Clinical trial results:
A Phase II Randomized Trial of the Combination of Ridaforolimus and Exemestane, Compared to Ridaforolimus, Dalotuzumab and Exemestane in High Proliferation, Estrogen Receptor Positive

Summary

EudraCT number	2012-000335-11
Trial protocol	ES SE CZ BE PT DE DK IT
Global end of trial date	15 March 2018

Results information

Result version number	v2 (current)
This version publication date	07 May 2020
First version publication date	07 March 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	8669-064

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01605396
WHO universal trial number (UTN)	-
Other trial identifiers	MK-8669-064: Merck Registration Number

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	15 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to evaluate the efficacy of the triplet of ridaforolimus, dalotuzumab and exemestane compared to the combination of ridaforolimus and exemestane in post-menopausal participants with breast cancer. The primary hypothesis of the study is that the triplet of ridaforolimus, dalotuzumab and exemestane will improve progression free survival (PFS) compared to ridaforolimus and exemestane.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 July 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Peru: 2
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	80
EEA total number of subjects	36

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)	54
From 65 to 84 years	25
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 196 screened participants, 80 were randomized to either ridaforolimus plus dalotuzumab plus exemestane or ridaforolimus plus exemestane.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ridaforolimus + Dalotuzumab + Exemestane

Arm description:

Participants receive ridaforolimus 10 mg orally (PO) every 5 days (QD x 5) plus dalotuzumab 10 mg/kg intravenously (IV) every week (QW) plus exemestane 25 mg PO every day (QD) in 28-day cycles until documented disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Ridaforolimus
Investigational medicinal product code	
Other name	MK-8669
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ridaforolimus 10 mg tablet, administered PO at a dose of 10 mg (triplet) or 30 mg (doublet) depending upon randomization, on Days 1-5, 8-12, 15-19, & 22-26 of 28-day cycle.

Investigational medicinal product name	Dalotuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dalotuzumab 10 mg/kg administered IV weekly on Days 1, 8, 15, and 22 of 28-day cycle.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane 25 mg tablet administered PO QD.

Arm title	Ridaforolimus + Exemestane

Arm description:

Participants receive ridaforolimus 30 mg PO QD x 5 plus exemestane 25 mg PO QD treatment in 28-day cycles until documented disease progression or unacceptable toxicity.

Arm type	Experimental

Investigational medicinal product name	Ridaforolimus
Investigational medicinal product code	
Other name	MK-8669
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ridaforolimus 10 mg tablet, administered PO at a dose of 10 mg (triplet) or 30 mg (doublet) depending upon randomization, on Days 1-5, 8-12, 15-19, & 22-26 of 28-day cycle.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane 25 mg tablet administered PO QD.

Number of subjects in period 1	Ridaforolimus + Dalotuzumab + Exemestane	Ridaforolimus + Exemestane
Started	40	40
Treated	39	40
Completed	0	0
Not completed	40	40
Transfer Off Study	4	5
Physician decision	2	2
Consent withdrawn by subject	4	2
Adverse event, non-fatal	5	3
Progressive Disease	23	27
Non-Compliance With Study Drug	1	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ridaforolimus + Dalotuzumab + Exemestane
Reporting group description:	
Participants receive ridaforolimus 10 mg orally (PO) every 5 days (QD x 5) plus dalotuzumab 10 mg/kg intravenously (IV) every week (QW) plus exemestane 25 mg PO every day (QD) in 28-day cycles until documented disease progression or unacceptable toxicity.	
Reporting group title	Ridaforolimus + Exemestane
Reporting group description:	
Participants receive ridaforolimus 30 mg PO QD x 5 plus exemestane 25 mg PO QD treatment in 28-day cycles until documented disease progression or unacceptable toxicity.	

Reporting group values	Ridaforolimus + Dalotuzumab + Exemestane	Ridaforolimus + Exemestane	Total
Number of subjects	40	40	80
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	60.7	57.7	
standard deviation	± 9.0	± 11.8	-
Sex: Female, Male Units: Subjects			
Female	40	40	80
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	9	14	23
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	3
White	26	24	50
More than one race	3	1	4
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	4	8
Not Hispanic or Latino	35	34	69
Unknown or Not Reported	1	2	3

End points

End points reporting groups

Reporting group title	Ridaforolimus + Dalotuzumab + Exemestane

Reporting group description:

Participants receive ridaforolimus 10 mg orally (PO) every 5 days (QD x 5) plus dalotuzumab 10 mg/kg intravenously (IV) every week (QW) plus exemestane 25 mg PO every day (QD) in 28-day cycles until documented disease progression or unacceptable toxicity.

Reporting group title	Ridaforolimus + Exemestane

Reporting group description:

Participants receive ridaforolimus 30 mg PO QD x 5 plus exemestane 25 mg PO QD treatment in 28-day cycles until documented disease progression or unacceptable toxicity.

Primary: Progression-free Survival (PFS) According to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR)

End point title	Progression-free Survival (PFS) According to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR)

End point description:

PFS was defined as the time from randomization to progressive disease, or death, whichever occurs first. Response was assessed according to RECIST 1.1 by BICR. According to RECIST 1.1, progressive disease (PD) was defined as a 20% relative increase in the sum of diameters (SOD) of target lesions, taking as reference the nadir SOD and an absolute increase of >5 mm in the SOD, or the appearance of new lesions. PFS was analysed using the Kaplan-Meier method and median PFS (95% confidence interval [CI]) in weeks was reported for each treatment arm. Per protocol, participants remained on assigned treatment until disease progression. Participants who discontinued study treatment for reasons other than disease progression continued to be assessed by imaging until objective documentation of progression. All participants (including participants who discontinued study treatment) were followed for survival until investigator notification to discontinue. All randomized participants were analysed

End point type	Primary

End point timeframe:

From Day 1 through last post-study efficacy follow-up (up to ~19 months)

End point values	Ridaforolimus + Dalotuzumab + Exemestane	Ridaforolimus + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Weeks				
median (confidence interval 95%)	23.29 (8.71 to 38.43)	31.86 (16.00 to 39.29)		

Statistical analyses

Statistical analysis title	PFS: HR Comparison of Treatment

Statistical analysis description:

Hazard ratio (HR) and p-value for treatment difference based on Cox regression model with Efron tie handling for treatment comparison (Ridaforolimus + Dalotuzumab + Exemestane arm versus

Ridaforolimus + Exemestane arm).

Comparison groups	Ridaforolimus + Dalotuzumab + Exemestane v Ridaforolimus + Exemestane
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.565
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.81
upper limit	1.72

Secondary: Percent Change from Baseline in Sum of Target Lesion Diameters at Week 16

End point title	Percent Change from Baseline in Sum of Target Lesion Diameters at Week 16

End point description:

The percent change from baseline to Week 16 in the sum of target lesion diameters as determined by anatomic imaging was defined as the line length (i.e., diameter) for each target lesion identified at baseline summed across all lesions at baseline, and separately at each post-baseline time point. The primary analysis was conducted using a constrained longitudinal data analysis (cLDA) method and target lesion measurements according to the BICR. Percent change from baseline in sum of target lesion diameters at Week 16 was reported for each treatment arm. All randomized participants with available Week 16 target lesion measurements were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Ridaforolimus + Dalotuzumab + Exemestane	Ridaforolimus + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	32		
Units: percent change				
arithmetic mean (standard deviation)	-19.3 (± 20.4)	-10.7 (± 28.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Objective Response (Objective Response Rate [ORR]) According to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR).

End point title	Percentage of Participants with Objective Response (Objective Response Rate [ORR]) According to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Based on Blinded Independent Central Review (BICR).

End point description:

ORR was defined as the percentage of participants whose best response was complete response (CR; disappearance of all non-nodal target lesions and any pathological lymph nodes must have become normal) or partial response (PR; at least a 30% decrease in the SOD of target lesions, taking as reference the baseline SOD) according to RECIST 1.1 and based on BICR. ORR was reported for each treatment arm. Per protocol, participants remained on assigned treatment until disease progression. Participants who discontinued study treatment for reasons other than disease progression continued to be assessed by imaging until objective documentation of progression. All randomized participants were analysed.

End point type	Secondary

End point timeframe:

From Day 1 through last post-study efficacy follow-up (up to ~19 months)

End point values	Ridaforolimus + Dalotuzumab + Exemestane	Ridaforolimus + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Percentage of Participants				
number (confidence interval 95%)	15.0 (5.7 to 29.8)	25.0 (12.7 to 41.2)		

Statistical analyses

Statistical analysis title	ORR: Difference in Response Rates

Statistical analysis description:

Miettinen and Nurminen's method was used to compare ORR between the two treatment arms (Ridaforolimus + Dalotuzumab + Exemestane arm versus Ridaforolimus + Exemestane arm), and to calculate a p-value and 95% confidence interval (CI) for the difference in response rates.

Comparison groups	Ridaforolimus + Dalotuzumab + Exemestane v Ridaforolimus + Exemestane
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.267
Method	Miettinen and Nurminen's Method
Parameter estimate	Difference of Percentages
Point estimate	-10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.8
upper limit	8

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of analysis were censored at the date last known to be alive. OS was analysed using the Kaplan-Meier method and median OS (95% confidence interval [CI]) in weeks was reported for each treatment arm. Per protocol, all participants (including participants who discontinued study treatment) were followed for survival until investigator notification to discontinue.
All randomized participants were analysed. A value of 9999 indicates that median OS (95% CI) could not be calculated due to an insufficient number of deaths on study (i.e. median OS was not reached).

End point type	Secondary

End point timeframe:

From Day 1 through last post-study efficacy follow-up (up to ~19 months)

End point values	Ridaforolimus + Dalotuzumab + Exemestane	Ridaforolimus + Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Weeks				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (60.6 to 9999)		

Statistical analyses

Statistical analysis title	OS: HR Comparison of Treatment

Statistical analysis description:

HR and p-value for treatment difference based on Cox regression model with Efron tie handling for treatment comparison (Ridaforolimus + Dalotuzumab + Exemestane arm versus Ridaforolimus + Exemestane arm).

Comparison groups	Ridaforolimus + Dalotuzumab + Exemestane v Ridaforolimus + Exemestane
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.562
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	4.13

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 through Post Treatment visit at 4 weeks after last dose of treatment (up to ~17 months)

Adverse event reporting additional description:

All randomized participants who received at least one dose of study treatment. For nine participants who continued to receive treatment under compassionate use after database lock, safety data was not included in any study database but was reported to global safety.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Ridaforolimus + Dalotuzumab + Exemestane

Reporting group description:

Participants receive ridaforolimus 10 mg orally (PO) every 5 days (QD x 5) plus dalotuzumab 10 mg/kg intravenously (IV) every week (QW) plus exemestane 25 mg PO every day (QD) in 28-day cycles until documented disease progression or unacceptable toxicity.

Reporting group title	Ridaforolimus + Exemestane

Reporting group description:

Participants received ridaforolimus 30 mg PO QD x 5 plus exemestane 25 mg PO QD treatment in 28-day cycles until documented disease progression or unacceptable toxicity.

Serious adverse events	Ridaforolimus + Dalotuzumab + Exemestane	Ridaforolimus + Exemestane	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 39 (20.51%)	17 / 40 (42.50%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	1 / 39 (2.56%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			

Oesophagitis chemical			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sinus tachycardia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 39 (2.56%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice cholestatic			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
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			
Hydropneumothorax			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 39 (2.56%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mood altered			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
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			
Chondrocalcinosis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ridaforolimus + Dalotuzumab + Exemestane	Ridaforolimus + Exemestane	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 39 (100.00%)	40 / 40 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 39 (5.13%)	4 / 40 (10.00%)	
occurrences (all)	2	5	
Lymphoedema			
subjects affected / exposed	1 / 39 (2.56%)	4 / 40 (10.00%)	
occurrences (all)	1	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 39 (25.64%)	14 / 40 (35.00%)	
occurrences (all)	13	15	
Chest pain			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	4	
Chills			
subjects affected / exposed	2 / 39 (5.13%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Fatigue			
subjects affected / exposed	11 / 39 (28.21%)	7 / 40 (17.50%)	
occurrences (all)	13	9	
Local swelling			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Oedema peripheral			

subjects affected / exposed	3 / 39 (7.69%)	10 / 40 (25.00%)	
occurrences (all)	6	12	
Pyrexia			
subjects affected / exposed	4 / 39 (10.26%)	5 / 40 (12.50%)	
occurrences (all)	7	5	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	2 / 39 (5.13%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 39 (20.51%)	10 / 40 (25.00%)	
occurrences (all)	10	13	
Dyspnoea			
subjects affected / exposed	4 / 39 (10.26%)	8 / 40 (20.00%)	
occurrences (all)	4	10	
Epistaxis			
subjects affected / exposed	10 / 39 (25.64%)	4 / 40 (10.00%)	
occurrences (all)	15	7	
Interstitial lung disease			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Oropharyngeal pain			
subjects affected / exposed	2 / 39 (5.13%)	3 / 40 (7.50%)	
occurrences (all)	2	3	
Pneumonitis			
subjects affected / exposed	2 / 39 (5.13%)	3 / 40 (7.50%)	
occurrences (all)	2	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 39 (2.56%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Insomnia			
subjects affected / exposed	0 / 39 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	4	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	3 / 39 (7.69%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 39 (15.38%)	3 / 40 (7.50%)	
occurrences (all)	9	3	
Blood cholesterol increased			
subjects affected / exposed	2 / 39 (5.13%)	4 / 40 (10.00%)	
occurrences (all)	2	5	
Neutrophil count decreased			
subjects affected / exposed	1 / 39 (2.56%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Platelet count decreased			
subjects affected / exposed	1 / 39 (2.56%)	5 / 40 (12.50%)	
occurrences (all)	1	5	
Weight decreased			
subjects affected / exposed	3 / 39 (7.69%)	6 / 40 (15.00%)	
occurrences (all)	3	6	
White blood cell count decreased			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 39 (2.56%)	6 / 40 (15.00%)	
occurrences (all)	1	7	
Dysgeusia			
subjects affected / exposed	14 / 39 (35.90%)	6 / 40 (15.00%)	
occurrences (all)	16	6	
Headache			
subjects affected / exposed	6 / 39 (15.38%)	13 / 40 (32.50%)	
occurrences (all)	6	18	
Neuropathy peripheral			
subjects affected / exposed	2 / 39 (5.13%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Tremor			

subjects affected / exposed	2 / 39 (5.13%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 39 (15.38%)	9 / 40 (22.50%)	
occurrences (all)	8	11	
Leukopenia			
subjects affected / exposed	1 / 39 (2.56%)	3 / 40 (7.50%)	
occurrences (all)	1	5	
Neutropenia			
subjects affected / exposed	3 / 39 (7.69%)	3 / 40 (7.50%)	
occurrences (all)	4	6	
Thrombocytopenia			
subjects affected / exposed	1 / 39 (2.56%)	3 / 40 (7.50%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 39 (15.38%)	4 / 40 (10.00%)	
occurrences (all)	7	7	
Abdominal pain upper			
subjects affected / exposed	4 / 39 (10.26%)	2 / 40 (5.00%)	
occurrences (all)	4	2	
Constipation			
subjects affected / exposed	7 / 39 (17.95%)	8 / 40 (20.00%)	
occurrences (all)	7	11	
Diarrhoea			
subjects affected / exposed	14 / 39 (35.90%)	15 / 40 (37.50%)	
occurrences (all)	31	28	
Dry mouth			
subjects affected / exposed	3 / 39 (7.69%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Dyspepsia			
subjects affected / exposed	1 / 39 (2.56%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 39 (2.56%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	9 / 39 (23.08%)	9 / 40 (22.50%)	
occurrences (all)	18	11	
Oral pain			
subjects affected / exposed	3 / 39 (7.69%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Stomatitis			
subjects affected / exposed	30 / 39 (76.92%)	36 / 40 (90.00%)	
occurrences (all)	54	88	
Toothache			
subjects affected / exposed	1 / 39 (2.56%)	3 / 40 (7.50%)	
occurrences (all)	1	4	
Vomiting			
subjects affected / exposed	8 / 39 (20.51%)	8 / 40 (20.00%)	
occurrences (all)	20	8	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Dermatitis acneiform			
subjects affected / exposed	2 / 39 (5.13%)	3 / 40 (7.50%)	
occurrences (all)	2	4	
Dry skin			
subjects affected / exposed	3 / 39 (7.69%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Erythema			
subjects affected / exposed	2 / 39 (5.13%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Nail disorder			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	4	
Onycholysis			
subjects affected / exposed	2 / 39 (5.13%)	2 / 40 (5.00%)	
occurrences (all)	2	2	

Pruritus			
subjects affected / exposed	1 / 39 (2.56%)	5 / 40 (12.50%)	
occurrences (all)	2	7	
Rash			
subjects affected / exposed	8 / 39 (20.51%)	8 / 40 (20.00%)	
occurrences (all)	12	13	
Skin lesion			
subjects affected / exposed	1 / 39 (2.56%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 39 (12.82%)	5 / 40 (12.50%)	
occurrences (all)	6	6	
Back pain			
subjects affected / exposed	2 / 39 (5.13%)	6 / 40 (15.00%)	
occurrences (all)	2	7	
Bone pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Joint swelling			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Muscle spasms			
subjects affected / exposed	7 / 39 (17.95%)	1 / 40 (2.50%)	
occurrences (all)	7	1	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 39 (5.13%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Myalgia			
subjects affected / exposed	4 / 39 (10.26%)	2 / 40 (5.00%)	
occurrences (all)	4	2	
Pain in extremity			

subjects affected / exposed	1 / 39 (2.56%)	6 / 40 (15.00%)	
occurrences (all)	1	8	
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Cystitis			
subjects affected / exposed	4 / 39 (10.26%)	0 / 40 (0.00%)	
occurrences (all)	4	0	
Gingivitis			
subjects affected / exposed	2 / 39 (5.13%)	2 / 40 (5.00%)	
occurrences (all)	2	3	
Herpes zoster			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Nasopharyngitis			
subjects affected / exposed	3 / 39 (7.69%)	3 / 40 (7.50%)	
occurrences (all)	4	5	
Upper respiratory tract infection			
subjects affected / exposed	1 / 39 (2.56%)	6 / 40 (15.00%)	
occurrences (all)	2	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 39 (38.46%)	11 / 40 (27.50%)	
occurrences (all)	16	13	
Hypercholesterolaemia			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Hyperglycaemia			
subjects affected / exposed	11 / 39 (28.21%)	10 / 40 (25.00%)	
occurrences (all)	14	20	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 39 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2013	Global Amendment 3 (AM3) reduced the sample size of the protocol from 150 participants to approximately 84 participants, updated the safety analysis, and removed the interim efficacy analysis.
05 August 2014	Global Amendment 4 (AM4) ended further efficacy measurements on study, revised safety monitoring to include only serious adverse events, and ended survival follow-up on study as a result of study objectives having been met. Participants receiving study medication could continue to be treated at the discretion of the investigator until disease progression or unacceptable toxicity, subject to availability of study medications and not to exceed 2-3 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported