



Clinical trial results:

A Phase 2, Open-Label, Single-Arm, Multidose Study to Investigate the Effects of Orteronel on the QT/QTc Interval in Patients with Metastatic Castration-Resistant Prostate Cancer

Summary

EudraCT number	2012-000136-26
Trial protocol	GR IE FR
Global end of trial date	21 January 2015

Results information

Result version number	v1 (current)
This version publication date	04 May 2016
First version publication date	04 May 2016

Trial information

Trial identification

Sponsor protocol code	C21012
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01549951
WHO universal trial number (UTN)	U1111-1179-5656

Notes:

Sponsors

Sponsor organisation name	Millennium Pharmaceuticals, Inc.
Sponsor organisation address	61 Aldwych, London, United Kingdom, WC2B 4AE
Public contact	Study Manager, Millennium Medical and Drug Information Center, 001 866-835-2233, GlobalOncologyMedinfo@takeda.com
Scientific contact	Study Manager, Millennium Medical and Drug Information Center, 001 866-835-2233, GlobalOncologyMedinfo@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this phase 2, open-label, single-arm, multidose, multicenter study is to investigate the effects of Orteronel plus Prednisone on the QT/QTc interval in patients with Metastatic Castration-Resistant Prostate Cancer

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Romania: 1
Worldwide total number of subjects	50
EEA total number of subjects	27

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)	18
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 16 investigative sites in Canada, France, Greece, Ireland, Romania, and the United States from 29 May 2012 to 21 January 2015.

Pre-assignment

Screening details:

Male subjects with a historical diagnosis of metastatic castration-resistant prostate cancer (mCRPC) were enrolled in this single arm study to receive orteronel 400 milligram (mg) along with prednisone 5 mg twice daily for 28 days in each treatment cycle.

Period 1

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

Arms

Arm title	Orteronel + Prednisone
-----------	------------------------

Arm description:

Orteronel 400 mg, tablets, orally, twice daily along with prednisone 5 mg, tablets, orally, twice daily for 2 treatment cycles of 28 days each. Gonadotropin-releasing hormone analogue therapy was supplied as a commercially available dosage formulation.

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

Dosage and administration details:

Orteronel 400 mg, tablets, orally, twice daily for 2 treatment cycles of 28 days each.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 5 mg, tablets, orally, twice daily for 2 treatment cycles of 28 days each.

Number of subjects in period 1	Orteronel + Prednisone
Started	50
Primary reason off study treatment	50
Completed	0
Not completed	50
Consent withdrawn by subject	2
Adverse event, non-fatal	15

Unsatisfactory therapeutic response	1
Symptomatic deterioration	1
Unknown	2
Progressive disease	29

Baseline characteristics

Reporting groups

Reporting group title	Orteronel + Prednisone
-----------------------	------------------------

Reporting group description:

Orteronel 400 mg, tablets, orally, twice daily along with prednisone 5 mg, tablets, orally, twice daily for 2 treatment cycles of 28 days each. Gonadotropin-releasing hormone analogue therapy was supplied as a commercially available dosage formulation.

Reporting group values	Orteronel + Prednisone	Total	
Number of subjects	50	50	
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)	18	18	
From 65-84 years	32	32	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	68.7		
standard deviation	± 8.85	-	
Gender, Male/Female			
Units: subjects			
Female	0	0	
Male	50	50	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	27	27	
Unknown or Not Reported	22	22	
Race/Ethnicity, Customized			
Units: Subjects			
White	27	27	
Black/African American	3	3	
Not reported	20	20	
Eastern Cooperative Oncology Group (ECOG) performance status			
ECOG assessed subject's performance status on 5point scale: 0=Fully active/able to carry on all pre-disease activities without restriction;1=restricted in physically strenuous activity,ambulatory/able to carry out light or sedentary work;2=ambulatory (greater than[>] 50 percent[%] of waking hours),capable of all self care,unable to carry out any work activities;3=capable of only limited selfcare,confined to bed/chair>50% of waking hours;4=completely disabled,cannot carry on any selfcare,totally confined to bed/chair;5=dead. Subject with performance status as 0 and 1 have been			
Units: Subjects			

'0'	38	38	
'1'	12	12	
Histological classification			
Carcinoma was classified as adenocarcinoma in situ (local), not otherwise specified (NOS) and adenocarcinoma, NOS.			
Units: Subjects			
Adenocarcinoma in situ, NOS	8	8	
Adenocarcinoma, NOS	42	42	
Height			
Units: centimeters (cm)			
arithmetic mean	175.32		
standard deviation	± 7.521	-	
Weight			
Units: kilograms (kg)			
arithmetic mean	87.63		
standard deviation	± 14.797	-	
Time from initial prostate cancer diagnosis			
Time from initial diagnosis was defined as (first dose date - initial diagnosis date + 1) / 365.25.			
Units: years			
arithmetic mean	6.32		
standard deviation	± 5.325	-	

End points

End points reporting groups

Reporting group title	Orteronel + Prednisone
Reporting group description: Orteronel 400 mg, tablets, orally, twice daily along with prednisone 5 mg, tablets, orally, twice daily for 2 treatment cycles of 28 days each. Gonadotropin-releasing hormone analogue therapy was supplied as a commercially available dosage formulation.	

Primary: Maximum Change From Baseline in QTc Interval Based on the Fridericia Correction (QTcF) Method

End point title	Maximum Change From Baseline in QTc Interval Based on the Fridericia Correction (QTcF) Method ^[1]
-----------------	--

End point description:

Triplicate 12-lead electrocardiogram (ECG) measurements (each recording separated by approximately 1 minute) were performed and average was calculated. The time corresponding to beginning of depolarization to repolarization of the ventricles (QT interval) was adjusted for RR interval using QT and RR from each ECG by Fridericia's formula ($QTcF = QT$ divided by cube root of RR). Results of change in QTcF analyzed from 12-lead ECGs performed at each time point were averaged for analysis and a maximum across all post-dosing time points was used. Baseline is defined as the average of the triplicate 12-lead ECG measurements taken at the specified time prior to dosing. ECG analysis population was defined as all subjects with at least 1 available baseline and at least 1 on-treatment ECG who received at least 1 dose of any study drug.

End point type	Primary
----------------	---------

End point timeframe:

Cycle 1 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose; Cycle 2 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose

Notes:

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

Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: millisecond (msec)				
arithmetic mean (standard deviation)	-1.4 (± 19.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in QTc Based on the Bazett Correction (QTcB) Method, PR, QRS and Uncorrected QT Interval

End point title	Maximum Change From Baseline in QTc Based on the Bazett Correction (QTcB) Method, PR, QRS and Uncorrected QT Interval
-----------------	---

End point description:

Triplicate 12-lead ECG measurements (each recording separated by approximately 1 minutes) were performed and average was calculated. The time corresponding to beginning of depolarization to

repolarization of the ventricles (QT interval) was adjusted for RR interval using QT and RR from each ECG by Bazette's formula ($QTcB = QT \text{ divided by square root of } RR$). Results of change in QTcB, PR, QRS and uncorrected QT analyzed from 12-lead ECGs performed at each time point were averaged for analysis and a maximum across all post-dosing time points was used. Baseline is defined as the average of the triplicate 12-lead ECG measurements taken at the specified time prior to dosing. ECG analysis population was defined as all subjects with at least 1 available baseline and at least 1 on-treatment ECG who received at least 1 dose of any study drug.

End point type	Secondary
End point timeframe:	
Cycle 1 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose; Cycle 2 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose	

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: msec				
arithmetic mean (standard deviation)				
QTcB Interval (N=43)	9.7 (± 22.61)			
PR Interval (N=48)	-4.2 (± 7.4)			
QRS Interval (N=48)	-1 (± 2.8)			
Uncorrected QT Interval (N=48)	-12.5 (± 17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Heart Rate

End point title	Changes From Baseline in Heart Rate
End point description:	
<p>Triplicate 12-lead Electrocardiogram (ECG) measurements were performed and average was calculated. Supine heart rate was measured as beats per minute (bpm). Results of change in heart rate analyzed from 12-lead ECGs performed at each time point were averaged for analysis and a maximum across all post-dosing time points was used. Baseline is defined as the average of the triplicate 12-lead ECG measurements taken at the specified time prior to dosing. ECG analysis population was defined as all subjects with at least 1 available baseline and at least 1 on-treatment ECG who received at least 1 dose of any study drug.</p>	
End point type	Secondary
End point timeframe:	
Cycle 1 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose; Cycle 2 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose	

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: bpm				
arithmetic mean (standard deviation)	5.7 (± 8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Change From Baseline in ECG Morphology

End point title	Number of Subjects Reporting Change From Baseline in ECG Morphology
-----------------	---

End point description:

Subjects with incidence of ECG morphology abnormalities were observed. Types of abnormalities included appearance of abnormal U waves, T waves inversion, elevation of ST segment, depression of ST segment, second or third degree heart block, right or left bundle branch block, atrial fibrillation/flutter, and myocardial infarction. New morphological changes were observed in abnormal U waves, depression of ST segment, and T waves inversion. Here, 'new' refers to change not present at baseline, ie, at any evaluation predose, and only seen postbaseline. Results of change in ECG morphology analyzed from 12-lead ECG at each time point were averaged for analysis and a maximum across all post-dosing time points was used. Baseline is defined as the average of the triplicate 12-lead ECG measurements taken at the specified time prior to dosing. ECG analysis population was defined as all subjects with at least 1 available baseline and at least 1 on-treatment ECG who received at least 1 dose of any study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycle 1 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose; Cycle 2 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: subjects				
number (not applicable)				
Abnormal U waves	1			
ST segment depression	8			
T-wave inversion	3			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-6): Area Under the Plasma Concentration-Time Curve From Time 0 to 6 Hours Postdose for Orteronel and M-I metabolite

End point title	AUC(0-6): Area Under the Plasma Concentration-Time Curve From Time 0 to 6 Hours Postdose for Orteronel and M-I
-----------------	--

End point description:

AUC(0-6) is measure of area under the curve over the dosing interval (tau) (AUC(0-tau)), where tau is the length of the dosing interval - 6 hours in this study). Average results at each time point were analyzed and a maximum across all post-dosing time points was used. Baseline is defined as the average of the triplicate 12-lead ECG measurements taken at the specified time prior to dosing. Pharmacokinetic (PK) population was defined as all subjects who had sufficient dosing data and plasma concentration-time data to permit calculations of PK parameters.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycle 1 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose; Cycle 2 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: nanogram hours per milliliter (ng*hr/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=50)	7570.4 (± 3673.31)			
Cycle 2 Day 1 (n=44)	12971.6 (± 6071.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between the QTcF Change From Baseline and Plasma Concentrations of Orteronel

End point title	Correlation Between the QTcF Change From Baseline and Plasma Concentrations of Orteronel
-----------------	--

End point description:

Coefficient of correlation was measured using linear mixed effects model for the association between two variables; change from baseline versus the plasma concentration. Subjects's effects on the intercept and plasma concentration slope were included in the model as random effects terms. Plasma concentrations were re scaled for model convergence. Average results at each time point were analyzed and a maximum across all post-dosing time points was used. Baseline is defined as the average of the triplicate 12-lead ECG measurements taken at the specified time prior to dosing. ECG analysis population was defined as all subjects with at least 1 available baseline and at least 1 on-treatment ECG who received at least 1 dose of any study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycle 1 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose; Cycle 2 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: correlation coefficient				
least squares mean (standard error)	-0.002603 (± 0.001053)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Orteronel and M-I metabolite

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Orteronel and M-I metabolite
-----------------	--

End point description:

Tmax: Time to reach the maximum plasma concentration (Cmax), equal to time (hours) to Cmax. Average results at each time point were analyzed and a maximum across all post-dosing time points was used. Baseline is defined as the average of the triplicate 12-lead ECG measurements taken at the specified time prior to dosing. PK population was defined as all subjects who had sufficient dosing data and plasma concentration-time data to permit calculations of PK parameters.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycle 1 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose; Cycle 2 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: hours				
median (full range (min-max))				
Orteronel: Cycle 1 Day 1 (n=50)	2 (1 to 5)			
Orteronel: Cycle 2 Day 1 (n=44)	1.6 (0.5 to 6)			
M-I metabolite: Cycle 1 Day 1 (n=50)	4.5 (1.5 to 6.2)			
M-I metabolite: Cycle 2 Day 1 (n=44)	3 (0 to 6.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Plasma Concentration for Orteronel and M-I metabolite

End point title	Cmax: Maximum Observed Plasma Concentration for Orteronel and M-I metabolite
-----------------	--

End point description:

Maximum observed plasma concentration (C_{max}) is the peak plasma concentration of a drug after administration, obtained directly from the plasma concentration-time curve. Average results at each time point were analyzed and a maximum across all post-dosing time points was used. Baseline is defined as the average of the triplicate 12-lead ECG measurements taken at the specified time prior to dosing. PK population was defined as all subjects who had sufficient dosing data and plasma concentration-time data to permit calculations of PK parameters.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycle 1 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose; Cycle 2 (28 day cycle), Day 1: pre-dose and at multiple timepoints (up to 6 hours) post-dose

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Orteronel: Cycle 1 Day 1 (n=50)	1904 (± 1000.98)			
Orteronel: Cycle 2 Day 1 (n=44)	3017.9 (± 1512.33)			
M-I metabolite: Cycle 1 Day 1 (n=50)	263.5 (± 161.22)			
M-I metabolite: Cycle 2 Day 1 (n=44)	597.5 (± 333.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting One or More Treatment-emergent Adverse Events

End point title	Number of Subjects Reporting One or More Treatment-emergent Adverse Events
-----------------	--

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug. Safety analysis set was defined as all subjects who received at least 1 dose of any study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to 30 days after last dose of study drug (Day 86)

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: subjects				
number (not applicable)	48			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Clinically Significant Abnormalities in Vital Signs

End point title	Number of Subjects Reporting Clinically Significant Abnormalities in Vital Signs
-----------------	--

End point description:

The number of subjects with any clinically significant abnormalities in vital signs collected throughout study. Vital signs included body temperature (oral), sitting blood pressure (after the subject has rested for at least 5 minutes), and pulse (bpm). Safety analysis set was defined as all subjects who received at least 1 dose of any study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to 30 days after last dose of study drug (Day 86)

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Clinically Significant Abnormalities in Laboratory Values

End point title	Number of Subjects Reporting Clinically Significant Abnormalities in Laboratory Values
-----------------	--

End point description:

The number of subjects with any clinically significant abnormalities in safety laboratory values collected throughout study. Safety analysis set was defined as all subjects who received at least 1 dose of any study drug.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline up to 30 days after last dose of study drug (Day 86)

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: subjects				
number (not applicable)	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Clinically Significant Abnormalities in Physical Findings

End point title	Number of Subjects Reporting Clinically Significant Abnormalities in Physical Findings
End point description:	
Physical examination consists of examinations of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) physical examinations other than body systems described in (1) to (10). Safety analysis set was defined as all subjects who received at least 1 dose of any study drug.	
End point type	Secondary
End point timeframe:	
Baseline up to 30 days after last dose of study drug (Day 86)	

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Clinically Significant Abnormalities in ECG

End point title	Number of Subjects Reporting Clinically Significant Abnormalities in ECG
End point description:	
The number of subjects who reported clinically significant abnormalities in ECG were measured throughout study. ECGs were performed after the subject had been supine for at least 10 minutes. Safety analysis set was defined as all subjects who received at least 1 dose of any study drug.	

End point type	Secondary
End point timeframe:	
Baseline up to 30 days after last dose of study drug (Day 86)	

End point values	Orteronel + Prednisone			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of double-blind study drug and no more than 30 days after the last dose of double-blind study drug (Day 86).

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the subject or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	15.0
--------------------	------

Reporting groups

Reporting group title	Orteronel + Prednisone
-----------------------	------------------------

Reporting group description:

Orteronel 400 mg, tablets, orally, twice daily along with prednisone 5 mg, tablets, orally, twice daily for 2 treatment cycles of 28 days each. Gonadotropin-releasing hormone analogue therapy was supplied as a commercially available dosage formulation.

Serious adverse events	Orteronel + Prednisone		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 50 (34.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Myocardial infarction			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular disorder			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Proctitis haemorrhagic			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pumonary embolism			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia pseudomonal			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Orteronel + Prednisone		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 50 (96.00%)		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	7		
Weight decreased			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	9		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Blood lactate dehydrogenase increased			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood alkaline phosphatase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 50 (6.00%)</p> <p>3</p> <p>4 / 50 (8.00%)</p> <p>6</p>		
<p>Injury, poisoning and procedural complications</p> <p>Fall</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 50 (6.00%)</p> <p>3</p>		
<p>Vascular disorders</p> <p>Hot flush</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypertension</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 50 (14.00%)</p> <p>7</p> <p>3 / 50 (6.00%)</p> <p>4</p>		
<p>Nervous system disorders</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysgeusia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Paraesthesia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 50 (10.00%)</p> <p>5</p> <p>4 / 50 (8.00%)</p> <p>5</p> <p>4 / 50 (8.00%)</p> <p>5</p> <p>3 / 50 (6.00%)</p> <p>4</p>		
<p>General disorders and administration site conditions</p> <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Asthenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>12 / 50 (24.00%)</p> <p>18</p> <p>11 / 50 (22.00%)</p> <p>13</p>		

Oedema peripheral subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 9		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all)	18 / 50 (36.00%) 18 16 / 50 (32.00%) 22 7 / 50 (14.00%) 10 9 / 50 (18.00%) 12 5 / 50 (10.00%) 5 3 / 50 (6.00%) 3 3 / 50 (6.00%) 4		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	12 / 50 (24.00%) 16 3 / 50 (6.00%) 3		

Dyspnoea exertional subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Bronchitis subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Skin and subcutaneous tissue disorders Rash macular subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 5		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 6		
Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5		
Muscle spasms subjects affected / exposed occurrences (all)	9 / 50 (18.00%) 13		
Pain in extremity subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 5		
Arthralgia subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 4		
Bone pain subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Back pain subjects affected / exposed occurrences (all)	11 / 50 (22.00%) 12		

Musculoskeletal chest pain subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	10 / 50 (20.00%) 12		
Dehydration subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5		
Diabetes mellitus subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Hypokalaemia subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported