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

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 ≥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

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 >= 30% Reduction from Bas	24			
Number of Subjects with >= 50% Reduction from Base	12			
Number of Subjects with >= 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	All subjects

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				

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

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	1 / 135 (0.74%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 135 (6.67%)		
occurrences (all)	9		
Anaemia of chronic disease			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Leukocytosis			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Hearing disability			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Inner ear disorder			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Eye disorders			
Blepharospasm			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Cataract			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	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			
Onychoclasis				
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	1 / 135 (0.74%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 135 (11.85%)		
occurrences (all)	16		
Back pain			
subjects affected / exposed	17 / 135 (12.59%)		
occurrences (all)	17		
Bone pain			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Groin pain			
subjects affected / exposed	4 / 135 (2.96%)		
occurrences (all)	4		
Intervertebral disc protrusion			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	2 / 135 (1.48%)		
occurrences (all)	2		
Limb discomfort			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 135 (0.74%)		
occurrences (all)	1		
Muscle twitching			
subjects affected / exposed	8 / 135 (5.93%)		
occurrences (all)	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 "≥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