Clinical trial results:
A Safety Study of Oraxol (HM30181 + oral paclitaxel) in Cancer Patients

Summary

EudraCT number	2017-004578-33
Trial protocol	GB
Global end of trial date	15 June 2021

Results information

Result version number	v1 (current)
This version publication date	01 January 2023
First version publication date	01 January 2023

Trial information

Trial identification

Sponsor protocol code	KX-ORAX-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1170-6641

Notes:

Sponsors

Sponsor organisation name	Athenex, Inc. doing business as Kinex Pharmaceuticals, Inc.
Sponsor organisation address	20 Commerce Drive, Cranford, United States, NJ 07016
Public contact	Ashleigh Lamson, Athenex, Inc. , 1-716 427-2950, ashleighlamson@athenex.com
Scientific contact	Rudolf Kwan, MD, Athenex, Inc. , 1-716 427-2950, rkwan@kinexpharma.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	15 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2021
Global end of trial reached?	Yes
Global end of trial date	15 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine the safety and tolerability of Oraxol.

Protection of trial subjects:

This study was conducted in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Subjects were monitored for adverse events with any serious adverse events (SAEs) reported to the study sponsor and reviewed by the KX-ORAX-003 data safety monitoring board. Monitoring visits to each site were conducted to assess adherence to the study protocol, data accuracy and compliance with GCP and local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	New Zealand: 30
Worldwide total number of subjects	44
EEA total number of subjects	0

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	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible participants were adults with cancer for whom weekly IV paclitaxel therapy was indicated (including subjects who had completed the KX-ORAX-002 trial). Subjects were recruited from 8 sites in 4 countries (UK, Taiwan, Australia and New Zealand).

Pre-assignment

Screening details:

45 participants were screened. One participant was excluded due to a screening failure (failure to meet all inclusion criteria).

Pre-assignment period milestones

Number of subjects started	45[1]
Number of subjects completed	44

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening Failure: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 45 patients signed the ICF however there was 1 screen failure. 44 patients were dosed according to the protocol.

Period 1

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

Arms

Arm title	Oraxol

Arm description:

All subjects (Group A) received oral HM30181A × 3 consecutive days weekly (1 hour before paclitaxel) + oral paclitaxel capsule on 3 consecutive days weekly.
Group B: (sub-group) in addition to Group A treatment also received oral paclitaxel tablets on 3 consecutive days weekly (for 1 week only at Week 5 or later) and underwent a second pharmacokinetic (PK) period to determine bioavailability.

Arm type	Experimental
Investigational medicinal product name	HM30181A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral HM30181A (supplied as 15-mg HM30181AK-US tablets equivalent to 12.9 mg of encequidar free base). Administrated 15 mg daily on 3 consecutive days weekly (1 hour before paclitaxel).

Investigational medicinal product name	Paclitaxel (capsule)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details: Oral paclitaxel capsule 30mg. Administrated 205 mg/m2 daily on 3 consecutive days weekly.	
Investigational medicinal product name	Paclitaxel (tablet)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Group B only: Oral paclitaxel tablet 30mg. Administrated 205 mg/m2 daily on 3 consecutive days weekly (for 1 week only at Week 5 or later)

Number of subjects in period 1	Oraxol
Started	44
Completed	0
Not completed	44
Physician decision	1
Consent withdrawn by subject	3
Adverse event, non-fatal	7
Progressive disease	33

Baseline characteristics

Reporting groups	
Reporting group title	Oraxol
Reporting group description:	
Oraxol (oral paclitaxel + HM30181A): Oral HM30181A 15 mg daily × 3 consecutive days weekly (1 hour before paclitaxel) plus oral paclitaxel 205 mg/m2 daily × 3 consecutive days weekly	

Reporting group values	Oraxol	Total	
Number of subjects	44	44	
Age categorical			
The youngest subject was 32 years, the oldest 77 years (in Group B the youngest subject was 43 years, the oldest 75 years)			
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	14	14	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	58.9		
standard deviation	± 10.6	-	
Gender categorical			
Units: Subjects			
Female	30	30	
Male	14	14	
Ethnic group			
Units: Subjects			
Asian - China	1	1	
Asian - Other	10	10	
Native Hawaiian or Other Pacific Islander	1	1	
White	32	32	
Primary Cancer Diagnosis			
Units: Subjects			
Breast	25	25	
Esophageal	4	4	
Gastric	3	3	
Bile duct	2	2	
Ovarian	2	2	
Prostate	2	2	
Vascular	2	2	
Other	4	4	

Weight			
Units: kg			
arithmetic mean	71.7		
standard deviation	± 15.5	-	
Height			
Units: cm			
arithmetic mean	166.4		
standard deviation	± 8.2	-	
Body Surface Area (BSA)			
Units: m2			
arithmetic mean	1.8		
standard deviation	± 0.2	-	

Subject analysis sets

Subject analysis set title	Oraxol (Group B)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subgroup of participants (i.e., Group B) to determine the bioavailability of paclitaxel tablets versus paclitaxel capsules

Reporting group values	Oraxol (Group B)		
Number of subjects	10		
Age categorical			
The youngest subject was 32 years, the oldest 77 years (in Group B the youngest subject was 43 years, the oldest 75 years)			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	6		
From 65-84 years	4		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	60.2		
standard deviation	± 10.7		
Gender categorical			
Units: Subjects			
Female	5		
Male	5		
Ethnic group			
Units: Subjects			
Asian - China	0		
Asian - Other	4		
Native Hawaiian or Other Pacific Islander	0		
White	6		

Primary Cancer Diagnosis Units: Subjects			
Breast	5		
Esophageal	2		
Gastric	1		
Bile duct	0		
Ovarian	0		
Prostate	0		
Vascular	1		
Other	1		
Weight Units: kg			
arithmetic mean	72.8		
standard deviation	± 16.6		
Height Units: cm			
arithmetic mean	165.6		
standard deviation	± 5.9		
Body Surface Area (BSA) Units: m2			
arithmetic mean	1.8		
standard deviation	± 0.2		

End points

End points reporting groups

Reporting group title	Oraxol

Reporting group description:

All subjects (Group A) received oral HM30181A × 3 consecutive days weekly (1 hour before paclitaxel) + oral paclitaxel capsule on 3 consecutive days weekly.
Group B: (sub-group) in addition to Group A treatment also received oral paclitaxel tablets on 3 consecutive days weekly (for 1 week only at Week 5 or later) and underwent a second pharmacokinetic (PK) period to determine bioavailability.

Subject analysis set title	Oraxol (Group B)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A subgroup of participants (i.e., Group B) to determine the bioavailability of paclitaxel tablets versus paclitaxel capsules

Primary: Number of subjects with at least one treatment emergent adverse event (TEAE)

End point title	Number of subjects with at least one treatment emergent adverse event (TEAE)[1]

End point description:

Adverse events with an onset after dosing and those pre-existing AEs that worsen during the study. The TEAE classified as "related" are those judged “definitely related,” “probably related,” or “possibly related” to Oraxol by the investigator.

End point type	Primary

End point timeframe:

From signing of informed consent form (ICF) to final study visit

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 quantitative statistical analysis was performed for this end point.

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Subjects				
TEAE - overall	43			
TEAE - related to Oraxol	41			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with at least one serious adverse event (SAE)

End point title	Number of subjects with at least one serious adverse event (SAE)[2]

End point description:

Number of serious adverse events (SAEs) experienced by subjects who had received Oraxol. A SAE was defined as any untoward medical occurrence that at any dose: resulted in death, was life threatening (i.e., the participant was at immediate risk of death from the AE as it occurred), required inpatient hospitalization/prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect (in the child of a participant who was

exposed to the study drug). Other important medical events that may not have been immediately life threatening or resulted in death or hospitalization but, when based on appropriate medical judgment, may have jeopardized the participant or may have required intervention to prevent one of the outcomes in the definition of SAE listed above, were also to be considered SAEs.

End point type	Primary

End point timeframe:

Signing of informed consent form (ICF) to final study visit

Notes:

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

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Subjects				
Serious TEAE - all events	14			
Serious TEAE - related to Oraxol	7			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinically important changes in vital signs

End point title	Number of subjects with clinically important changes in vital signs[3]

End point description:

Number of subjects with changes in vital signs (heart rate [HR], respiratory rate [RR], systolic and diastolic blood pressure [BP], body temperature) during study treatment where change assessed as clinically important

End point type	Primary

End point timeframe:

From baseline to final study visit

Notes:

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

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Subjects				
Change in HR - CS	0			
Change in BP - CS	0			
Change in RR - CS	0			
Change in body temperature - CS	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinically important abnormality on ECG (PR, QRS, QT and QTc intervals)

End point title	Number of subjects with clinically important abnormality on ECG (PR, QRS, QT and QTc intervals)[4]

End point description:

Number of subjects with a clinically significant ECG abnormality (as interpreted by the investigator) during study treatment.

End point type	Primary

End point timeframe:

From baseline to final visit

Notes:

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

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Subject				
ECG - clinically significant abnormality	0			

Statistical analyses

No statistical analyses for this end point

Primary: ECOG Performance Status at Final Visit

End point title	ECOG Performance Status at Final Visit[5]

End point description:

Easter Cooperative Oncology Group (ECOG) Performance Status (PS) at final study visit. ECOG PS is used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis (on decreasing scale from PS =0 being fully active). All patients recruited to the trial had PS of either 0 or 1 when recruited to the trial as per the study inclusion criteria.

End point type	Primary

End point timeframe:

Final study visit

Notes:

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

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: ECOG score				
ECOG PS Score 0	10			
ECOG PS Score 1	25			
ECOG PS Score 2	1			

ECOG PS Score 3	3			
ECOG PS Score 4	0			
ECOG PS Score 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with a shift in laboratory values (Hematology) from baseline to worst toxicity grade during treatment

End point title	Number of subjects with a shift in laboratory values (Hematology) from baseline to worst toxicity grade during treatment[6]

End point description:

Changes in laboratory values (hematology) during study treatment as defined by maximum CTCAE toxicity grade (Grade 0 = within normal levels, Grade 1 = mild, 2 = moderate, 3 severe, 4 = life threatening; 5 = death related to AE)

End point type	Primary

End point timeframe:

From baseline to final study visit

Notes:

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

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Subjects				
Hemoglobin decreased - grade 3	2			
Hemoglobin decreased - grade 2	9			
Hemoglobin decreased - grade 1	25			
Hemoglobin decreased - grade 0	8			
Platelet count decreased - grade 2	1			
Platelet count decreased - grade 1	7			
Platelet count decreased - grade 0	36			
White blood cell decreased - grade 4	2			
White blood cell decreased - grade 3	5			
White blood cell decreased - grade 2	12			
White blood cell decreased - grade 1	13			
White blood cell decreased - grade 0	12			
Lymphocyte count decreased - grade 4	1			
Lymphocyte count decreased - grade 3	9			
Lymphocyte count decreased - grade 2	15			
Lymphocyte count decreased - grade 1	8			
Lymphocyte count decreased - grade 0	11			
Neutrophil count decreased - grade 4	3			
Neutrophil count decreased - grade 3	6			
Neutrophil count decreased - grade 2	8			
Neutrophil count decreased - grade 1	4			

Neutrophil count decreased - grade 0	23			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with a shift in laboratory values (Chemistry) from baseline to worst toxicity grade during treatment

End point title	Number of subjects with a shift in laboratory values (Chemistry) from baseline to worst toxicity grade during treatment[7]

End point description:

Changes in laboratory values (Chemistry) as defined by maximum CTCAE toxicity grade during study treatment
(Grade 0 = within normal levels, Grade 1 = Mild, 2 = moderate, 3 severe, 4 = life threatening; 5 =death related to AE)

End point type	Primary

End point timeframe:

From baseline to final study visit

Notes:

[7] - 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 quantitative statistical analysis was performed for this end point.

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Subjects				
Hyperkalemia-grade 2	5			
Hyperkalemia-grade 1	2			
Hyperkalemia-grade 0	37			
Hypokalemia-grade 3	1			
Hypokalemia-grade 1	2			
Hypokalemia-grade 0	41			
Hypernatremia-grade 1	4			
Hypernatremia-grade 0	40			
Hyponatremia-grade 3	2			
Hyponatremia-grade 1	6			
Hyponatremia-grade 0	36			
Alanine aminotransferase increased-grade 1	17			
Alanine aminotransferase increased-grade 0	27			
Alkaline phosphatase increased-grade 3	1			
Alkaline phosphatase increased-grade 2	4			
Alkaline phosphatase increased-grade 1	13			
Alkaline phosphatase increased-grade 0	26			
Aspartate aminotransferase increased-grade 2	2			

Aspartate aminotransferase increased-grade 1	14			
Aspartate aminotransferase increased-grade 0	26			
Gamma-glutamyl transferase (GGT) increased-grade 3	9			
Gamma-glutamyl transferase (GGT) increased-grade 2	2			
Gamma-glutamyl transferase (GGT) increased-grade 1	15			
Gamma-glutamyl transferase (GGT) increased-grade 0	18			
Blood bilirubin increased-grade 2	1			
Blood bilirubin increased-grade 1	1			
Blood bilirubin increased-grade 0	42			
Creatinine increased-grade 2	1			
Creatinine increased-grade 1	35			
Creatinine increased-grade 0	8			
Hypoalbuminemia-grade 3	1			
Hypoalbuminemia-grade 2	10			
Hypoalbuminemia-grade 1	11			
Hypoalbuminemia-grade 0	22			
Hypercalcemia-grade 1	3			
Hypercalcemia-grade 0	38			
Cholesterol high-grade 2	1			
Cholesterol high-grade 1	32			
Cholesterol high-grade 0	11			
Hyperglycemia-grade 3	2			
Hyperglycemia-grade 2	4			
Hyperglycemia-grade 1	14			
Hyperglycemia-grade 0	24			
Hypoglycemia-grade 2	2			
Hypoglycemia-grade 1	2			
Hypoglycemia-grade 0	40			
Hypertriglyceridemia-grade 2	3			
Hypertriglyceridemia-grade 1	26			
Hypertriglyceridemia-grade 0	15			
Hyperuricemia-grade 4	1			
Hyperuricemia-grade 1	8			
Hyperuricemia-grade 0	34			
Hypocalcemia-grade 2	1			
Hypocalcemia-grade 1	13			
Hypocalcemia-grade 0	27			

Statistical analyses

No statistical analyses for this end point

Secondary: To Evaluate the Plasma Pharmacokinetics of Oral Paclitaxel capsules (Cmax)

End point title	To Evaluate the Plasma Pharmacokinetics of Oral Paclitaxel capsules (Cmax)

End point description:

Cmax (0-24h): Maximum observed plasma concentration (Cmax) of paclitaxel -between Day 1 and Day 2 dosing
Cmax (24-48h): Cmax of paclitaxel between Day 2 and Day 3 dosing
Cmax (48-56 h): Cmax of paclitaxel after Day 3 dosing

End point type	Secondary

End point timeframe:

Cmax (0-24h): 24 hours after administration of study drug
Cmax (24-48h): 24 - 48 hours after administration of study drug
Cmax (48-56 h): 48 to 56 hours following administration of study drug

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
Cmax(0-24h)	265.8 (± 108.0)			
Cmax(24-48h)	228.9 (± 104.3)			
Cmax(48-56h)	256.9 (± 130.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: To Evaluate the Plasma Pharmacokinetics of Oral Paclitaxel capsules (AUC0-t))

End point title	To Evaluate the Plasma Pharmacokinetics of Oral Paclitaxel capsules (AUC0-t))

End point description:

Area under the concentration × time curve from time 0 to the last determined concentration-time point

End point type	Secondary

End point timeframe:

Predose to the last determined concentration-time point

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: ng•h/mL				
arithmetic mean (standard deviation)	2963.9 (± 964.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: To Evaluate the Plasma Pharmacokinetics of Oral Paclitaxel capsules (Tmax)

End point title	To Evaluate the Plasma Pharmacokinetics of Oral Paclitaxel capsules (Tmax)

End point description:

Tmax (0-24 h): Time to reach maximum plasma concentration (Tmax) of paclitaxel -between Day 1 and Day 2 dosing
Tmax (24-48 h): Tmax of paclitaxel between Day 2 and Day 3 dosing
Tmax (48-56 h): Tmax of paclitaxel after Day 3 dosing

End point type	Secondary

End point timeframe:

Tmax (0-24 h): 24 hours after administration of study drug
Tmax (24-48 h): 24 to 48 hours after administration of study drug
Tmax (48-56 h): 48 to 56 hours following administration of study drug

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: hour				
arithmetic mean (standard deviation)				
Tmax (0-24 h)	1.6 (± 0.9)			
Tmax (24-48 h)	25.6 (± 0.8)			
Tmax (48-56 h)	49.4 (± 0.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of PK parameters of oral paclitaxel capsules at Week 4 (or later) from this study versus Week 1 in Study KX-ORAX-002 (rollover participants)

End point title	Comparison of PK parameters of oral paclitaxel capsules at Week 4 (or later) from this study versus Week 1 in Study KX-ORAX-002 (rollover participants)

End point description:

PK parameters of oral paclitaxel capsules at Week 4 (or later) from Study KX-ORAX-003 versus Week 1 in Study KX-ORAX-002 were compared in PK Analysis Set participants who also had PK data from the KX-ORAX-002 Study

End point type	Secondary

End point timeframe:

Equivalence of paclitaxel PK parameters administered as Oraxol at Week 4 (or later) (KX-ORAX-003) and Week 1 (KX-ORAX-002)

End point values	Oraxol			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: ratio				
geometric mean (confidence interval 90%)				
Cmax	78.7 (73.0 to 84.9)			
Ctrough24	99.3 (83.5 to 118.1)			
Ctrough48	96.4 (82.4 to 112.9)			
AUC0-t	87.6 (83.0 to 92.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of PK parameters of paclitaxel tablet and capsule formulations following oral administration

End point title	Comparison of PK parameters of paclitaxel tablet and capsule formulations following oral administration

End point description:

PK parameters of oral paclitaxel tablets versus oral paclitaxel capsules were compared in Group B participants

End point type	Secondary

End point timeframe:

First PK Period at Week 4 (or later) for paclitaxel capsules and for the Second PK Period at Week 5 (or later) for paclitaxel tablets

End point values	Oraxol (Group B)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: ratio				
geometric mean (confidence interval 90%)				
AUC0-t	179.7 (135.3 to 234.5)			
Cmax	185.8 (132.0 to 261.5)			
Ctrough24	124.7 (107.4 to 144.7)			

Ctrough48	164.6 (137.2 to 197.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From signing of informed consent form (ICF) to final study visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Oraxol

Reporting group description: -

Serious adverse events	Oraxol		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 44 (31.82%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lymph nodes			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Radiation pneumonitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular tachycardia			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain oedema			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Mucosal inflammation			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Volvulus			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia	Additional description: The SAE of pneumonia was considered by the Investigator as unlikely to be related to study treatment; however, the Sponsor considered the event to be possibly related to study treatment.		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock	Additional description: The SAE of septic shock was considered by the Investigator to be associated with disease progression, and unlikely to be related to study treatment; however, the Sponsor considered the event to be possibly related to study treatment.		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Oraxol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 44 (97.73%)		
Vascular disorders			
Hypertension			

subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Flushing			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	7 / 44 (15.91%)		
occurrences (all)	7		
Chest pain			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Axillary pain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	14 / 44 (31.82%)		
occurrences (all)	14		
Mucosal inflammation			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Reproductive system and breast disorders			

Uterine prolapse			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	8		
Epistaxis			
subjects affected / exposed	7 / 44 (15.91%)		
occurrences (all)	7		
Dyspnoea			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Dysphonia			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Nasal inflammation			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Haemoptysis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nasal mucosal disorder			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nasal oedema			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Sputum increased			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Upper-airway cough syndrome			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Agitation			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	7 / 44 (15.91%)		
occurrences (all)	7		
Alanine aminotransferase increased			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Aspartate aminotransferase increased			

subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
White blood cell count decreased			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Blood uric acid increased			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Breath sounds abnormal			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Anal injury			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Concussion			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Face injury			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Muscle strain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Skin injury			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Spinal fracture			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Wound complication			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Headache			

subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Axonal neuropathy			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Hemiparesis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Hyperaesthesia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nerve compression	Additional description: Nerve root compression		
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Numb chin syndrome			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Parosmia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	5		
Brain oedema			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	7 / 44 (15.91%)		
occurrences (all)	7		
Coagulopathy			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Iron deficiency anaemia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Diplopia			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Ocular hyperaemia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	27 / 44 (61.36%)		
occurrences (all)	27		
Nausea			

subjects affected / exposed	23 / 44 (52.27%)			
occurrences (all)	23			
Constipation				
subjects affected / exposed	9 / 44 (20.45%)			
occurrences (all)	9			
Vomiting				
subjects affected / exposed	17 / 44 (38.64%)			
occurrences (all)	17			
Gastrooesophageal reflux disease				
subjects affected / exposed	5 / 44 (11.36%)			
occurrences (all)	5			
Abdominal pain				
subjects affected / exposed	4 / 44 (9.09%)			
occurrences (all)	4			
Dyspepsia				
subjects affected / exposed	4 / 44 (9.09%)			
occurrences (all)	4			
Flatulence				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences (all)	3			
Toothache				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences (all)	3			
Abdominal discomfort				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	2			
Abdominal distension				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	2			
Abdominal pain upper				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	2			
Dysphagia				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	2			
Gastritis				

subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Ascites			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Lip dry			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Oesophageal ulcer			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Tongue ulceration			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	14 / 44 (31.82%)		
occurrences (all)	14		
Onychomadesis			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Nail disorder			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Dry skin			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		

Eczema asteatotic				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Erythema				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Madarosis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Nail bed tenderness				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Nail growth abnormal				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Nail hypertrophy				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Nail ridging				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Onychalgia				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Pain of skin				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Rash macular				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Rash maculo-papular				

subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Skin sensitisation			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Haematuria			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nocturia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	6		
Musculoskeletal chest pain			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	5		
Muscular weakness			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Arthralgia			

subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Bone pain			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Groin pain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Joint swelling			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Osteitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Rotator cuff syndrome			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Infections and infestations			
Paronychia			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	6		
Oral candidiasis			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		

Herpes zoster				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences (all)	3			
Lower respiratory tract infection				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	2			
Upper respiratory tract infection				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	2			
Urinary tract infection				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences (all)	3			
Cellulitis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Vulvovaginal candidiasis				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences (all)	2			
Bacterial vaginosis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Folliculitis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Gingivitis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Herpes virus infection				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			
Hordeolum				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences (all)	1			

Nail infection subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1			
Pharyngitis subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1			
Rhinitis subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1			
Urinary tract infection pseudomonal subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1			
Uterine infection subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1			
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1			
Tooth infection subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1			
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	9 / 44 (20.45%) 9			
Dehydration subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1			
Fluid retention subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1			
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1			
Hypernatraemia				

subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2016	Protocol Amendment Number 1: Added dosing instructions following unacceptable toxicity as well as if body weight changed ≥10% or in the case of missing dose(s) Added instructions regarding management of nausea/vomiting and directions if vomiting occurred within 4 hours postdose on PK sampling days Increased thresholds for hemoglobin (from ≥9 g/L to ≥100 g/L) and ANC (from ≥1.0 × 10*9/L to ≥1.5 × 10*9/L) eligibility criteria demonstrating adequate hematological status at Screening/Baseline Added warfarin as well as strong inducers of CYP3A4 and CYP2C8 as prohibited concomitant medications Added instructions for management of clinically significant ECG abnormality
20 April 2017	Protocol Amendment Number 2: Added subgroup of participants (i.e., Group B) to determine the bioavailability of paclitaxel tablets versus paclitaxel capsules Added allowance of pre-emptive PICC line placement Added eligibility criteria to allow for when ALP >5 × ULN at Screening/Baseline if liver or bone metastasis were present and the major fraction of ALP was from bone metastasis, at the discretion of the Investigator Allowed for reduced frequency of ECG assessments after Week 4 Added strong inhibitors and strong inducers of P-gp as prohibited concomitant medications
10 July 2017	Protocol Amendment Number 3: Added threshold for GGT (<10 × ULN) eligibility criteria demonstrating adequate liver function at Screening/Baseline Reduced the frequency of laboratory testing after Week 48 from weekly to every 3 weeks per Investigator discretion unless otherwise indicated
19 November 2017	Protocol Amendment Number 4: Reduced threshold for hemoglobin (from ≥100 g/L to ≥90 g/L) eligibility criteria demonstrating adequate hematological status at Screening/Baseline Provided that the study may be conducted internationally
31 July 2018	Protocol Amendment Number 6: Prolonged duration of contraception use after the last dose of study drug

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported