Clinical trial results:
A Phase II, Double-Blind, Randomised Study to Assess the Efficacy of AZD6244 (Hyd-Sulfate) in Combination with Dacarbazine Compared with Dacarbazine Alone in First Line Patients with BRAF Mutation Positive Advanced Cutaneous or Unknown Primary Melanoma

Summary

EudraCT number	2008-006344-19
Trial protocol	DE GB CZ FR SE HU ES NL
Global end of trial date	20 November 2011

Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	22 April 2016

Trial information

Trial identification

Sponsor protocol code	D1532C00006

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Charter Way, Macclesfield, United Kingdom, SK10 2NA
Public contact	Gabriella Mariani, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Gabriella Mariani, AstraZeneca, ClinicalTrialTransparency@astrazeneca.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	20 November 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2011
Global end of trial reached?	Yes
Global end of trial date	20 November 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy in terms of OS of AZD6244 in combination with dacarbazine, compared with dacarbazine alone, in first-line patients with BRAF mutation-positive advanced cutaneous or unknown primary melanoma.

Protection of trial subjects:

Patients were to avoid excessive sun exposure and use adequate sunscreen protection if sun exposure was anticipated

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 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	Brazil: 6
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	91
EEA total number of subjects	71

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)	67
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Tumour evaluation and confirmation of BRAF mutation status using patient's tumour sample, serum and plasma sample for extraction of cfDNA, demography, medical and surgical history, previous anti-cancer treatment, disease staging, smoking status, height, eligibility check.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Data analyst, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	selumetinib 75mg BD +dacarbazine

Arm description:

selumetinib 75mg twice daily + Dacarbazine

Arm type	Experimental
Investigational medicinal product name	selumetinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75mg BD

Arm title	Placebo BD + Dacarbazine

Arm description:

Placebo twice daily + Dacarbazine

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

BD

Number of subjects in period 1	selumetinib 75mg BD +dacarbazine	Placebo BD + Dacarbazine
Started	45	46
Received Treatment	44	45
Completed	44	45
Not completed	1	1
Consent withdrawn by subject	1	1

Baseline characteristics

Reporting groups	
Reporting group title	selumetinib 75mg BD +dacarbazine
Reporting group description: selumetinib 75mg twice daily + Dacarbazine	
Reporting group title	Placebo BD + Dacarbazine
Reporting group description: Placebo twice daily + Dacarbazine	

Reporting group values	selumetinib 75mg BD +dacarbazine	Placebo BD + Dacarbazine	Total
Number of subjects	45	46	91
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	32	35	67
From 65-84 years	13	11	24
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	55.7	51.6	
standard deviation	± 14.89	± 16.21	-
Gender, Male/Female Units: Participants			
Female	23	18	41
Male	22	28	50

Subject analysis sets	
Subject analysis set title	selumetinib 75mg BD + dacarbazine
Subject analysis set type	Intention-to-treat
Subject analysis set description: selumetinib 75mg twice daily + dacarbazine	
Subject analysis set title	Placebo + dacarbazine
Subject analysis set type	Intention-to-treat
Subject analysis set description: Matched Placebo + dacarbazine	

Reporting group values	selumetinib 75mg BD + dacarbazine	Placebo + dacarbazine	
Number of subjects	45	46	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	32	35	
From 65-84 years	13	11	
85 years and over	0	0	
Age Continuous | Units: Years			
arithmetic mean	55.7	51.6	
standard deviation	± 14.89	± 16.21	
Gender, Male/Female Units: Participants			
Female	23	18	
Male	22	28	

End points

End points reporting groups

Reporting group title	selumetinib 75mg BD +dacarbazine
Reporting group description: selumetinib 75mg twice daily + Dacarbazine	
Reporting group title	Placebo BD + Dacarbazine
Reporting group description: Placebo twice daily + Dacarbazine	
Subject analysis set title	selumetinib 75mg BD + dacarbazine
Subject analysis set type	Intention-to-treat
Subject analysis set description: selumetinib 75mg twice daily + dacarbazine	
Subject analysis set title	Placebo + dacarbazine
Subject analysis set type	Intention-to-treat
Subject analysis set description: Matched Placebo + dacarbazine	

Primary: Overall Survival

End point title	Overall Survival
End point description: Time from randomization to death due to any cause	
End point type	Primary
End point timeframe: Randomzation to data cutoff	

End point values	selumetinib 75mg BD + dacarbazine	Placebo + dacarbazine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	46		
Units: Days				
median (full range (min-max))	424 (63 to 760)	321 (66 to 739)		

Statistical analyses

Statistical analysis title	Overall Survival Analysis
Statistical analysis description: If the true hazard ratio (HR) is 0.57, 58 deaths provides at least 80% power to demonstrate a statistically significant difference for OS, assuming a 1-sided 10% significance level.	
Comparison groups	selumetinib 75mg BD + dacarbazine v Placebo + dacarbazine

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3873 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.67
upper limit	1.28

Notes:

[1] - 1-sided p-value

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Time from randomization to objective disease progression, according to RECIST 1.0, or death.

End point type	Secondary

End point timeframe:

Randomization to data cutoff

End point values	selumetinib 75mg BD + dacarbazine	Placebo + dacarbazine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	46		
Units: Days				
median (full range (min-max))	169 (37 to 596)	92 (32 to 660)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Patients classified as a responder have a best response of partial response of complete response as per RECIST 1.0

End point type	Secondary

End point timeframe:

randomization up to and including PFS event

End point values	selumetinib 75mg BD + dacarbazine	Placebo + dacarbazine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	46		
Units: Participants				
Response	18	12		
Complete Response	1	1		
Partial Response	17	11		
Non-response	27	34		
Stable Disease >=6 weeks	13	10		
Progression	14	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in target lesion tumour size at week 12

End point title	Change in target lesion tumour size at week 12

End point description:

End point type	Secondary

End point timeframe:
randomization to week 12

End point values	selumetinib 75mg BD + dacarbazine	Placebo + dacarbazine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	46		
Units: % change				
median (full range (min-max))	-8.85 (-65.22 to 121.77)	0.22 (-72.5 to 295.79)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Following randomisation on Day 1 until 30 days after the last dose of the last study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	Placebo BD + Dacarbazine
Reporting group description: Placebo twice daily + Dacarbazine	
Reporting group title	selumetinib 75mg BD +dacarbazine
Reporting group description: selumetinib 75mg twice daily + Dacarbazine	

Serious adverse events	Placebo BD + Dacarbazine	selumetinib 75mg BD +dacarbazine	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 45 (17.78%)	22 / 44 (50.00%)	
number of deaths (all causes)	34	30	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intracranial tumour haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial thrombosis limb			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Alanine aminotransferase increased			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left atrial dilatation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Febrile neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Periorbital oedema			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 45 (2.22%)	3 / 44 (6.82%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Groin Pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 45 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo BD + Dacarbazine	selumetinib 75mg BD +dacarbazine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 45 (97.78%)	44 / 44 (100.00%)	
Vascular disorders			
HYPERTENSION			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	8 / 44 (18.18%)	
occurrences (all)	1	9	
LYMPHOEDEMA			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	11 / 44 (25.00%)	
occurrences (all)	2	11	
General disorders and administration			

site conditions			
ASTHENIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)	12 / 44 (27.27%)	
occurrences (all)	8	22	
CHILLS			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	3 / 44 (6.82%)	
occurrences (all)	1	4	
FACE OEDEMA			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	3 / 44 (6.82%)	
occurrences (all)	1	4	
FATIGUE			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 45 (33.33%)	16 / 44 (36.36%)	
occurrences (all)	23	21	
GENERALISED OEDEMA			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	6 / 44 (13.64%)	
occurrences (all)	2	7	
LOCALISED OEDEMA			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	4	
OEDEMA PERIPHERAL			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)	19 / 44 (43.18%)	
occurrences (all)	3	27	
PYREXIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)	5 / 44 (11.36%)	
occurrences (all)	9	8	
Respiratory, thoracic and mediastinal disorders			

COUGH			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)	3 / 44 (6.82%)	
occurrences (all)	4	3	
DYSPNOEA EXERTIONAL			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 45 (13.33%)	8 / 44 (18.18%)	
occurrences (all)	7	10	
EPISTAXIS			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	3 / 44 (6.82%)	
occurrences (all)	1	4	
DYSPNOEA			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	3 / 44 (6.82%)	
occurrences (all)	2	3	
Psychiatric disorders			
ANXIETY			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)	5 / 44 (11.36%)	
occurrences (all)	5	5	
BRADYPHRENIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)	0 / 44 (0.00%)	
occurrences (all)	3	0	
DEPRESSION			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	3 / 44 (6.82%)	
occurrences (all)	2	3	
INSOMNIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)	3 / 44 (6.82%)	
occurrences (all)	3	3	
Investigations			

ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 45 (6.67%)	4 / 44 (9.09%)	
occurrences (all)	3	4	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	5 / 44 (11.36%)	
occurrences (all)	1	6	
BLOOD CREATININE PHOSPHOKINASE INCREASED			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	7 / 44 (15.91%)	
occurrences (all)	0	9	
BLOOD PRESSURE INCREASED			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	4 / 44 (9.09%)	
occurrences (all)	0	5	
WEIGHT INCREASED			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	3	
Nervous system disorders			
DIZZINESS			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	6 / 44 (13.64%)	
occurrences (all)	2	12	
DYSGEUSIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)	4 / 44 (9.09%)	
occurrences (all)	4	4	
HEADACHE			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 45 (26.67%)	5 / 44 (11.36%)	
occurrences (all)	17	6	
LETHARGY			
alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 45 (8.89%)	2 / 44 (4.55%)	
occurrences (all)	4	2	
PARAESTHESIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)	3 / 44 (6.82%)	
occurrences (all)	6	3	
SYNCOPE			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	4 / 44 (9.09%)	
occurrences (all)	0	4	
Blood and lymphatic system disorders			
ANAEMIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	4 / 44 (9.09%)	
occurrences (all)	2	4	
LEUKOPENIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)	1 / 44 (2.27%)	
occurrences (all)	3	2	
NEUTROPENIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 45 (15.56%)	7 / 44 (15.91%)	
occurrences (all)	11	19	
Thrombocytopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 45 (13.33%)	11 / 44 (25.00%)	
occurrences (all)	9	19	
Eye disorders			
EYELID OEDEMA			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	4	
PERIORBITAL OEDEMA			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 45 (2.22%)	4 / 44 (9.09%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
Abdominal Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)	9 / 44 (20.45%)	
occurrences (all)	4	10	
Abdominal Pain Upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)	4 / 44 (9.09%)	
occurrences (all)	4	4	
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 45 (28.89%)	12 / 44 (27.27%)	
occurrences (all)	19	18	
DIARRHOEA			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 45 (28.89%)	21 / 44 (47.73%)	
occurrences (all)	18	46	
DRY MOUTH			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	6 / 44 (13.64%)	
occurrences (all)	0	6	
DYSPEPSIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	6 / 44 (13.64%)	
occurrences (all)	3	6	
FLATULENCE			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)	1 / 44 (2.27%)	
occurrences (all)	5	1	
GASTROOESOPHAGEAL REFLUX DISEASE			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 45 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	3	
NAUSEA			
alternative assessment type: Non-systematic			
subjects affected / exposed	25 / 45 (55.56%)	28 / 44 (63.64%)	
occurrences (all)	48	57	
STOMATITIS			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 45 (11.11%)	8 / 44 (18.18%)	
occurrences (all)	6	10	
VOMITING			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 45 (31.11%)	20 / 44 (45.45%)	
occurrences (all)	22	39	
Skin and subcutaneous tissue disorders			
DERMATITIS ACNEIFORM			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	23 / 44 (52.27%)	
occurrences (all)	1	32	
DRY SKIN			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	10 / 44 (22.73%)	
occurrences (all)	2	12	
ECZEMA			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	5 / 44 (11.36%)	
occurrences (all)	1	6	
ERYTHEMA			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	4 / 44 (9.09%)	
occurrences (all)	1	5	
EXFOLIATIVE RASH			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 45 (2.22%)	3 / 44 (6.82%)	
occurrences (all)	4	2	
HAIR COLOUR CHANGES			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	4 / 44 (9.09%)	
occurrences (all)	0	4	
NIGHT SWEATS			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)	3 / 44 (6.82%)	
occurrences (all)	4	3	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	5 / 44 (11.36%)	
occurrences (all)	0	6	
PRURITUS			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	3 / 44 (6.82%)	
occurrences (all)	3	3	
SKIN CHAPPED			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	4 / 44 (9.09%)	
occurrences (all)	0	5	
SKIN FISSURES			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	3	
ALOPECIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 45 (4.44%)	6 / 44 (13.64%)	
occurrences (all)	2	6	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 45 (6.67%)	4 / 44 (9.09%)	
occurrences (all)	3	5	
BACK PAIN			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 45 (6.67%)	7 / 44 (15.91%)	
occurrences (all)	4	7	
MYALGIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 45 (2.22%)	3 / 44 (6.82%)	
occurrences (all)	1	5	
PAIN IN EXTREMITY			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 45 (8.89%)	3 / 44 (6.82%)	
occurrences (all)	5	3	
Infections and infestations			
FOLLICULITIS			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	5 / 44 (11.36%)	
occurrences (all)	0	6	
NASOPHARYNGITIS			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 45 (13.33%)	3 / 44 (6.82%)	
occurrences (all)	7	5	
PARONYCHIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	6 / 44 (13.64%)	
occurrences (all)	0	8	
RASH PUSTULAR			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	6 / 44 (13.64%)	
occurrences (all)	0	7	
UPPER RESPIRATORY TRACT INFECTION			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 45 (4.44%)	4 / 44 (9.09%)	
occurrences (all)	4	5	
URINARY TRACT INFECTION			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	5 / 44 (11.36%)	
occurrences (all)	0	9	
Metabolism and nutrition disorders			
DECREASED APPETITE			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 45 (24.44%)	10 / 44 (22.73%)	
occurrences (all)	13	11	
HYPOKALAEMIA			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 45 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	3	

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