Clinical trial results:
A Phase I Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas and High Grade Gliomas

Summary

EudraCT number	2016-000758-37
Trial protocol	Outside EU/EEA
Global end of trial date	04 October 2010

Results information

Result version number	v1 (current)
This version publication date	10 November 2016
First version publication date	10 November 2016

Trial information

Trial identification

Sponsor protocol code	NO18517

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00532948
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH 4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.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	04 October 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2010
Global end of trial reached?	Yes
Global end of trial date	04 October 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the maximum tolerated dose (MTD) of capecitabine administered concurrently with radiation therapy (RT) to children with newly diagnosed non-disseminated, intrinsic brainstem gliomas or newly diagnosed non-disseminated high-grade gliomas.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all participants and/or their legally authorized representative. Participants signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug. The Pediatric Brain Tumor Consortium (PBTC) Monitoring Committee reviewed all reported toxicities on a weekly basis and communicated any areas of concern to the Study Chair. The study progress was reported in the PBTC semi-annual meeting book. The PBTC Data Safety Monitoring Board reviewed the protocol's progress at least semi-annually.

Background therapy:

Radiation therapy for 6 weeks

Evidence for comparator:

NA

Actual start date of recruitment	24 May 2007
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 States: 24
Worldwide total number of subjects	24
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	20
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All 24 participants in the study were enrolled at Pediatric Brain Tumor Consortium (PBTC) institutions in the United States of America (USA), from 24 May 2007 through 27 October 2009.

Pre-assignment

Screening details:

The study consisted of two periods of dosing: A dose-finding treatment period of 11 weeks and a post radiation treatment phase that lasted for 9 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Capecitabine 500 milligrams per square meter (mg/m^2)

Arm description:

Capecitabine 500 mg/m^2 was administered twice daily (b.i.d) orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Arm type	Experimental
Investigational medicinal product name	Capecitabine RDT
Investigational medicinal product code	Ro 09-1978
Other name	Xeloda RDT
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 500 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Arm title	Capecitabine 650 mg/m^2

Arm description:

Capecitabine 650 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Arm type	Experimental
Investigational medicinal product name	Capecitabine RDT
Investigational medicinal product code	Ro 09-1978
Other name	Xeloda RDT
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 650 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Arm title	Capecitabine 850 mg/m^2

Arm description:

Capecitabine 850 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Arm type	Experimental
Investigational medicinal product name	Capecitabine RDT
Investigational medicinal product code	Ro 09-1978
Other name	Xeloda RDT
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 850 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Number of subjects in period 1	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2
Started	4	14	6
Completed	0	9	2
Not completed	4	5	4
Failure to return	-	1	-
Death	3	3	4
Violation of selection criteria at entry	-	1	-
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Capecitabine 500 milligrams per square meter (mg/m^2)
Reporting group description:	
Capecitabine 500 mg/m^2 was administered twice daily (b.i.d) orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.	
Reporting group title	Capecitabine 650 mg/m^2
Reporting group description:	
Capecitabine 650 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.	
Reporting group title	Capecitabine 850 mg/m^2
Reporting group description:	
Capecitabine 850 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.	

Reporting group values	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2
Number of subjects	4	14	6
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	4	13	3
Adolescents (12-17 years)	0	1	3
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	7.5	8.4	13
standard deviation	± 1.73	± 2.65	± 3.41
Gender categorical Units: Subjects			
Female	1	12	2
Male	3	2	4

Reporting group values	Total		
Number of subjects	24		
Age categorical 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)	20		
Adolescents (12-17 years)	4		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	15		
Male	9		

End points

End points reporting groups

Reporting group title	Capecitabine 500 milligrams per square meter (mg/m^2)

Reporting group description:

Capecitabine 500 mg/m^2 was administered twice daily (b.i.d) orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Reporting group title	Capecitabine 650 mg/m^2

Reporting group description:

Capecitabine 650 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Reporting group title	Capecitabine 850 mg/m^2

Reporting group description:

Capecitabine 850 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consisted of all eligible patients who received at least one dose of capecitabine.

Primary: Maximum Tolerated Dose of Capecitabine

End point title	Maximum Tolerated Dose of Capecitabine[1]

End point description:

The Maximum Tolerated Dose (MTD) was the dose level at which 6 evaluable patients had been treated and at most one patient experienced a dose limiting toxicity (DLT) and the next highest dose level was too toxic. Dose escalation occurred if 0 out of 3 or at most 1 out of 6 patients experienced DLT while being treated at a dose level; otherwise the dose was declared unsafe and thus above the MTD. Safety population was used for analysis of this end point.

End point type	Primary

End point timeframe:

Up to 11 weeks.

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 statistical analysis has been specified for this end point.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: milligrams	650			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Dose Limiting Toxicities

End point title	Number of Participants with Dose Limiting Toxicities[2]

End point description:

Dose limiting toxicity (DLT) was defined as any of the events which occurred during the 11 week dose-finding period: any event that leads to interruption of planned radiation for 5 consecutive days or 10 days total; Grade 4 neutropenia or thrombocytopenia; Grade 3 thrombocytopenia that required a platelet transfusion on 2 or more occasions; any Grade 3 or 4 non-hematologic toxicity (with the exception of Grade 3 nausea or vomiting of < 5 days duration, Grade 3 transaminases that returned to baseline value within 7 days of study drug interruption and that did not recur upon re-challenge with study drug, and/or Grade 3 fever or infection of <5 days duration); Grade 2 non-hematologic toxicities that persisted for >7 days and required treatment interruption, or any other capecitabine-related adverse events (AE) that required need for dose reduction or discontinuation of therapy. Safety population was used for analysis of this end point.

End point type	Primary

End point timeframe:

Up to 11 weeks

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 statistical analysis has been specified for this end point.

End point values	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	12	6	
Units: Participants	0	3	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events

End point description:

An AE is an unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Toxicity was monitored and graded according to the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Adverse events that were not included in the CTCAE version 3.0 were reported and graded under the other AE within the appropriate category. Safety population was used for analysis of this end point.

End point type	Secondary

End point timeframe:

Up to 06 years

End point values	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	12	6	
Units: Participants	3	12	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Baseline Shift From Normal to Low or High in Hematology Parameters

End point title	Number of Participants With Baseline Shift From Normal to Low or High in Hematology Parameters

End point description:

For hematology, the parameters assessed were: Hemoglobin, hematocrit, platelet count, RBC, WBC, lymphocytes, monocytes, granulocytes (blasts), neutrophils (segs, bands), eosinophils, and basophils. The safety population consisted of all eligible patients who received at least one dose of capecitabine. Participants available at a particular time point were included in analysis.

End point type	Secondary

End point timeframe:

Up to 06 years

End point values	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	2	6	
Units: Participants				
Haematocrit, normal to low, n=3,1,5	2	1	4	
Haematocrit, normal to high, n=3,1,5	0	0	0	
Hemoglobin, normal to low, n=4,2,6	0	0	2	
Hemoglobin, normal to high, n=4,2,6	0	0	0	
White blood cell, normal to low, n=3,1,5	0	0	0	
White blood cell, normal to high, n=3,1,5	1	1	1	
Platelets, normal to low, n=4,2,6	0	1	0	
Platelets, normal to high, n=4,2,6	0	0	1	
Red blood cells, normal to low, n=3,1,3	2	0	1	
Red blood cells, normal to high, n=3,1,3	0	1	0	
Neutrophils (segmented), normal to low, n=3,0,5	0	0	0	
Neutrophils (segmented), normal to high, n=3,0,5	0	0	0	
Basophils (relative), normal to low, n=0,1,2	0	0	0	
Basophils (relative), normal to high, n=0,1,2	0	1	2	
Lymphocytes (relative), normal to low, n=3,1,5	0	0	0	

Lymphocytes (relative), normal to high, n=3,1,5	0	0	0	
Monocytes (relative), normal to low, n=3,1,4	0	0	0	
Monocytes (relative), normal to high, n=3,1,4	1	0	3	
Eosinophils (relative), normal to low, n=1,1,3	0	1	0	
Eosinophils (relative), normal to high, n=1,1,3	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Baseline Shift From Normal to Low or High in Blood Chemistry Parameters

End point title	Number of Participants With Baseline Shift From Normal to Low or High in Blood Chemistry Parameters

End point description:

For blood chemistry, the parameters assessed were: Sodium, potassium, calcium, magnesium, chloride, bicarbonate, total protein, albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), Lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, indirect bilirubin, creatinine (serum creatinine or creatinine clearance), glucose. The safety population consisted of all eligible patients who received at least one dose of capecitabine. Participants available at a particular time point were included in analysis.

End point type	Secondary

End point timeframe:

Up to 06 years

End point values	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	2	6	
Units: Participants				
Lactic dehydrogenase, normal to low, n=0,0,0	0	0	0	
Lactic dehydrogenase, normal to high, n=0,0,0	0	0	0	
Indirect bilirubin, normal to low, n=1,1,1	0	0	0	
Indirect bilirubin, normal to high, n=1,1,1	0	1	0	
BUN, normal to low, n=3,1,5	0	0	2	
BUN, normal to high, n=3,1,5	0	1	1	
Alkaline phosphatase, normal to low, n=1,1,4	0	0	1	
Alkaline phosphatase, normal to high, n=1,1,4	0	0	0	
Direct bilirubin, normal to low, n=2,1,1	0	0	0	

Direct bilirubin, normal to high, n=2,1,1	0	0	0	
Total bilirubin, normal to low, n=4,2,6	0	0	0	
Total bilirubin, normal to high, n=4,2,6	0	0	0	
Fasting glucose, normal to low, n=1,0,4	0	0	0	
Fasting glucose, normal to high, n=1,0,4	0	0	0	
Protein, normal to low, n=1,0,2	1	0	1	
Protein, normal to high, n=1,0,2	0	0	0	
Serum albumin, normal to low, n=3,1,5	2	0	1	
Serum albumin, normal to high, n=3,1,5	0	0	0	
Serum creatinine, normal to low, n=4,2,6	0	0	0	
Serum creatinine, normal to high, n=4,2,6	0	0	2	
ASAT (SGOT), normal to low, n=1,0,4	0	0	0	
ASAT (SGOT), normal to high, n=1,0,4	0	0	2	
ALAT (SGPT), normal to low, n=4,2,6	0	0	0	
ALAT (SGPT), normal to high, n=4,2,6	2	2	4	
Calcium, normal to low, n=3, 1,5	1	1	0	
Calcium, normal to high, n=3,1,5	0	0	1	
Phosphate, normal to low, n=3,1,5	1	0	1	
Phosphate, normal to high, n=3,1,5	0	0	1	
Potassium, normal to low, n=3, 1,5	2	0	0	
Potassium, normal to high, n=3,1,5	0	1	0	
Sodium, normal to low, n=3,1,5	1	1	3	
Sodium, normal to high, n=3,1,5	0	0	0	
Magnesium, normal to low, n=3,1,5	0	0	0	
Magnesium, normal to high, n=3,1,5	1	1	0	
Chloride, normal to low, n=3,1,5	0	0	1	
Chloride, normal to high, n=3,1,5	0	1	1	
Bicarbonate, normal to low, n=3,0,5	0	0	0	
Bicarbonate, normal to high, n=3,0,5	0	0	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration of Capecitabine and Its Metabolites (5'-Deoxy-5-Fluorocytidine [5'-DFCR], 5'-Deoxy-5-Fluorouridine [5'-DFUR], 5-Fluorouracil [5-FU] and Alpha-fluoro-beta-alanine [FBAL])

End point title	Maximum Observed Plasma Concentration of Capecitabine and Its Metabolites (5'-Deoxy-5-Fluorocytidine [5'-DFCR], 5'-Deoxy-5-Fluorouridine [5'-DFUR], 5-Fluorouracil [5-FU] and Alpha-fluoro-beta-alanine [FBAL])

End point description:

The maximum observed plasma concentration (Cmax) of capecitabine and its metabolites. Participants who consented to participating in the Pharmacokinetic (PK) studies were randomized to either sampling Series A or Series B. The collection time points included 2 different series, Series A (Baseline [pre-dose], 10 mins, 30 mins, 1, 2.5, 6, 8 and 10 hours after dosing) and Series B (Baseline [pre-dose], 15 minutes, 45 minutes, 1.5, 4, 8 and 10 hours after dosing). The safety population consisted of all eligible patients who received at least one dose of capecitabine. Participants available at a particular time point were included in analysis.

End point type	Secondary

End point timeframe:

Day 1 and Day 14

End point values	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	3	
Units: ng/mL				
arithmetic mean (standard deviation)				
Capecitabine, Day 1, n= 2, 4, 3	1440 (± 750)	3080 (± 1340)	1890 (± 1420)	
Capecitabine, Day 14, n=2,2,2	2100 (± 1770)	5440 (± 3270)	3710 (± 156)	
5’-DFCR, Day 1, n=2,4,3	2050 (± 813)	2190 (± 626)	2180 (± 1690)	
5’-DFCR, Day 14, n=2,2,2	2980 (± 2020)	3500 (± 1470)	3200 (± 233)	
5’-DFUR, Day 1, n=2,4,3	1910 (± 834)	2640 (± 1700)	3770 (± 3300)	
5’-DFUR, Day 14, n=2,2,2	3300 (± 2800)	3120 (± 445)	5020 (± 1220)	
5-FU, Day 1, n=2,4,3	47.8 (± 23.9)	77.3 (± 52.7)	178 (± 205)	
5-FU, Day 14, n=2,2,2	183 (± 196)	95.4 (± 27.8)	257 (± 107)	
FBAL, Day 1, n=2,4,3	1350 (± 134)	1740 (± 365)	2050 (± 1640)	
FBAL, Day 14, n=2,2,2	1770 (± 410)	2430 (± 84.9)	2140 (± 304)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Plasma Concentration of Capecitabine and Its Metabolites (5’-DFCR, 5’-DFUR, 5-FU and FBAL)

End point title	Time to Maximum Plasma Concentration of Capecitabine and Its Metabolites (5’-DFCR, 5’-DFUR, 5-FU and FBAL)

End point description:

Time to maximum plasma concentration (Tmax) is the corresponding time at which Cmax occurs of capecitabine and its metabolites. Participants who consented to participating in the PK studies were randomized to either sampling Series A or Series B. The collection time points included 2 different series, Series A (Baseline [pre-dose], 10 mins, 30 mins, 1, 2.5, 6, 8 and 10 hours after dosing) and Series B (Baseline [pre-dose], 15 minutes, 45 minutes, 1.5, 4, 8 and 10 hours after dosing). Safety population were analysed for this endpoint. Participants available at a particular time point were included in analysis.

End point type	Secondary

End point timeframe:

Day 1 and Day 14

End point values	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	3	
Units: hour				
median (full range (min-max))				
Capecitabine, Day 1, n= 2, 4, 3	0.58 (0.17 to 1)	0.63 (0.25 to 1)	0.85 (0.83 to 10)	
Capecitabine, Day 14, n=2,2,2	1.33 (0.17 to 2.48)	0.82 (0.8 to 0.83)	0.61 (0.5 to 0.72)	
5'-DFCR, Day 1, n=2,4,3	1 (1 to 1)	0.75 (0.5 to 2.5)	1.55 (0.85 to 10)	
5'-DFCR, Day 14, n=2,2,2	1.49 (0.5 to 2.48)	1.18 (0.5 to 1.53)	0.61 (0.5 to 1.53)	
5'-DFUR, Day 1, n=2,4,3	1 (1 to 1)	0.9 (0.7 to 2.5)	1.5 (0.75 to 10)	
5'-DFUR, Day 14, n=2,2,2	1.5 (0.5 to 2.5)	0.82 (0.8 to 0.83)	0.61 (0.5 to 0.72)	
5-FU, Day 1, n=2,4,3	1 (1 to 1)	0.75 (0.5 to 2.5)	1.5 (0.75 to 10)	
5-FU, Day 14, n=2,2,2	1.5 (0.5 to 2.5)	0.83 (0.8 to 0.83)	1 (0.5 to 1.5)	
FBAL, Day 1, n=2,4,3	2.53 (2.5 to 2.53)	1.5 (1.5 to 2.5)	1.55 (1.42 to 10)	
FBAL, Day 14, n=2,2,2	1.74 (1 to 2.5)	2.2 (1.5 to 2.8)	2.03 (1.57 to 2.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: The Area Under the Plasma Concentration-time Curve From Time of Dosing to the Last Measurable Concentration of Capecitabine and Its Metabolites (5'-DFCR, 5'-DFUR, 5-FU and FBAL)

End point title	The Area Under the Plasma Concentration-time Curve From Time of Dosing to the Last Measurable Concentration of Capecitabine and Its Metabolites (5'-DFCR, 5'-DFUR, 5-FU and FBAL)

End point description:

The area under the plasma concentration-time curve from time of dosing to the last measurable concentration (AUC last) of capecitabine and its metabolites are reported. Participants who consented to participating in the PK studies were randomized to either sampling Series A or Series B. The collection time points included 2 different series, Series A (Baseline [pre-dose], 10 mins, 30 mins, 1, 2.5, 6, 8 and 10 hours after dosing) and Series B (Baseline [pre-dose], 15 minutes, 45 minutes, 1.5, 4, 8 and 10 hours after dosing). The safety population was used for this analysis. Participants available at a particular time point were included in analysis.

End point type	Secondary

End point timeframe:

Day 1 and Day 14

End point values	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	3	
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Capecitabine, Day 1, n= 2, 4, 3	3370 (± 607)	5160 (± 3700)	3470 (± 1170)	
Capecitabine, Day 14, n=2,2,2	2890 (± 655)	9660 (± 3340)	5670 (± 971)	
5'-DFCR, Day 1, n=2,4,3	5250 (± 755)	5140 (± 3440)	4180 (± 2380)	
5'-DFCR, Day 14, n=2,2,2	4300 (± 27.2)	9250 (± 1400)	6520 (± 452)	
5'-DFUR, Day 1, n=2,4,3	4790 (± 784)	4300 (± 1600)	6650 (± 3740)	
5'-DFUR, Day 14, n=2,2,2	4240 (± 929)	8010 (± 1890)	10500 (± 445)	
5-FU Day 1, n=2,4,3	81.6 (± 29.7)	114 (± 40.9)	271 (± 205)	
5-FU Day 14, n=2,2,2	181 (± 84.7)	253 (± 16.3)	499 (± 78.8)	
FBAL, Day 1, n=2,4,3	5990 (± 951)	8110 (± 1640)	7010 (± 4490)	
FBAL, Day 14, n=2,2,2	5720 (± 690)	10700 (± 574)	10400 (± 1760)	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti Tumor Activity

End point title	Anti Tumor Activity

End point description:

Tumor response refers to the best response prior to failure (disease progression, death or second malignancy). Information concerning response and tumor measurements are only partially available and thus analysis is not performed. Efficacy data of the present study (NO18517 - NCT00532948) were pre-specified to be combined with efficacy data of the Phase 2 portion of this Study, NO21125 (NCT01118377) for analysis. Results are currently posted in the record of Study NO21125. No data displayed because Outcome Measure has zero total participants analyzed. Safety population was used for analysis of this end point.

End point type	Secondary

End point timeframe:

Up to 06 years

End point values	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	0[4]	0[5]	
Units: Participants				

Notes:

[3] - No data displayed because Outcome Measure has zero total participants analyzed.

[4] - No data displayed because Outcome Measure has zero total participants analyzed.

[5] - No data displayed because Outcome Measure has zero total participants analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 6 years

Adverse event reporting additional description:

The safety population consisted of all eligible patients who received at least one dose of capecitabine RDT.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Capecitabine 500 milligrams per square meter (mg/m^2)

Reporting group description:

Capecitabine 500 mg/m^2 was administered twice daily (b.i.d) orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Reporting group title	Capecitabine 650 mg/m^2

Reporting group description:

Capecitabine 650 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Reporting group title	Capecitabine 850 mg/m^2

Reporting group description:

Capecitabine 850 mg/m^2 was administered b.i.d orally for 14 days, followed by 7 day rest. The treatment was administered for 3 cycles with radiation therapy period and 3 cycles without radiation therapy.

Serious adverse events	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	1 / 12 (8.33%)	3 / 6 (50.00%)
number of deaths (all causes)	3	3	4
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			

subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin exfoliation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Capecitabine 500 milligrams per square meter (mg/m^2)	Capecitabine 650 mg/m^2	Capecitabine 850 mg/m^2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	12 / 12 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	5	2
Surgical and medical procedures			
Oculomotor nerve operation			
subjects affected / exposed	1 / 4 (25.00%)	3 / 12 (25.00%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Trochlear nerve operation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 4 (75.00%)	7 / 12 (58.33%)	3 / 6 (50.00%)
occurrences (all)	6	7	6
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Chest pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oedema			

subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Penile erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Apnoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Personality change			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Euphoric mood			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Psychotic disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 4 (50.00%)	10 / 12 (83.33%)	3 / 6 (50.00%)
occurrences (all)	3	22	6
Haemoglobin			
subjects affected / exposed	1 / 4 (25.00%)	5 / 12 (41.67%)	4 / 6 (66.67%)
occurrences (all)	3	10	6
Neutrophil count			
subjects affected / exposed	2 / 4 (50.00%)	4 / 12 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	5	1
Platelet count decreased			
subjects affected / exposed	2 / 4 (50.00%)	5 / 12 (41.67%)	0 / 6 (0.00%)
occurrences (all)	2	8	0
Weight increased			
subjects affected / exposed	1 / 4 (25.00%)	3 / 12 (25.00%)	2 / 6 (33.33%)
occurrences (all)	2	5	2
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	3	2
Blood bicarbonate decreased			
subjects affected / exposed	2 / 4 (50.00%)	1 / 12 (8.33%)	2 / 6 (33.33%)
occurrences (all)	3	1	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	2	0
Gamma−glutamyltransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Blood chloride increased			

subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Radiation mucositis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Thermal burn			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Radiation skin injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	3 / 4 (75.00%)	8 / 12 (66.67%)	1 / 6 (16.67%)
occurrences (all)	4	8	1
Facial nerve disorder			
subjects affected / exposed	3 / 4 (75.00%)	8 / 12 (66.67%)	1 / 6 (16.67%)
occurrences (all)	4	9	1
Headache			
subjects affected / exposed	2 / 4 (50.00%)	6 / 12 (50.00%)	2 / 6 (33.33%)
occurrences (all)	4	8	3
VIth nerve disorder			

subjects affected / exposed	2 / 4 (50.00%)	5 / 12 (41.67%)	0 / 6 (0.00%)
occurrences (all)	4	6	0
Speech disorder			
subjects affected / exposed	1 / 4 (25.00%)	4 / 12 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	4	1
Vagus nerve disorder			
subjects affected / exposed	2 / 4 (50.00%)	3 / 12 (25.00%)	1 / 6 (16.67%)
occurrences (all)	2	3	1
Peripheral motor neuropathy			
subjects affected / exposed	2 / 4 (50.00%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	3	2	1
Glossopharyngeal nerve disorder			
subjects affected / exposed	2 / 4 (50.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Hyperreflexia			
subjects affected / exposed	0 / 4 (0.00%)	4 / 12 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Nystagmus			
subjects affected / exposed	1 / 4 (25.00%)	3 / 12 (25.00%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Convulsion			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	1	1	3
Cognitive disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Dizziness			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Haemorrhagic stroke			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Hypoglossal nerve disorder			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Trigeminal nerve disorder			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Cerebellar syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cranial nerve disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Depressed level of consciousness			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dysarthria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Extrapyramidal disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	3 / 4 (75.00%)	10 / 12 (83.33%)	3 / 6 (50.00%)
occurrences (all)	13	36	7
Leukopenia			
subjects affected / exposed	3 / 4 (75.00%)	9 / 12 (75.00%)	2 / 6 (33.33%)
occurrences (all)	4	14	5
Eye disorders			
Diplopia			
subjects affected / exposed	2 / 4 (50.00%)	3 / 12 (25.00%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Vision blurred			

subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Extraocular muscle disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 4 (75.00%)	8 / 12 (66.67%)	2 / 6 (33.33%)
occurrences (all)	7	19	2
Constipation			
subjects affected / exposed	2 / 4 (50.00%)	3 / 12 (25.00%)	3 / 6 (50.00%)
occurrences (all)	4	3	3
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	3 / 12 (25.00%)	4 / 6 (66.67%)
occurrences (all)	0	3	5
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	4 / 6 (66.67%)
occurrences (all)	1	3	4
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	3	2	1
Stomatitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Irritable bowel syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Skin and subcutaneous tissue disorders			
Skin exfoliation			
subjects affected / exposed	1 / 4 (25.00%)	8 / 12 (66.67%)	4 / 6 (66.67%)
occurrences (all)	1	12	5
Skin hyperpigmentation			
subjects affected / exposed	1 / 4 (25.00%)	3 / 12 (25.00%)	3 / 6 (50.00%)
occurrences (all)	1	3	3
Alopecia			
subjects affected / exposed	1 / 4 (25.00%)	4 / 12 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	4	1
Dermatitis exfoliative			
subjects affected / exposed	0 / 4 (0.00%)	4 / 12 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	5	1
Dry skin			
subjects affected / exposed	0 / 4 (0.00%)	3 / 12 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Hyperhidrosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Acne			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Decubitus ulcer			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ecchymosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ingrowing nail			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			

Pollakiuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Endocrine disorders			
Cushingoid			
subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)	3 / 12 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Neck pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Gingival infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Otitis media			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	2

Gastrointestinal candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Oral infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Otitis externa			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 4 (75.00%)	2 / 12 (16.67%)	3 / 6 (50.00%)
occurrences (all)	3	2	3
Hyponatraemia			
subjects affected / exposed	1 / 4 (25.00%)	5 / 12 (41.67%)	2 / 6 (33.33%)
occurrences (all)	1	8	2
Hypocalcaemia			
subjects affected / exposed	2 / 4 (50.00%)	4 / 12 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	4	1
Hypophosphataemia			
subjects affected / exposed	3 / 4 (75.00%)	3 / 12 (25.00%)	1 / 6 (16.67%)
occurrences (all)	6	5	1
Hypermagnesaemia			
subjects affected / exposed	2 / 4 (50.00%)	3 / 12 (25.00%)	1 / 6 (16.67%)
occurrences (all)	4	5	1
Hypokalaemia			

subjects affected / exposed	2 / 4 (50.00%)	2 / 12 (16.67%)	2 / 6 (33.33%)
occurrences (all)	4	2	2
Hypercalcaemia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 12 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	2	2
Decreased appetite			
subjects affected / exposed	2 / 4 (50.00%)	0 / 12 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	2
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 12 (8.33%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Hypernatraemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Hypoglycaemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 12 (8.33%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Dehydration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 12 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2008	Text was updated in protocol page 28, Section 5.6.3.Non – Hematological Toxicity, sub section 5.6.3.1 General toxicities to clarify for dose modification due to Nonhematological Toxicity –DLT.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported