



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 | v1 |
| This version publication date | 07 March 2019 |
| First version publication date | 07 March 2019 |

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 standard deviation | 60.7 ± 9.0 | 57.7 ± 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)

| | |
|--|---------------------------------|
| End point title | Progression-free Survival (PFS) |
| End point description: PFS was defined as the time from randomization to progressive disease, or death, whichever occurs first. Response was assessed according to Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by a blinded independent central review (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 analyzed using the Kaplan-Meier method and median PFS (95% confidence interval [CI]) in weeks was reported for each treatment arm. All randomized participants were analyzed. | |
| End point type | Primary |
| End point timeframe: From Day 1 through post-study follow-up visit (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])

| | |
|-----------------|--|
| End point title | Percentage of Participants with Objective Response (Objective Response Rate [ORR]) |
|-----------------|--|

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. All randomized participants were analyzed.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Day 1 through post-study follow-up visit (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 analyzed using the Kaplan-Meier method and median OS (95% confidence interval [CI]) in months was reported for each treatment arm. All randomized participants were analyzed. 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 post-study follow-up visit (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:

Up to 30 days after last dose of treatment (up to 15.83 months)

Adverse event reporting additional description:

All randomized participants who received at least one dose of study treatment and had data up to the 29-April-2014 database lock. 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 | | | |

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

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

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | 1 / 40 (2.50%) 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 occurrences (all) | 1 / 39 (2.56%) 1 | 6 / 40 (15.00%) 8 | |
| Infections and infestations Cellulitis subjects affected / exposed occurrences (all) Cystitis subjects affected / exposed occurrences (all) Gingivitis subjects affected / exposed occurrences (all) Herpes zoster subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 4 / 39 (10.26%) 4 2 / 39 (5.13%) 2 0 / 39 (0.00%) 0 3 / 39 (7.69%) 4 1 / 39 (2.56%) 2 | 0 / 40 (0.00%) 0 0 / 40 (0.00%) 0 2 / 40 (5.00%) 3 3 / 40 (7.50%) 3 3 / 40 (7.50%) 5 6 / 40 (15.00%) 6 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypercholesterolaemia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 15 / 39 (38.46%) 16 0 / 39 (0.00%) 0 11 / 39 (28.21%) 14 0 / 39 (0.00%) 0 | 11 / 40 (27.50%) 13 3 / 40 (7.50%) 3 10 / 40 (25.00%) 20 3 / 40 (7.50%) 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