Clinical trial results:
INVESTIGATION OF THE EFFICACY OF LAPATINIB PLUS TEMOZOLOMIDE COMBINATION, IN RECURRENT HIGH GRADE GLIOMAS. A PHASE I/II STUDY.

Summary

EudraCT number	2007-006656-19
Trial protocol	GR
Global end of trial date	02 October 2014

Results information

Result version number	v1 (current)
This version publication date	30 June 2019
First version publication date	30 June 2019

Trial information

Trial identification

Sponsor protocol code	HE 17/08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ACTRN: ACTRN12611000418976

Notes:

Sponsors

Sponsor organisation name	Hellenic Cooperative Oncology Group
Sponsor organisation address	Hatzikostandi 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	14 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I:The main objective is to determine the maximum tolerated dose and recommended phase II dose of lapatinib when given in combination with temozolomide in patients with recurrent or refractory glioblastoma multiforme and to assess the safety, tolerability and toxicity profile of this regimen in these patients.

Phase II:The primary objective is to evaluate the activity of lapatinib/temozolomide combination in patients with recurrent high-grade gliomas by determining the optimal response to treatment.

Protection of trial subjects:

This 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 January 2009
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: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	22
From 65 to 84 years	8

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in the study from 12 January 2009 until 21 January 2013 from 4 sites in Greece.

Pre-assignment

Screening details:

All potentially eligible subjects underwent screening in order to confirm that all eligibility criteria were met prior to the first administration of the study treatment.

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	Phase I

Arm description:

In the phase I study patients will be enrolled in cohorts of 3. They will receive fixed dose temozolomide [200 mg/m2 orally (po) once daily for 5 days] in cycles of 28 days and escalating doses of lapatinib. The starting dose of lapatinib will be 1000 mg administered orally (po) once daily (OD) every day of the 28 day cycle. Three dose levels of lapatinib will be explored (1000, 1250 and 1500 mg). Patients will receive lapatinib/ temozolomide combination until disease progression or unacceptable toxicity. Cohorts of 3 patients will receive escalating doses of lapatinib until the maximum tolerated dose is determined (MTD) as recorded in week 4 of treatment.

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:

Cohort 1
Lapatinib 1000 mg/d for 28 d + temozolomide 200 mg/m2 d 1-5 q28d
Cohort 2
Lapatinib 1250 mg/d for 28 d + temozolomide 200 mg/m2 d 1-5 q28d
Cohort 3
Lapatinib 1500 mg/d for 28 d + temozolomide 200 mg/m2 d 1-5 q28d

Arm title	Phase II

Arm description:

Patients received lapatinib 1000 mg (recommended dose resulting from Phase I of the study) orally once a day and temozolomide 200 mg / m2 once daily for 5 days in 28-day cycles. Treatment continued until disease progression, occurrence of unacceptable toxicity or withdrawal of consent by the patient.

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:

Temozolomide 200 mg/m2 orally (po) once daily for 5 days along with Lapatinib 1000 mg orally (po) once daily (dose as defined from phase I). The cycle duration was 28 days. Treatment continued until

disease progression, unacceptable toxicity or consent withdrawal.

Number of subjects in period 1	Phase I	Phase II
Started	16	14
Completed	12	0
Not completed	4	14
Clinical progression	-	1
Disease progression	1	-
Adverse event, non-fatal	2	-
Death	-	1
Progression	-	12
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase I

Reporting group description:

In the phase I study patients will be enrolled in cohorts of 3. They will receive fixed dose temozolomide [200 mg/m2 orally (po) once daily for 5 days] in cycles of 28 days and escalating doses of lapatinib. The starting dose of lapatinib will be 1000 mg administered orally (po) once daily (OD) every day of the 28 day cycle. Three dose levels of lapatinib will be explored (1000, 1250 and 1500 mg). Patients will receive lapatinib/ temozolomide combination until disease progression or unacceptable toxicity. Cohorts of 3 patients will receive escalating doses of lapatinib until the maximum tolerated dose is determined (MTD) as recorded in week 4 of treatment.

Reporting group title	Phase II

Reporting group description:

Patients received lapatinib 1000 mg (recommended dose resulting from Phase I of the study) orally once a day and temozolomide 200 mg / m2 once daily for 5 days in 28-day cycles. Treatment continued until disease progression, occurrence of unacceptable toxicity or withdrawal of consent by the patient.

Reporting group values	Phase I	Phase II	Total
Number of subjects	16	14	30
Age categorical Units: Subjects			
Adults (18-64 years)	10	12	22
From 65-84 years	6	2	8
85 years and over	0	0	0
Age continuous Units: years			
median	60.3	47.3	
full range (min-max)	43.1 to 79.1	25.7 to 68.5	-
Gender categorical Units: Subjects			
Female	7	4	11
Male	9	10	19

End points

End points reporting groups

Reporting group title	Phase I

Reporting group description:

In the phase I study patients will be enrolled in cohorts of 3. They will receive fixed dose temozolomide [200 mg/m2 orally (po) once daily for 5 days] in cycles of 28 days and escalating doses of lapatinib. The starting dose of lapatinib will be 1000 mg administered orally (po) once daily (OD) every day of the 28 day cycle. Three dose levels of lapatinib will be explored (1000, 1250 and 1500 mg). Patients will receive lapatinib/ temozolomide combination until disease progression or unacceptable toxicity. Cohorts of 3 patients will receive escalating doses of lapatinib until the maximum tolerated dose is determined (MTD) as recorded in week 4 of treatment.

Reporting group title	Phase II

Reporting group description:

Patients received lapatinib 1000 mg (recommended dose resulting from Phase I of the study) orally once a day and temozolomide 200 mg / m2 once daily for 5 days in 28-day cycles. Treatment continued until disease progression, occurrence of unacceptable toxicity or withdrawal of consent by the patient.

Primary: Maximum Tolerated Dose of Lapatinib (L)

End point title	Maximum Tolerated Dose of Lapatinib (L)[1][2]

End point description:

Determine the maximum tolerated dose and recommended phase II dose of lapatinib (L) when given in combination with temozolomide (T) in patients with recurrent or refractory glioblastoma multiforme.

End point type	Primary

End point timeframe:

Three dose levels of lapatinib were explored (1000, 1250 and 1500 mg). Patients received lapatinib (L)/ temozolomide (T) combination until disease progression or unacceptable toxicity.

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: Descriptive statistics including the number of patients for each dose level of the phase I were used.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The determination of the maximum tolerated dose was the primary endpoint of the phase I part of the trial. Therefore, the number of patients in each dose level was provided. The number of patients with dose limiting toxicities was also noted in the provided table.

End point values	Phase I			
Subject group type	Reporting group			
Number of subjects analysed	16[3]			
Units: number of subjects entered per dose leve				
Level 1: T (200mg/m2), L (1000 mg)	11			
Level 2: T (200 mg/m2), L (1250 mg) (2 DLTs)	4			
Level 3: T (200 mg/m2), L (1500 mg)	1			

Notes:

[3] - Patient in level 3 was enrolled prior to previous level's toxicity evaluation (protocol violation).

Statistical analyses

No statistical analyses for this end point

Primary: Activity of lapatinib/temozolomide

End point title	Activity of lapatinib/temozolomide[4][5]

End point description:

The primary objective of the Phase II was to evaluate the activity of lapatinib/temozolomide combination in patients with recurrent high-grade gliomas by determining the optimal response to treatment.

End point type	Primary

End point timeframe:

MRI scans carried out at baseline, at the end of week 8, and every 8 weeks thereafter until progression, unacceptable toxicity or consent withdrawal.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since this was a single arm phase I/II trial and all patients were treated with lapatinib and temozolomide, no comparisons between different treatment groups could be performed. Descriptive statistics including the frequencies of best responses achieved are provided for all patients enrolled in phase II.
[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The activity of lapatinib/temozolomide was the primary endpoint of the phase II part of the study. Thus, the frequencies of best responses achieved are provided for all patients enrolled in phase II.

End point values	Phase II			
Subject group type	Reporting group			
Number of subjects analysed	14[6]			
Units: number of patients				
Complete response	0			
Partial response	1			
Stable disease	7			
Progressive disease	5			
Not evaluable	1			

Notes:

[6] - Enrollment was halted upon 13th patient's entry. 1 more patient was enrolled-registration violation.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Toxicity profile

End point title	Safety and Toxicity profile

End point description:

Determine the safety and tolerability (toxicity profile) of this regimen.

End point type	Secondary

End point timeframe:

Adverse Events (AEs) (hematological and non-hematological toxicities) of all participants were recorded and assessed upon signature of the informed consent form until 30 days after the last administration of study.

End point values	Phase I	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: number of patients				
Any adverse event	16	12		
Fatal adverse events	0	1		
Serious adverse events	7	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP)

End point title	Time to progression (TTP)[7]

End point description:

End point type	Secondary

End point timeframe:

TTP was calculated from date of treatment initiation until tumor progression or last contact, whichever occurred first.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Time to progression was a secondary endpoint of the phase II part of the trial. Therefore, the median TTP with the corresponding 95% confidence interval was provided for all phase II patients.

End point values	Phase II			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: months				
median (confidence interval 95%)	4.3 (1.4 to 6.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)[8]

End point description:

End point type	Secondary

End point timeframe:

OS was calculated from the date of treatment initiation to the date of death or last contact.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Overall survival was a secondary endpoint of the phase II part of the trial. Therefore, the median overall survival with the corresponding 95% confidence interval was provided for all phase II

patients.

End point values	Phase II			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: months				
median (confidence interval 95%)	10.2 (5.1 to 11.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) (hematological and non-hematological toxicities) of all participants were recorded and assessed upon signature of the inform consent form until 30 days after last administration of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Phase 1

Reporting group description:

Temozolomide was administered at a fixed dose of 200 mg/m2 p.o. (d 1-5 q28d). Patients were advised to take temozolomide on an empty stomach (either 1 hour before or 1 hour after meals). Up to 3 dose levels of lapatinib were explored (1000, 1250, 1500 mg), in cohorts of at least 3 patients, as described in the trial design section. Patients were advised to take lapatinib on an empty stomach (either 1 hour before or 1 hour after meals).

Reporting group title	Phase 2

Reporting group description:

Patients received lapatinib 1000 mg (recommended dose resulting from Phase I of the study) orally once a day and temozolomide 200 mg / m2 once daily for 5 days in 28-day cycles. Treatment continued until disease progression, occurrence of unacceptable toxicity or withdrawal of consent by the patient.

Serious adverse events	Phase 1	Phase 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 16 (43.75%)	3 / 14 (21.43%)	
number of deaths (all causes)	16	10	
number of deaths resulting from adverse events	0	1	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiopulmonary failure			

subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain head			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 16 (6.25%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain edema			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombopenia			
subjects affected / exposed	4 / 16 (25.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leucopenia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			

subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection	Additional description: Septic shock		
subjects affected / exposed	2 / 16 (12.50%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Phase 1	Phase 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	12 / 14 (85.71%)	
General disorders and administration site conditions			
Unsteady gait			
subjects affected / exposed	1 / 16 (6.25%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	5 / 16 (31.25%)	2 / 14 (14.29%)	
occurrences (all)	8	2	
Mucositis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Fever			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Oedema	Additional description: Limb		
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Abnormal gait			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Flu-like syndrome			

subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Bloody vaginal discharge			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Choking sensation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Hiccups			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Sleep disorder	Additional description: Reversal sleeping		
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Investigations			
Haemoglobin			
subjects affected / exposed	6 / 16 (37.50%)	4 / 14 (28.57%)	
occurrences (all)	37	16	

Leukocyte count decreased			
subjects affected / exposed	5 / 16 (31.25%)	3 / 14 (21.43%)	
occurrences (all)	36	13	
Neutrophil count decreased			
subjects affected / exposed	5 / 16 (31.25%)	1 / 14 (7.14%)	
occurrences (all)	26	7	
Platelet count decreased			
subjects affected / exposed	7 / 16 (43.75%)	4 / 14 (28.57%)	
occurrences (all)	57	9	
Alkaline phosphatase increased			
subjects affected / exposed	3 / 16 (18.75%)	0 / 14 (0.00%)	
occurrences (all)	9	0	
Alanine aminotransferase increased			
subjects affected / exposed	5 / 16 (31.25%)	4 / 14 (28.57%)	
occurrences (all)	14	5	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 16 (18.75%)	2 / 14 (14.29%)	
occurrences (all)	9	2	
Blood bilirubin increased			
subjects affected / exposed	6 / 16 (37.50%)	1 / 14 (7.14%)	
occurrences (all)	12	1	
Cholesterol high			
subjects affected / exposed	1 / 16 (6.25%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 16 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
Creatinine			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
LDH			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nervous system disorders			

Burning sensation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	2 / 16 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Memory impairment			
subjects affected / exposed	1 / 16 (6.25%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Sensory neuropathy			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Seizure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	3 / 16 (18.75%)	3 / 14 (21.43%)	
occurrences (all)	3	4	
Syncope			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	3 / 16 (18.75%)	0 / 14 (0.00%)	
occurrences (all)	5	0	
Pyramidal tract syndrome	Additional description: pyramidal tract dysfunction		
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 16 (6.25%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Epiphora	Additional description: Watery eye		

subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	2 / 16 (12.50%)	2 / 14 (14.29%)	
occurrences (all)	6	2	
Diarrhoea			
subjects affected / exposed	4 / 16 (25.00%)	3 / 14 (21.43%)	
occurrences (all)	6	3	
Dry mouth			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	3 / 16 (18.75%)	3 / 14 (21.43%)	
occurrences (all)	7	5	
Vomiting			
subjects affected / exposed	2 / 16 (12.50%)	2 / 14 (14.29%)	
occurrences (all)	5	2	
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	4 / 14 (28.57%)	
occurrences (all)	0	4	
Flatulence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Mucositis oral			
subjects affected / exposed	0 / 16 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	

Gum bleeding			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Tooth pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 16 (6.25%)	1 / 14 (7.14%)	
occurrences (all)	1	2	
Skin hyperpigmentation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 16 (6.25%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	3 / 16 (18.75%)	6 / 14 (42.86%)	
occurrences (all)	5	6	
Urticaria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Cystitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Bladder pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Bone pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Joint pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Muscle weakness	Additional description: Lower extremity		
subjects affected / exposed	1 / 16 (6.25%)	2 / 14 (14.29%)	
occurrences (all)	1	3	
Infections and infestations			
Infection	Additional description: With normal ANC		
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Urinary infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Flu			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Furunculosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	4 / 16 (25.00%)	2 / 14 (14.29%)	
occurrences (all)	14	7	
Hyperkalemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Hypertriglyceridemia			

subjects affected / exposed	2 / 16 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
Hyperuricemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	10	0	
Hypoalbuminaemia			
subjects affected / exposed	4 / 16 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	11	1	
Hypoglycaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
Hypokalaemia			
subjects affected / exposed	3 / 16 (18.75%)	2 / 14 (14.29%)	
occurrences (all)	9	2	
Hyponatraemia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
Hypocalcaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2012	Amendment includes: - Protocol amendment v2.0, - Revision of protocol title, - amendment of study design, primary- secondary objectives - revision of one inclusion criterion - increase in study duration - dose modification - revision of the response response criteria - amendment on study's statistical plan therefore reduce of sample size to 66 patients - add new study sites - change of principal investigator in approved site

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported