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

Summary

EudraCT number	2016-001045-12
Trial protocol	Outside EU/EEA
Global end of trial date	23 April 2013

Results information

Result version number	v1 (current)
This version publication date	24 December 2016
First version publication date	24 December 2016

Trial information

Trial identification

Sponsor protocol code	NO21125

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01118377
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	23 April 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the Progression-free Survival (PFS) distribution for newly diagnosed participants with intrinsic brainstem gliomas (IBSGs) treated with the combination of capecitabine pediatric film-coated tablets and radiation therapy (RT) and compare to Pediatric Brain Tumor Consortium (PBTC) historical controls

Protection of trial subjects:

This study was conducted in compliance with all applicable laws and regulations of the state and institution where the participant was treated, in accordance with the Declaration of Helsinki, and according to the guidelines in the protocol, including appendices.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 45
Worldwide total number of subjects	45
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)	37
Adolescents (12-17 years)	8
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

35 participants from study NO21125 and 10 participants from study NO18517 were enrolled, out of which 1 participant did not receive treatment.

Period 1

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

Arms

Arm title	Capecitabine + Radiation Therapy

Arm description:

Participants received 9 weeks of capecitabine 650 milligram per square meter (mg/m^2) orally (po) twice daily (bid) plus radiation therapy (180 centigray per day [cGy/day] 5 days a week, total target dose of 56 Gy) followed by a 2-week rest period. Participants then received 3 cycles of capecitabine 1250 mg/m^2 po bid for 14 days followed by a 7-day rest period without radiation therapy.

Arm type	Experimental
Investigational medicinal product name	Radiation Therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radionuclide generator
Routes of administration	Local use

Dosage and administration details:

Participants received 9 weeks of radiation therapy (180 cGy/day 5 days a week, total target dose of 56 Gy).

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	RO0091978
Other name	Xeloda
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 9 weeks of capecitabine 650 mg/m^2 po bid followed by a 2-week rest period. Participants then received 3 cycles of capecitabine 1250 mg/m^2 po bid for 14 days followed by a 7-day rest period.

Number of subjects in period 1	Capecitabine + Radiation Therapy
Started	45
Treated	44
Completed	3
Not completed	42
Did Not Receive Study Medication	1
Death	38

Failure to Return	3

Baseline characteristics

Reporting groups	
Reporting group title	Capecitabine + Radiation Therapy
Reporting group description:	
Participants received 9 weeks of capecitabine 650 milligram per square meter (mg/m^2) orally (po) twice daily (bid) plus radiation therapy (180 centigray per day [cGy/day] 5 days a week, total target dose of 56 Gy) followed by a 2-week rest period. Participants then received 3 cycles of capecitabine 1250 mg/m^2 po bid for 14 days followed by a 7-day rest period without radiation therapy.	

Reporting group values	Capecitabine + Radiation Therapy	Total	
Number of subjects	45	45	
Age categorical			
Units: Subjects			

Age continuous			
Baseline characteristics data were reported for 'treated' (44) participants.			
Units: years			
arithmetic mean	7.5		
standard deviation	± 3.69	-	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	23	23	

End points

End points reporting groups

Reporting group title	Capecitabine + Radiation Therapy

Reporting group description:

Participants received 9 weeks of capecitabine 650 milligram per square meter (mg/m^2) orally (po) twice daily (bid) plus radiation therapy (180 centigray per day [cGy/day] 5 days a week, total target dose of 56 Gy) followed by a 2-week rest period. Participants then received 3 cycles of capecitabine 1250 mg/m^2 po bid for 14 days followed by a 7-day rest period without radiation therapy.

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)[1]

End point description:

PFS was defined as time from initiation of treatment to the earliest date of failure (disease progression, death from any cause, or a second malignancy) or to the last assessment date for participants who did not fail. Disease progression was defined as progressive neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (e.g., anticonvulsant or corticosteroid toxicity, electrolyte disturbances, sepsis, hyperglycemia, weaning of steroids, radiation necrosis etc.); or greater than 25% increase in bi-dimensional measurement of tumor, as compared with previous scan; or appearance of new lesion; or increase in doses of dexamethasone required to maintain stable neurologic status or imaging. Kaplan-Meier estimates were used. All participants enrolled in Study NO21125 who were considered eligible by Pediatric Brain Tumor Consortium (PBTC) and received at least 1 dose of capecitabine were included in intent-to-treat (ITT) population.

End point type	Primary

End point timeframe:

Baseline to the end of the study (up to approximately 2 years)

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 was planned for this study.

End point values	Capecitabine + Radiation Therapy			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: months				
median (confidence interval 95%)	4.9 (4.5 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time from the initiation of therapy to the date of death from any cause or to the date the participant was last known to be alive for surviving participants. Kaplan-Meier estimates were used for evaluation. ITT population.

End point type	Secondary

End point timeframe:

Baseline to the end of the study (up to approximately 2 years)

End point values	Capecitabine + Radiation Therapy			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: months				
median (confidence interval 95%)	10.3 (7.7 to 12.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Best Tumor Response of Complete Response (CR) or Partial Response (PR)

End point title	Percentage of Participants With a Best Tumor Response of Complete Response (CR) or Partial Response (PR)

End point description:

Tumor response was defined as either a CR or a PR prior to failure (disease progression, death from any cause, or a second malignancy). CR was defined as the complete disappearance on magnetic response imaging of all enhancing tumor and mass effect on a stable or decreasing dose of dexamethasone (or only receiving adrenal replacement doses) accompanied by a stable or improving neurologic examination that was maintained for at least 12 weeks. PR was defined as a greater than or equal to 50% reduction in tumor size by bi-dimensional measurement on a stable or decreasing dose of dexamethasone accompanied by a stable or improving neurologic examination that was maintained for at least 12 weeks. ITT population.

End point type	Secondary

End point timeframe:

Baseline to the end of the study (up to approximately 2 years)

End point values	Capecitabine + Radiation Therapy			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: percentage of participants				
number (confidence interval 95%)	2.3 (0.1 to 12)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after the last treatment (up to approximately 2 years)

Adverse event reporting additional description:

Safety population: All enrolled participants who received at least 1 dose of capecitabine. One of the 45 participants did not receive treatment and was not included in the safety population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Capecitabine + Radiation Therapy

Reporting group description:

Participants received 9 weeks of capecitabine 650 mg/m^2 orally (po) twice daily (bid) plus radiation therapy (180 cGy/day 5 days a week, total target dose of 56 Gy) followed by a 2-week rest period. Participants then received 3 cycles of capecitabine 1250 mg/m^2 po bid for 14 days followed by a 7-day rest period without radiation therapy.

Serious adverse events	Capecitabine + Radiation Therapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 44 (52.27%)		
number of deaths (all causes)	38		
number of deaths resulting from adverse events			
Investigations			
Neutrophil count decreased			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Wound dehiscence				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Central nervous system necrosis				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	3 / 44 (6.82%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Neurological symptom				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			
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	2 / 44 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pyrexia			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Device malfunction			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Irritability			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
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			

Anaemia				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Aspiration				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Hypoxia				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephrolithiasis				
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				
Clostridial infection				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Enterocolitis infectious				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nail infection				
subjects affected / exposed	1 / 44 (2.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	2 / 44 (4.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoalbuminaemia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Capecitabine + Radiation Therapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 44 (100.00%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 44 (40.91%)		
occurrences (all)	28		
Pyrexia			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	7		
Irritability			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Pain			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	7		
Nasal congestion			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Rhinitis allergic			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	6		
Insomnia			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	33 / 44 (75.00%)		
occurrences (all)	69		
Lymphocyte count decreased			
subjects affected / exposed	32 / 44 (72.73%)		
occurrences (all)	219		
White blood cell count decreased			
subjects affected / exposed	27 / 44 (61.36%)		
occurrences (all)	107		
Platelet count decreased			
subjects affected / exposed	25 / 44 (56.82%)		
occurrences (all)	46		
Blood bilirubin increased			
subjects affected / exposed	14 / 44 (31.82%)		
occurrences (all)	27		

Neutrophil count decreased subjects affected / exposed occurrences (all)	14 / 44 (31.82%) 31		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	11 / 44 (25.00%) 14		
Weight increased subjects affected / exposed occurrences (all)	11 / 44 (25.00%) 21		
Gamma−glutamyltransferase increased subjects affected / exposed occurrences (all)	5 / 44 (11.36%) 5		
Haemoglobin subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 10		
Weight decreased subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 4		
Haemoglobin increased subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Neutrophil count subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 8		
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	20 / 44 (45.45%) 32		
Ataxia subjects affected / exposed occurrences (all)	9 / 44 (20.45%) 13		
Facial nerve disorder			

subjects affected / exposed	9 / 44 (20.45%)		
occurrences (all)	12		
VIth nerve disorder			
subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	9		
Hemiparesis			
subjects affected / exposed	6 / 44 (13.64%)		
occurrences (all)	8		
Dysarthria			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	6		
Somnolence			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	6		
Vagus nerve disorder			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Central nervous system necrosis			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Tremor			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 44 (36.36%)		
occurrences (all)	32		
Lymphopenia			
subjects affected / exposed	9 / 44 (20.45%)		
occurrences (all)	53		
Leukopenia			
subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	25		

Eye disorders			
Extraocular muscle paresis			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	35 / 44 (79.55%)		
occurrences (all)	83		
Nausea			
subjects affected / exposed	15 / 44 (34.09%)		
occurrences (all)	22		
Constipation			
subjects affected / exposed	14 / 44 (31.82%)		
occurrences (all)	15		
Abdominal pain			
subjects affected / exposed	11 / 44 (25.00%)		
occurrences (all)	15		
Diarrhoea			
subjects affected / exposed	11 / 44 (25.00%)		
occurrences (all)	27		
Stomatitis			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	8		
Abdominal distension			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Palmar−plantar erythrodysaesthesia syndrome			
subjects affected / exposed	16 / 44 (36.36%)		
occurrences (all)	33		
Dermatitis acneiform			
subjects affected / exposed	7 / 44 (15.91%)		
occurrences (all)	8		
Dry skin			
subjects affected / exposed	7 / 44 (15.91%)		
occurrences (all)	7		

Skin exfoliation subjects affected / exposed occurrences (all)	7 / 44 (15.91%) 15		
Alopecia subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 6		
Skin hyperpigmentation subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 6		
Pruritus subjects affected / exposed occurrences (all)	5 / 44 (11.36%) 5		
Dermatitis exfoliative subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Rash maculo−papular subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	4 / 44 (9.09%) 5		
Endocrine disorders Cushingoid subjects affected / exposed occurrences (all)	14 / 44 (31.82%) 14		
Adrenal insufficiency subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3		
Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences (all)	9 / 44 (20.45%) 12		
Pain in extremity subjects affected / exposed occurrences (all)	6 / 44 (13.64%) 8		

Back pain			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	3		
Infections and infestations			
Mucosal infection			
subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	11		
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	21 / 44 (47.73%)		
occurrences (all)	46		
Hypokalaemia			
subjects affected / exposed	18 / 44 (40.91%)		
occurrences (all)	40		
Hypocalcaemia			
subjects affected / exposed	17 / 44 (38.64%)		
occurrences (all)	33		
Hypermagnesaemia			
subjects affected / exposed	16 / 44 (36.36%)		
occurrences (all)	30		
Hyperglycaemia			
subjects affected / exposed	15 / 44 (34.09%)		
occurrences (all)	23		
Hyponatraemia			
subjects affected / exposed	16 / 44 (36.36%)		
occurrences (all)	25		
Hypophosphataemia			
subjects affected / exposed	14 / 44 (31.82%)		
occurrences (all)	23		
Decreased appetite			
subjects affected / exposed	11 / 44 (25.00%)		
occurrences (all)	12		
Hypercalcaemia			
subjects affected / exposed	8 / 44 (18.18%)		
occurrences (all)	17		
Hypernatraemia			

subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	6		
Hypoglycaemia			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2010	In addition to administrative changes, correction of errata and clarifications, the pharmacokinetic (PK) sampling schedule was changed (and it was stipulated that the exact time of PK sampling be recorded for PK modeling) and the age range for participation in the PK sub-study was removed.
16 April 2010	Administrative changes
06 June 2011	Administrative changes, clarifications and edits were introduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported