



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
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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
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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
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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
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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 standard deviation	71.7 ± 15.5	-	
Height Units: cm arithmetic mean standard deviation	166.4 ± 8.2	-	
Body Surface Area (BSA) Units: m ² arithmetic mean standard deviation	1.8 ± 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 standard deviation	60.2 ± 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
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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)
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Subject analysis set type	Sub-group analysis
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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]
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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
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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]
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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
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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]
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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
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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]
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End point description:

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

End point type	Primary
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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]
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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
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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]
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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
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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			
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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 (C_{max})

End point title	To Evaluate the Plasma Pharmacokinetics of Oral Paclitaxel capsules (C _{max})
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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)			
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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Reporting groups

Reporting group title	Oraxol
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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 occurrences (all)	2 / 44 (4.55%) 2		
Flushing subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
General disorders and administration site conditions			
Oedema peripheral subjects affected / exposed occurrences (all)	7 / 44 (15.91%) 7		
Chest pain subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Influenza like illness subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2		
Axillary pain subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Pain subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Pyrexia subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Fatigue subjects affected / exposed occurrences (all)	14 / 44 (31.82%) 14		
Mucosal inflammation subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 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 occurrences (all)	1 / 44 (2.27%) 1		
Pneumonitis subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Pulmonary embolism subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Sputum increased subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2		
Agitation subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Anxiety subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Sleep disorder subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Investigations Neutrophil count decreased subjects affected / exposed occurrences (all)	7 / 44 (15.91%) 7		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Aspartate aminotransferase increased			

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

subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Contusion subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Face injury subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Ligament sprain subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Muscle strain subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Skin injury subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Spinal fracture subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Wound subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Wound complication subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Cardiac disorders Supraventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 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			
subjects affected / exposed	1 / 44 (2.27%)	Additional description: Nerve root compression	
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 occurrences (all)	1 / 44 (2.27%) 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 erythrodysesthesia 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 occurrences (all)	1 / 44 (2.27%) 1		
Rash pruritic subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Skin sensitisation subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Haematuria subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Nocturia subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Proteinuria subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 6		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	5 / 44 (11.36%) 5		
Muscular weakness subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Pain in extremity subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Arthralgia			

subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Bone pain subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2		
Neck pain subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2		
Groin pain subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Joint swelling subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Myalgia subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Osteitis subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Rotator cuff syndrome subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Infections and infestations			
Paronychia subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 6		
Oral candidiasis subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 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	1 / 44 (2.27%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Uterine infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 44 (20.45%)		
occurrences (all)	9		
Dehydration			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Fluid retention			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	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 $\geq 10\%$ 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 $\geq 1.0 \times 10^9/L$ to $\geq 1.5 \times 10^9/L$) 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 $> 5 \times$ 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 ($< 10 \times$ 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