%)	2 / 72 (2.78%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Blood glucose increased			
subjects affected / exposed	1 / 25 (4.00%)	7 / 72 (9.72%)	1 / 7 (14.29%)
occurrences (all)	2	7	2
Blood insulin increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Body temperature fluctuation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QRS complex abnormal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 25 (4.00%)	2 / 72 (2.78%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram abnormal			

subjects affected / exposed	0 / 25 (0.00%)	2 / 72 (2.78%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 25 (8.00%)	5 / 72 (6.94%)	1 / 7 (14.29%)
occurrences (all)	2	9	1
Glycosylated haemoglobin increased			
subjects affected / exposed	2 / 25 (8.00%)	4 / 72 (5.56%)	0 / 7 (0.00%)
occurrences (all)	5	8	0
Haemoglobin decreased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Vitamin D decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Insulin-like growth factor decreased			
subjects affected / exposed	0 / 25 (0.00%)	4 / 72 (5.56%)	0 / 7 (0.00%)
occurrences (all)	0	6	0
Weight decreased			
subjects affected / exposed	3 / 25 (12.00%)	5 / 72 (6.94%)	2 / 7 (28.57%)
occurrences (all)	3	6	3
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 25 (0.00%)	2 / 72 (2.78%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Fall			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injection related reaction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Inflammation of wound			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle strain			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Joint injury subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Post procedural complication subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Post procedural swelling subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Skin injury subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Skin wound subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	0 / 72 (0.00%) 0	1 / 7 (14.29%) 1
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 72 (1.39%) 1	0 / 7 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	0 / 72 (0.00%) 0	0 / 7 (0.00%) 0
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	8 / 72 (11.11%) 14	0 / 7 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	8 / 72 (11.11%) 12	0 / 7 (0.00%) 0
Disturbance in attention subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	4 / 72 (5.56%) 5	1 / 7 (14.29%) 1
Headache			

subjects affected / exposed	5 / 25 (20.00%)	12 / 72 (16.67%)	2 / 7 (28.57%)
occurrences (all)	14	16	5
Formication			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Mental impairment			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Horner's syndrome			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	3	1	0
Nystagmus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	1 / 25 (4.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Syncope			
subjects affected / exposed	1 / 25 (4.00%)	2 / 72 (2.78%)	0 / 7 (0.00%)
occurrences (all)	1	3	0
Somnolence			
subjects affected / exposed	2 / 25 (8.00%)	1 / 72 (1.39%)	1 / 7 (14.29%)
occurrences (all)	3	1	1
Paraesthesia			
subjects affected / exposed	3 / 25 (12.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	4	1	0
Tremor			
subjects affected / exposed	1 / 25 (4.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
VIIth nerve paralysis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Visual field defect			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 72 (1.39%) 1	0 / 7 (0.00%) 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Anaemia			
subjects affected / exposed	3 / 25 (12.00%)	1 / 72 (1.39%)	2 / 7 (28.57%)
occurrences (all)	3	1	2
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Eustachian tube disorder			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	4 / 25 (16.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	5	1	0
Eye disorders			
Blindness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Conjunctival oedema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dry eye			

subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Eye haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Photopsia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Retinal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	3 / 25 (12.00%)	5 / 72 (6.94%)	0 / 7 (0.00%)
occurrences (all)	3	5	0
Vitreous haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 25 (0.00%)	3 / 72 (4.17%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	2
Abdominal pain			
subjects affected / exposed	5 / 25 (20.00%)	11 / 72 (15.28%)	2 / 7 (28.57%)
occurrences (all)	7	15	2
Abdominal distension			
subjects affected / exposed	1 / 25 (4.00%)	8 / 72 (11.11%)	1 / 7 (14.29%)
occurrences (all)	1	12	1
Abdominal pain lower			
subjects affected / exposed	3 / 25 (12.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0

Anorectal discomfort			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 25 (4.00%)	9 / 72 (12.50%)	2 / 7 (28.57%)
occurrences (all)	1	10	2
Constipation			
subjects affected / exposed	2 / 25 (8.00%)	7 / 72 (9.72%)	1 / 7 (14.29%)
occurrences (all)	2	7	1
Dental caries			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Dental discomfort			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	12 / 25 (48.00%)	43 / 72 (59.72%)	3 / 7 (42.86%)
occurrences (all)	18	81	4
Dry mouth			
subjects affected / exposed	4 / 25 (16.00%)	4 / 72 (5.56%)	0 / 7 (0.00%)
occurrences (all)	6	4	0
Dyspepsia			
subjects affected / exposed	1 / 25 (4.00%)	3 / 72 (4.17%)	0 / 7 (0.00%)
occurrences (all)	1	3	0
Dysphagia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Epigastric discomfort			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Faeces discoloured			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	2 / 25 (8.00%)	4 / 72 (5.56%)	0 / 7 (0.00%)
occurrences (all)	2	5	0

Frequent bowel movements			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	1 / 25 (4.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	11 / 25 (44.00%)	15 / 72 (20.83%)	1 / 7 (14.29%)
occurrences (all)	15	21	2
Periodontal disease			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Oral pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tongue discolouration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	6 / 25 (24.00%)	4 / 72 (5.56%)	1 / 7 (14.29%)
occurrences (all)	12	4	1

Hepatobiliary disorders			
Sphincter of Oddi dysfunction			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cholelithiasis			
subjects affected / exposed	3 / 25 (12.00%)	17 / 72 (23.61%)	0 / 7 (0.00%)
occurrences (all)	3	21	0
Hepatic steatosis			
subjects affected / exposed	0 / 25 (0.00%)	9 / 72 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	11	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 25 (20.00%)	4 / 72 (5.56%)	0 / 7 (0.00%)
occurrences (all)	9	6	0
Eczema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 25 (0.00%)	2 / 72 (2.78%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Erythema			
subjects affected / exposed	1 / 25 (4.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Hyperhidrosis			
subjects affected / exposed	2 / 25 (8.00%)	3 / 72 (4.17%)	0 / 7 (0.00%)
occurrences (all)	2	4	0
Hypersensitivity vasculitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Onychoclasia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Rash			

subjects affected / exposed	4 / 25 (16.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Pruritus			
subjects affected / exposed	4 / 25 (16.00%)	2 / 72 (2.78%)	0 / 7 (0.00%)
occurrences (all)	4	2	0
Urticaria			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Skin discolouration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Seborrhoea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Microalbuminuria			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Polyuria			
subjects affected / exposed	2 / 25 (8.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Renal cyst			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 25 (0.00%)	6 / 72 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	7	0
Bursitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	4 / 25 (16.00%)	5 / 72 (6.94%)	1 / 7 (14.29%)
occurrences (all)	5	7	2
Arthropathy			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Foot deformity			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Monarthritis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Myalgia			

subjects affected / exposed	0 / 25 (0.00%)	2 / 72 (2.78%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Osteoarthritis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Pain in jaw			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sensation of heaviness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Bone abscess			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	1 / 7 (14.29%)
occurrences (all)	0	1	1

Erysipelas			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	1 / 25 (4.00%)	2 / 72 (2.78%)	1 / 7 (14.29%)
occurrences (all)	1	4	1
Furuncle			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Fungal oesophagitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 25 (0.00%)	4 / 72 (5.56%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Oral fungal infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	7 / 72 (9.72%)	1 / 7 (14.29%)
occurrences (all)	3	8	2

Pneumonia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Postoperative wound infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pyelonephritis chronic			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	1 / 25 (4.00%)	1 / 72 (1.39%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Urinary tract infection			
subjects affected / exposed	2 / 25 (8.00%)	7 / 72 (9.72%)	2 / 7 (28.57%)
occurrences (all)	2	15	2
Upper respiratory tract infection			
subjects affected / exposed	2 / 25 (8.00%)	8 / 72 (11.11%)	0 / 7 (0.00%)
occurrences (all)	2	10	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Wound infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 25 (16.00%)	5 / 72 (6.94%)	2 / 7 (28.57%)
occurrences (all)	5	6	3
Dehydration			

subjects affected / exposed	3 / 25 (12.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0
Diabetes mellitus			
subjects affected / exposed	4 / 25 (16.00%)	16 / 72 (22.22%)	2 / 7 (28.57%)
occurrences (all)	5	20	2
Hypercholesterolaemia			
subjects affected / exposed	0 / 25 (0.00%)	4 / 72 (5.56%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Hyperglycaemia			
subjects affected / exposed	8 / 25 (32.00%)	26 / 72 (36.11%)	4 / 7 (57.14%)
occurrences (all)	10	35	4
Hyperuricaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 72 (1.39%)	2 / 7 (28.57%)
occurrences (all)	0	1	2
Hypoglycaemia			
subjects affected / exposed	2 / 25 (8.00%)	2 / 72 (2.78%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Hypokalaemia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 72 (1.39%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Polydipsia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 72 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Metabolic acidosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 72 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Type 2 diabetes mellitus			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 72 (1.39%) 1	0 / 7 (0.00%) 0
Vitamin D deficiency subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 3	2 / 72 (2.78%) 2	0 / 7 (0.00%) 0

Non-serious adverse events	Nelson s syndrome		
Total subjects affected by non-serious adverse events subjects affected / exposed	14 / 14 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Lipoma subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Malignant neoplasm progression subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Tumour pain subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Vascular disorders Flushing subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Hot flush subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 3		
Peripheral arterial occlusive disease subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Hypotension subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Hypertension subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Poor venous access			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Phlebitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Venous thrombosis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 6		
Chest discomfort subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Chest pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Drug withdrawal syndrome subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Hypothermia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Fatigue subjects affected / exposed occurrences (all)	7 / 14 (50.00%) 10		
Injection site erythema subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Injection site pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Injection site pruritus			

subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Local swelling subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Injection site urticaria subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Malaise subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Thirst subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Pyrexia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Reproductive system and breast disorders Endometrial hyperplasia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Amenorrhoea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Hypomenorrhoea			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Menorrhagia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			
Dysphonia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Cough subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Emphysema subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Respiratory disorder subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Pleurisy subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 5		
Respiratory tract congestion subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Confusional state			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Panic attack			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood corticotrophin increased			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Blood glucagon decreased			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	4		
Blood glucose increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Blood insulin increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Body temperature fluctuation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Electrocardiogram QRS complex abnormal			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Electrocardiogram abnormal			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Glycosylated haemoglobin increased			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Haemoglobin decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Vitamin D decreased			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Insulin-like growth factor decreased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Weight decreased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Fall subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Injection related reaction subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Inflammation of wound subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Muscle strain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Joint injury subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Post procedural complication subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Post procedural swelling subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Skin injury			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Skin wound subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Tachycardia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Sinus bradycardia subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 8		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 10		
Disturbance in attention subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	4 / 14 (28.57%) 12		
Formication subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Mental impairment subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Horner's syndrome subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Hypoaesthesia			

subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 4		
Nystagmus subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Migraine subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Syncope subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Somnolence subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Paraesthesia subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 4		
Tremor subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
VIIth nerve paralysis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Visual field defect subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 8		
Blood and lymphatic system disorders			
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Anaemia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Ear and labyrinth disorders			
Ear discomfort			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Ear pain			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Eustachian tube disorder			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	3		
Vertigo			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Eye disorders			
Blindness			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Conjunctival oedema			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Diplopia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Dry eye			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Eye pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Eye haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Photopsia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Retinal haemorrhage subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Vision blurred subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 7		
Vitreous haemorrhage subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Visual acuity reduced subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Abdominal pain subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 8		
Abdominal distension subjects affected / exposed occurrences (all)	4 / 14 (28.57%) 5		
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Anorectal discomfort subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Abdominal pain upper subjects affected / exposed occurrences (all)	7 / 14 (50.00%) 9		
Constipation subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Dental caries			

subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Dental discomfort			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	11 / 14 (78.57%)		
occurrences (all)	19		
Dry mouth			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Dysphagia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Epigastric discomfort			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Faeces discoloured			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	5		
Frequent bowel movements			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	4		
Glossodynia			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Haemorrhoids subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Nausea subjects affected / exposed occurrences (all)	9 / 14 (64.29%) 21		
Periodontal disease subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Oral pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Retching subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Tongue discolouration subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Toothache subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Vomiting subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 9		
Hepatobiliary disorders			
Sphincter of Oddi dysfunction subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Cholelithiasis subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 5		
Hepatic steatosis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	4		
Eczema			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Erythema			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Hypersensitivity vasculitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Night sweats			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	6		
Onychoclasia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Skin discolouration			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Seborrhoea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Microalbuminuria subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Pollakiuria subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Polyuria subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Renal cyst subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Urinary incontinence subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Urinary retention subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Endocrine disorders			
Adrenal insufficiency subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 9		
Bursitis			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	6		
Arthropathy			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	3		
Foot deformity			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Monarthritis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	4		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	6		
Osteoarthritis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	5		
Pain in jaw			

subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Sensation of heaviness subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Spinal pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Spinal osteoarthritis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Bone abscess subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Cellulitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Cystitis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0		
Erysipelas subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Ear infection subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Furuncle subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		

Fungal oesophagitis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Herpes virus infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	9		
Infection			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Herpes zoster			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Oral fungal infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	13		
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Postoperative wound infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pyelonephritis chronic			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Sinusitis			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Tooth infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Dehydration			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Diabetes mellitus			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Hypercholesterolaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Hyperglycaemia			

subjects affected / exposed	11 / 14 (78.57%)		
occurrences (all)	18		
Hyperuricaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	8		
Hypokalaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Polydipsia			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Metabolic acidosis			
subjects affected / exposed	0 / 14 (0.00%)		
occurrences (all)	0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2009	Amendment 1 was a local amendment for France adding discontinuation language for patients receiving antineoplastic therapy.
09 July 2010	Amendment 2 was a global amendment to include the addition of QT related cardiology consultation and Holter monitoring.
14 March 2011	Amendment 3 updated the PK sample collection of the protocol to correct the visit dates, which now reflect the schedule of assessments in the protocol.
10 October 2011	Amendment 4 implemented an additional extension phase of 2 years (extension phase 2) and updated the evaluation schedule to allow for the collection of imaging data for tumor evaluation from baseline and throughout the trial where applicable.
12 December 2011	Amendment 5 was issued to include additional hepatic-related safety measures as a result of an internal hepatic review of pasireotide trials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported