



Clinical trial results:

A Phase 1/2 Open-Label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Seviteronel in Subjects with Castration-Resistant Prostate Cancer

Summary

EudraCT number	2011-004103-20
Trial protocol	GB GR
Global end of trial date	23 January 2019

Results information

Result version number	v1 (current)
This version publication date	14 June 2019
First version publication date	14 June 2019

Trial information

Trial identification

Sponsor protocol code	INO-VT-464-CL-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02012920
WHO universal trial number (UTN)	-
Other trial identifiers	INO-VT-464-CL-001: INO-VT-464-CL-001

Notes:

Sponsors

Sponsor organisation name	Innocrin Pharmaceuticals Inc
Sponsor organisation address	4220 Apex Highway 55, Durham, North Carolina, United States,
Public contact	Innocrin Information, Innocrin Pharmaceuticals Inc, info@innocrinpharma.com
Scientific contact	Katherine Bowen, DLRC Ltd, 0044 1462372472, katherine.bowen@dlrc.co.uk

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	01 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2018
Global end of trial reached?	Yes
Global end of trial date	23 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the Phase 1 portion of the study are:

To determine the safety and tolerability of seviteronel in "treatment naïve" (not treated with previous abiraterone or enzalutamide) subjects with CRPC.

The primary objectives of the Phase 2 portion of the study are:

- Proportion of subjects who have $\geq 50\%$ PSA decline at any time on study from the start of treatment with seviteronel
- Median time to radiographic disease progression evaluated by computerized tomography (CT scan) or magnetic resonance imaging (MRI) and radionuclide bone scans by RECIST 1.1 or Prostate Cancer Clinical Trials Working Group 3 (PCWG3; Scher et al, 2016)

Protection of trial subjects:

The study protocol, patient information sheet, Informed Consent Form (ICF) and all other relevant study documentation and amendments were reviewed by Independent Ethics Committees. The study did not commence until formal approval had been granted.

Background therapy:

Abiraterone or enzalutamide

Evidence for comparator:

No comparator

Actual start date of recruitment	08 December 2011
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	United Kingdom: 19
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Switzerland: 9
Country: Number of subjects enrolled	United States: 103
Worldwide total number of subjects	135
EEA total number of subjects	23

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)	30
From 65 to 84 years	70
85 years and over	35

Subject disposition

Recruitment

Recruitment details:

The study was completed as planned (defined as discontinuation due to disease progression) by 33 subjects. 102 subjects dropped out of the study before completion.

Pre-assignment

Screening details:

Subjects attended a screening visit within 4 weeks prior to the first treatment.

Period 1

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

Arms

Arm title	seviteronel
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Arm description:

Subjects treated with seviteronel

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

Dosage and administration details:

The Phase 2 dose is 600mg, four 150mg tablets orally once daily.

Number of subjects in period 1	seviteronel
Started	135
Completed	33
Not completed	102
Adverse event, serious fatal	3
Study terminated	1
Physician decision	7
Consent withdrawn by subject	44
N/A	1
Adverse event, non-fatal	45
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	135	135	
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)	30	30	
From 65-84 years	70	70	
85 years and over	35	35	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	135	135	
PSA			
Baseline lab results of PSA			
Units: (ug/L)			
arithmetic mean	125.4		
standard deviation	± 280.5	-	
Testosterone			
Units: nmol/L			
arithmetic mean	0.23		
standard deviation	± 0.23	-	

End points

End points reporting groups

Reporting group title	seviteronel
Reporting group description:	
Subjects treated with seviteronel	

Primary: Max PSA change at any time

End point title	Max PSA change at any time ^[1]
End point description:	
One hundred thirty-one (131) of 135 subjects had post-dosing PSA results available	
End point type	Primary
End point timeframe:	
Whole study	

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: No comparative statistical analysis generated as study was open label

End point values	seviteronel			
Subject group type	Reporting group			
Number of subjects analysed	131			
Units: Subjects				
Number of Subjects with $\geq 30\%$ Reduction from Bas	24			
Number of Subjects with $\geq 50\%$ Reduction from Base	12			
Number of Subjects with $\geq 90\%$ Reduction from Bas	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Max reduction in sum of lesion diameter for target lesions

End point title	Max reduction in sum of lesion diameter for target lesions
End point description:	
End point type	Secondary
End point timeframe:	
Whole study	

End point values	seviteronel			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: % decrease				
arithmetic mean (standard deviation)	0.94 (± 31.974)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event within the date of the start of treatment until the end-of-study visit has been reported

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	All subjects
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Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 135 (33.33%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningioma			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to bone			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jugular vein thrombosis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchiectasis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Dyspnoea			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pulmonary embolism			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Atrial fibrillation			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsions local			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Myelitis transverse			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Toxic encephalopathy			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient global amnesia			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Obstruction			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	3 / 135 (2.22%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 135 (88.89%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Tumour pain			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Hot flush			

subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	12 / 135 (8.89%)		
occurrences (all)	12		
Hypotension			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	7		
Intermittent claudication			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Orthostatic hypotension			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	8		
Systolic hypertension			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Surgical and medical procedures			
Endodontic procedure			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Sinus operation			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 135 (11.85%)		
occurrences (all)	16		
Chest discomfort			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Fatigue			

subjects affected / exposed	68 / 135 (50.37%)		
occurrences (all)	68		
Gait disturbance			
subjects affected / exposed	10 / 135 (7.41%)		
occurrences (all)	10		
Influenza like illness			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Irritability			
subjects affected / exposed	5 / 135 (3.70%)		
occurrences (all)	5		
Malaise			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Mass			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Medical device change			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Mucosal dryness			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	18 / 135 (13.33%)		
occurrences (all)	18		
Pain			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Sensation of foreign body			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Suprapubic pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 135 (0.74%)</p> <p>1</p> <p>1 / 135 (0.74%)</p> <p>1</p>		
<p>Immune system disorders</p> <p>Hypersensitivity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Seasonal allergy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 135 (0.74%)</p> <p>1</p> <p>1 / 135 (0.74%)</p> <p>1</p>		
<p>Reproductive system and breast disorders</p> <p>Pelvic pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Perineal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Scrotal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 135 (0.74%)</p> <p>1</p> <p>1 / 135 (0.74%)</p> <p>1</p> <p>1 / 135 (0.74%)</p> <p>1</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Asthma</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Chronic obstructive pulmonary disease</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysphonia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 135 (0.74%)</p> <p>1</p> <p>2 / 135 (1.48%)</p> <p>2</p> <p>12 / 135 (8.89%)</p> <p>12</p> <p>1 / 135 (0.74%)</p> <p>1</p>		

Dyspnoea			
subjects affected / exposed	14 / 135 (10.37%)		
occurrences (all)	14		
Dyspnoea exertional			
subjects affected / exposed	5 / 135 (3.70%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Increased bronchial secretion			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Pleural effusion			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Pneumonia aspiration			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Pulmonary embolism			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Respiratory failure			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		

Sneezing			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Tachypnoea			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Abnormal dreams			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Affect lability			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Agitation			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Anger			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	11 / 135 (8.15%)		
occurrences (all)	11		
Confusional state			
subjects affected / exposed	20 / 135 (14.81%)		
occurrences (all)	20		
Decreased activity			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Depressed mood			

subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	12 / 135 (8.89%)		
occurrences (all)	12		
Disorientation			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Euphoric mood			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Hallucination			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Hallucination, visual			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	10 / 135 (7.41%)		
occurrences (all)	10		
Mania			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Mental disorder			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Mental status changes			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Mood swings			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Nervousness			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Nightmare			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Panic attack			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Sleep terror			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Somnambulism			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Suicidal ideation			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Blood corticotrophin increased			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Blood creatinine increased			

subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
International normalised ratio increased			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	14 / 135 (10.37%)		
occurrences (all)	14		
Weight increased			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Excoriation			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	22 / 135 (16.30%)		
occurrences (all)	22		
Hand fracture			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Humerus fracture			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Limb injury			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Rib fracture			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Tooth fracture			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Upper limb fracture			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	7		

Atrial flutter			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Atrioventricular block first degree			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Atrioventricular block second degree			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Cardiac failure congestive			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Extrasystoles			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Sinus tachycardia			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Tachycardia			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Ventricular extrasystoles			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Aphonia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Ataxia			

subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Balance disorder			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Burning sensation			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Cognitive disorder			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Complex regional pain syndrome			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Convulsions local			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	8		
Dizziness			
subjects affected / exposed	54 / 135 (40.00%)		
occurrences (all)	54		
Dizziness exertional			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Dizziness postural			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Dysarthria			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences (all)	6		
Dysgeusia			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences (all)	6		
Dyskinesia			

subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Encephalopathy			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Extrapyramidal disorder			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	18 / 135 (13.33%)		
occurrences (all)	18		
Hyperreflexia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Hypersomnia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Memory impairment			
subjects affected / exposed	22 / 135 (16.30%)		
occurrences (all)	22		
Muscle spasticity			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Myoclonus			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Neuritis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Paraesthesia			

subjects affected / exposed	6 / 135 (4.44%)		
occurrences (all)	6		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	5 / 135 (3.70%)		
occurrences (all)	5		
Psychomotor hyperactivity			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Repetitive speech			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Sensory disturbance			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Speech disorder			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Superior sagittal sinus thrombosis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	8		
Tremor			
subjects affected / exposed	57 / 135 (42.22%)		
occurrences (all)	57		
Vasogenic cerebral oedema			

subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed occurrences (all)	9 / 135 (6.67%) 9		
Anaemia of chronic disease			
subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Leukocytosis			
subjects affected / exposed occurrences (all)	2 / 135 (1.48%) 2		
Thrombocytopenia			
subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Ear and labyrinth disorders			
Hearing disability			
subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Inner ear disorder			
subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Tinnitus			
subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Vertigo			
subjects affected / exposed occurrences (all)	4 / 135 (2.96%) 4		
Eye disorders			
Blepharospasm			
subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Cataract			
subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Colour blindness acquired			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Diplopia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Eye pain			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Glaucoma			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Halo vision			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Oscillopsia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Photopsia			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Scleritis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Strabismus			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	19 / 135 (14.07%)		
occurrences (all)	19		
Visual acuity reduced			

subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Visual impairment			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences (all)	6		
Vitreous floaters			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Abdominal distension			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Abdominal pain lower			
subjects affected / exposed	5 / 135 (3.70%)		
occurrences (all)	5		
Abdominal pain upper			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Anorectal discomfort			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Breath odour			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	25 / 135 (18.52%)		
occurrences (all)	25		
Diarrhoea			
subjects affected / exposed	21 / 135 (15.56%)		
occurrences (all)	21		

Dry mouth			
subjects affected / exposed	18 / 135 (13.33%)		
occurrences (all)	18		
Duodenal ulcer			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	8		
Faecaloma			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Incontinence			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Food poisoning			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Haematochezia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Irritable bowel syndrome			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Lip swelling			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		

Nausea			
subjects affected / exposed	37 / 135 (27.41%)		
occurrences (all)	37		
Oral pain			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Periodontal disease			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Proctalgia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Sensitivity of teeth			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Tongue discolouration			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Umbilical hernia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	25 / 135 (18.52%)		
occurrences (all)	25		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	7		
Decubitus ulcer			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	7		
Ecchymosis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Onychoclasia			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Photosensitivity reaction			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	5 / 135 (3.70%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Rash erythematous			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Rash generalised			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Rash macular			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Rash pruritic			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Rash vesicular			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Skin discolouration			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Skin disorder			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Skin hypopigmentation			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Skin irritation			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Skin odour abnormal			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Dysuria			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		

Haematuria			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Hydronephrosis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Leukocyturia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Micturition urgency			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Nocturia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	12 / 135 (8.89%)		
occurrences (all)	12		
Renal failure			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Urethral haemorrhage			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences (all)	6		
Urinary retention			
subjects affected / exposed	5 / 135 (3.70%)		
occurrences (all)	5		
Urinary tract disorder			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Urinary tract obstruction			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		

Urine flow decreased subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	16 / 135 (11.85%) 16		
Back pain subjects affected / exposed occurrences (all)	17 / 135 (12.59%) 17		
Bone pain subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Groin pain subjects affected / exposed occurrences (all)	4 / 135 (2.96%) 4		
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	2 / 135 (1.48%) 2		
Joint swelling subjects affected / exposed occurrences (all)	2 / 135 (1.48%) 2		
Limb discomfort subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 135 (0.74%) 1		
Muscle twitching subjects affected / exposed occurrences (all)	8 / 135 (5.93%) 8		
Muscular weakness			

subjects affected / exposed	14 / 135 (10.37%)		
occurrences (all)	14		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Musculoskeletal pain			
subjects affected / exposed	5 / 135 (3.70%)		
occurrences (all)	5		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences (all)	6		
Pain in extremity			
subjects affected / exposed	10 / 135 (7.41%)		
occurrences (all)	10		
Pain in jaw			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Anal fungal infection			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Bacteraemia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		

Diverticulitis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Eye infection			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Flea infestation			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Herpes zoster			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Lower respiratory tract infection			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	3 / 135 (2.22%)		
occurrences (all)	3		
Oral herpes			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Perineal abscess			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Pneumonia staphylococcal			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		

Pyelonephritis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Rash pustular			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Respiratory tract infection viral			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	8		
Urinary tract infection			
subjects affected / exposed	7 / 135 (5.19%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	30 / 135 (22.22%)		
occurrences (all)	30		
Dehydration			
subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	9		
Diabetes mellitus			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Failure to thrive			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Hyperglycaemia			

subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	5 / 135 (3.70%)		
occurrences (all)	5		
Hypokalaemia			
subjects affected / exposed	6 / 135 (4.44%)		
occurrences (all)	6		
Hypomagnesaemia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Lactic acidosis			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Lactose intolerance			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2011	Clarification added regarding management of expanded dose-cohorts.
23 March 2012	Changes in instructions for taking study drug with food
04 September 2012	Additional information provided to assess the cardiac safety of study drug
29 October 2012	Clarification added surrounding acceptable minor disease progression. Changes in rules regarding cohort expansion.
25 April 2013	4 week dose titration stage added. Updated DLT definition. Change in the dose-level increment for potential doses above 600mg bid from 100 to 150 mg. Intra-patient dose escalation option added for patients that have at least cycle 3.
22 November 2013	Added new patient populations for the Phase 2 portion of the study. Added a Simon's optimal two-stage study design with futility analysis for new Phase 2 study populations. Removal of the Single Dose stage of the study in Phase 2
21 May 2015	Added new patient populations/cohorts for the Phase 2 portion of the study and the option for daily dosing without dose titration based upon a separate Phase 1 / 2 study of daily dosing with VT-464 (INO-VT-464-CL-004). Updated concomitant medication wording to allow short-course systemic corticosteroid use while on study.
30 June 2016	Updated concomitant medication wording and inclusion/ exclusion criteria to allow patients who are on replacement doses of corticosteroids when coming onto study to continue those steroids while on study. The bone flare wording was clarified to include the Prostate Cancer Clinical Trial Working Group 2 recommendations that new bone lesions at the first restaging scan at the end of Cycle 2 be used as the new baseline scan. The clinical trial material information was updated to account for capsules no longer being available for the study, and the introduction of a 75 mg tablet dosage form.
17 April 2017	Addition of dexamethasone 0.5 mg co-administration with seviteronel in all newly enrolled subjects. Removed all bid and multiple dosing language and sections as Phase 1 is complete and Phase 2 is single dose, daily 600mg treatment. Updated Phase 2 objectives reducing the number of study cohorts/groups from 5 to 2; added metrics to PSA response " $\geq 50\%$ PSA decline ≤ 12 weeks"; added median time to radiographic progression, imaging methodology and updated Prostate Cancer Working Group2 (PCWG2, 2008) to PCWG3, 2016.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

