Clinical trial results:
Lapatinib and Whole Brain Radiotherapy for patients with brain metastases from lung and breast tumors. A phase II study of the Hellenic Cooperative Oncology Group (HeCOG).

Summary

EudraCT number	2009-013128-22
Trial protocol	GR
Global end of trial date	04 August 2014

Results information

Result version number	v1 (current)
This version publication date	01 December 2018
First version publication date	01 December 2018

Trial information

Trial identification

Sponsor protocol code	HE 42/09

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01218529
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Cooperative Oncology Group
Sponsor organisation address	Hatzikonstandi 18, Athens, Greece, 11524
Public contact	Hellenic Cooperative Oncology Group, Hellenic Cooperative Oncology Group, hecogoff@otenet.gr
Scientific contact	Hellenic Cooperative Oncology Group, Hellenic Cooperative Oncology Group, hecogoff@otenet.gr

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 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Response rate in brain as assessed by volumetric analysis of brain MRI.

Protection of trial subjects:

The study was conducted in conformance with ICH GCP, all applicable laws and regulations. All participants were required to read and sign an Informed Consent Form prior to all screening and baseline assessments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 82
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	49
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in the study from 22 November 2010 until 20 May 2014 from 8 sites in Greece.

Pre-assignment

Screening details:

Baseline evaluations were performed within 4 weeks of the first dose of the investigational agent.

Period 1

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

Arms

Arm title	Whole Brain Radiation Therapy+Lapatinib

Arm description:

Whole brain radiation (30Gy in 10 fractions) + lapatinib 1250mg once daily for 2 weeks followed by lapatinib treatment 1500mg once daily for 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	GW572016
Other name	Tyverb, lapatinib ditosylate monohydrate
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Co-administration of lapatinib 1250 mg once daily during the Whole Brain Radiation Therapy period (2 weeks) and then monotherapy with lapatinib 1500mg once daily for 4 weeks.

Number of subjects in period 1	Whole Brain Radiation Therapy+Lapatinib
Started	82
Completed	44
Not completed	38
Consent withdrawn by subject	10
Adverse event, non-fatal	4
Death	8
Progression	12
Doctor's decision	3
Ineligible patient	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	82	82	
Age categorical Units: Subjects			
Adults (18-64 years)	49	49	
From 65-84 years	33	33	
85 years and over	0	0	
Age continuous Units: years			
median	61.5		
full range (min-max)	39 to 83	-	
Gender categorical Units: Subjects			
Female	40	40	
Male	42	42	

Subject analysis sets	
Subject analysis set title	Analysis cohort
Subject analysis set type	Full analysis

Subject analysis set description:

In total, 81 of the 82 enrolled patients were eligible for the study since one patient was diagnosed with SCLC (instead of NSCLC).

Subject analysis set title	Volumetric analysis cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Brain MRI scans, in a compact disk (CD) for central volumetric assessment, were available for 68 patients.

Reporting group values	Analysis cohort	Volumetric analysis cohort	
Number of subjects	81	68	
Age categorical Units: Subjects			
Adults (18-64 years)	49	42	
From 65-84 years	32	26	
85 years and over	0	0	
Age continuous Units: years			
median	61.5	61.5	
full range (min-max)	39 to 83	39 to 83	
Gender categorical Units: Subjects			
Female	40	31	

Male	41	37	

End points

End points reporting groups

Reporting group title	Whole Brain Radiation Therapy+Lapatinib

Reporting group description:

Whole brain radiation (30Gy in 10 fractions) + lapatinib 1250mg once daily for 2 weeks followed by lapatinib treatment 1500mg once daily for 4 weeks.

Subject analysis set title	Analysis cohort
Subject analysis set type	Full analysis

Subject analysis set description:

In total, 81 of the 82 enrolled patients were eligible for the study since one patient was diagnosed with SCLC (instead of NSCLC).

Subject analysis set title	Volumetric analysis cohort
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Brain MRI scans, in a compact disk (CD) for central volumetric assessment, were available for 68 patients.

Primary: Response rate in brain

End point title	Response rate in brain[1]

End point description:

Response rate in brain as assessed by volumetric analysis of brain magnetic resonance imaging (MRI).

End point type	Primary

End point timeframe:

Radiological assessment with brain MRI at 6 weeks from baseline evaluation.

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: The number of patients with partial response, stable and progressive disease among all patients with pre- and post-treatment volumetric assessment of brain metastases has been reported. No comparisons were performed since this was a singe arm phase II study.

End point values	Volumetric analysis cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	43[2]			
Units: number of patients				
PR	27			
SD	15			
PD	1			

Notes:

[2] - 43 patients with pre- and post-treatment volumetric assessment of brain metastases.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression in brain and/or non-Central Nervous System (CNS)

End point title	Time to progression in brain and/or non-Central Nervous System (CNS)

End point description:

TTP was measured from the date of registration until verified disease progression or last contact, whichever occurred first.

End point type	Secondary

End point timeframe:

At six weeks timepoint, radiological assessment with brain MRI took place to evaluate the response of the patients. The patients were followed-up every 12 weeks for disease progression and survival.

End point values	Analysis cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: months				
median (confidence interval 95%)	3.3 (1.7 to 4.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and tolerability

End point title	Safety and tolerability

End point description:

The safety profile was assessed in the safety population consisting of 81 patients that received at least one dose of the study drug.

End point type	Secondary

End point timeframe:

Upon signature of the Informed Consent Form until 4 weeks after completion of study treatment.

End point values	Whole Brain Radiation Therapy+Lapatinib			
Subject group type	Reporting group			
Number of subjects analysed	81[3]			
Units: number of patients				
Any adverse events	78			
Adverse events grade ≥3	38			
Adverse events grade ≥4	15			
Fatal adverse events	5			
Serious adverse events	22			

Notes:

[3] - All patients who received at least one dose of the study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: To explore the 20% volumetric reduction of brain metastatic lesions

End point title	To explore the 20% volumetric reduction of brain metastatic lesions

End point description:

End point type	Secondary

End point timeframe:

At the 6 weeks timepoint, radiological assessment with brain MRI took place to evaluate the response of the patients.

End point values	Volumetric analysis cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	43[4]			
Units: number of patients				
Reduction of at least 20% in either lesion	28			
Reduction of at least 20% in both lesions	17			

Notes:

[4] - 43 patients with pre- and post-treatment volumetric assessment of brain metastases.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events of all participants were recorded and assessed upon signature of the Informed Consent Form, until 30 days after the last administration of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Whole Brain Radiation Therapy+Lapatinib

Reporting group description:

Whole brain radiation (30Gy in 10 fractions) + lapatinib 1250mg once daily for 2 weeks followed by lapatinib treatment 1500mg once daily for 4 weeks.

Serious adverse events	Whole Brain Radiation Therapy+Lapatinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 81 (27.16%)		
number of deaths (all causes)	66		
number of deaths resulting from adverse events	5		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nerve root compression			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain oedema			

subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Fatigue			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mental disorder	Additional description: Somnolence		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection	Additional description: Infection with normal ANC/Skin cellulitis		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Gastrointestinal disorders			
Jejunal perforation			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

Diarrhoea				
subjects affected / exposed	3 / 81 (3.70%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Lung infection				
subjects affected / exposed	4 / 81 (4.94%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	2 / 2			
Pain	Additional description: Pain head			
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fungal infection				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Mucosal inflammation				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Whole Brain Radiation Therapy+Lapatinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 81 (95.06%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Rubeosis faciei			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	20 / 81 (24.69%)		
occurrences (all)	21		
Fever			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	3		
Discomfort			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Irritability			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	4		
Pain			
subjects affected / exposed	23 / 81 (28.40%)		
occurrences (all)	25		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Hiccups			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders-Other			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		

Voice changes subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1		
Epistaxis subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 3		
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1		
Confusional state subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2		
Psychosis subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1		
Bulimia subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1		
Investigations			
Leukopenia subjects affected / exposed occurrences (all)	9 / 81 (11.11%) 9		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	20 / 81 (24.69%) 22		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	9 / 81 (11.11%) 9		
Alkaline phosphatase increased subjects affected / exposed occurrences (all)	10 / 81 (12.35%) 10		
Amylase increased subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 4		
Blood bilirubin increased			

subjects affected / exposed	19 / 81 (23.46%)		
occurrences (all)	26		
Hypercholesterolaemia			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Blood creatine increased			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	8		
Gamma-glutamyltransferase increased			
subjects affected / exposed	15 / 81 (18.52%)		
occurrences (all)	15		
Injury, poisoning and procedural complications			
Vascular access complication			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Cardiac disorders			
Hypertension			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Memory impairment			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Mood altered			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Seizure			

subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Speech disorder			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	4		
Gait disturbance			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Hand cramps			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Paresis	Additional description: Deltoid muscle		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Migraine			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 81 (11.11%)		
occurrences (all)	10		

Lymphopenia			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	7		
Neutropenia			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	11 / 81 (13.58%)		
occurrences (all)	12		
Ear and labyrinth disorders			
Auditory/Ear-Other	Additional description: Hearing loss		
alternative dictionary used: CTCAE 3			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Ocular surface disease			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Flashing lights			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	19 / 81 (23.46%)		
occurrences (all)	25		
Dry mouth			

subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	9 / 81 (11.11%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Salivary gland disorder			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	6		
Oral hemorrhage			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Alopecia			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	7		
Dermatitis			

subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Dry skin			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	4		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Nail disorder			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	17 / 81 (20.99%)		
occurrences (all)	17		
Redness			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Upper respiratory tract infection			

subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Vaginitis viral	Additional description: Herpes		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Parotitis			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	25 / 81 (30.86%)		
occurrences (all)	26		
Hyperkalaemia			
subjects affected / exposed	10 / 81 (12.35%)		
occurrences (all)	11		
Hypermagnesaemia			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Hypernatraemia			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	4		
Hypertriglyceridaemia			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		
Hyperuricaemia			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	7		

Hypoalbuminaemia			
subjects affected / exposed	16 / 81 (19.75%)		
occurrences (all)	17		
Hypocalcaemia			
subjects affected / exposed	19 / 81 (23.46%)		
occurrences (all)	23		
Hypoglycaemia			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	7		
Hypokalaemia			
subjects affected / exposed	11 / 81 (13.58%)		
occurrences (all)	13		
Hyponatraemia			
subjects affected / exposed	19 / 81 (23.46%)		
occurrences (all)	24		
Hypophosphataemia			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Blood urea increased			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	6		
Protein total decreased			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Anorexia			
subjects affected / exposed	12 / 81 (14.81%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported