



Clinical trial results:

Phase 3B, Randomized Trail of Revlimid® (Lenalidomide) Versus Placebo Maintenance Therapy Following Melphalan Prednisone Velcade (Bortezomib) Induction Therapy In Newly Diagnosed Multiple Myeloma Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2013-001729-26 |
| Trial protocol | BE ES IT FR GR |
| Global end of trial date | 12 October 2020 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v2 (current) |
| This version publication date | 29 April 2023 |
| First version publication date | 28 October 2021 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | CC-5013-MM-026 |
|-----------------------|----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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 | 12 October 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 October 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Investigate efficacy and safety of maintenance therapy with lenalidomide versus placebo after melphalan prednisone Velcade (MPV) induction therapy in subjects with newly-diagnosed multiple myeloma (NDMM)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 20 May 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 6 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | France: 18 |
| Country: Number of subjects enrolled | Italy: 16 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Greece: 4 |
| Country: Number of subjects enrolled | Belgium: 2 |
| Worldwide total number of subjects | 46 |
| EEA total number of subjects | 46 |

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) | 1 |
| From 65 to 84 years | 45 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

46 participants randomized and treated

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 | Lenalidomide |

Arm description:

10mg/day PO from Days 1 to 21 (given in 28-day cycles)

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

Dosage and administration details:

10mg/day from Days 1 to 21 (given in 28-day cycles)

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo PO from Days 1 to 21 (given in 28-day cycles)

| | |
|--|----------|
| 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:

PO from Days 1 to 21 (given in 28-day cycles)

| Number of subjects in period 1 | Lenalidomide | Placebo |
|--------------------------------|--------------|---------|
| Started | 29 | 17 |
| Completed | 0 | 0 |
| Not completed | 29 | 17 |
| Adverse event, serious fatal | 17 | 7 |
| Consent withdrawn by subject | 1 | 1 |
| Adverse event, non-fatal | 1 | - |

| | | |
|-----------------------------|----|---|
| Progressive Disease | - | 1 |
| Study Terminated by Sponsor | 10 | 8 |

Baseline characteristics

Reporting groups

| | |
|--|--------------|
| Reporting group title | Lenalidomide |
| Reporting group description: | |
| 10mg/day PO from Days 1 to 21 (given in 28-day cycles) | |

| | |
|---|---------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo PO from Days 1 to 21 (given in 28-day cycles) | |

| Reporting group values | Lenalidomide | Placebo | Total |
|--|--------------|---------|-------|
| Number of subjects | 29 | 17 | 46 |
| 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) | 0 | 1 | 1 |
| From 65-84 years | 29 | 16 | 45 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 73.1 | 72.9 | |
| standard deviation | ± 4.41 | ± 6.77 | - |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 8 | 5 | 13 |
| Male | 21 | 12 | 33 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 17 | 9 | 26 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 12 | 8 | 20 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 4 | 1 | 5 |
| Not Hispanic or Latino | 13 | 8 | 21 |
| Unknown or Not Reported | 12 | 8 | 20 |

End points

End points reporting groups

| | |
|--|--------------|
| Reporting group title | Lenalidomide |
| Reporting group description: 10mg/day PO from Days 1 to 21 (given in 28-day cycles) | |
| Reporting group title | Placebo |
| Reporting group description: Placebo PO from Days 1 to 21 (given in 28-day cycles) | |

Primary: Overall Survival (OS)

| | |
|---|--------------------------------------|
| End point title | Overall Survival (OS) ^[1] |
| End point description: Overall Survival is defined as the time from the date of randomization to the date of death due to any cause. | |
| End point type | Primary |
| End point timeframe: Up to 76 months | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only summary statistics planned for this endpoint

| End point values | Lenalidomide | Placebo | | |
|----------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 17 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 52.5 (39.1 to 99999) | 99999 (30.1 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Participants with Adverse Events (AEs)

| | |
|--|---|
| End point title | Incidence of Participants with Adverse Events (AEs) |
| End point description: Incidence of participants with adverse events (AEs) that measure type, frequency and severity of AEs graded by National Cancer Institute Common Terminology Criteria (NCI CTCAE V 4.0) including any grade adverse events (AEs), Grade 3-4 AEs, AEs related to study drug, grade 3-4 AEs related to study drug, any grade serious adverse events (SAEs), and SAEs related to study drug. | |
| End point type | Secondary |
| End point timeframe: From first dose to up to 28 days post last dose (Up to 44 months) | |

| End point values | Lenalidomide | Placebo | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 17 | | |
| Units: Participants | | | | |
| Adverse Events (AEs) | 29 | 15 | | |
| Grade 3-4 AEs | 20 | 5 | | |
| AEs related to Study Drug | 22 | 6 | | |
| Grade 3-4 AEs related to Study Drug | 11 | 2 | | |
| Serious Adverse Events (SAEs) | 15 | 4 | | |
| SAEs related to Study Drug | 9 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Participants with Laboratory Abnormalities Shift from Baseline to Worst During Treatment

| | |
|-----------------|---|
| End point title | Incidence of Participants with Laboratory Abnormalities Shift from Baseline to Worst During Treatment |
|-----------------|---|

End point description:

Incidence of participants with laboratory abnormalities shift from baseline to worst during treatment in Hematology and Chemistry. Normal ranges will be used to determine the categories of high, low, and normal for lab tests that have no severity grade. low=participants with at least one value that was low relative to the normal range high=participants with at least one values that was high relative to the normal range both low and high=participants with at least one value that was low relative to the normal range and at least one value that was high relative to the normal range.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 44 months

| End point values | Lenalidomide | Placebo | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 17 | | |
| Units: Participants | | | | |
| Absolute neutrophils (Normal) | 17 | 4 | | |
| Hemoglobin (Low) | 1 | 0 | | |
| Hemoglobin (Normal) | 10 | 2 | | |
| Platelets (Low) | 1 | 1 | | |
| Platelets (Normal) | 10 | 2 | | |
| White Blood Cell Count (Low) | 2 | 0 | | |
| White Blood Cell Count (Normal) | 14 | 4 | | |
| Corrected Serum Calcium (Normal) | 11 | 3 | | |
| Corrected Serum Calcium (High) | 1 | 0 | | |
| Creatinine Clearance (Normal) | 11 | 2 | | |

| | | | | |
|-----------------------------|----|---|--|--|
| Creatinine Clearance (High) | 1 | 0 | | |
| Serum Calcium (Low) | 0 | 1 | | |
| Serum Calcium (Normal) | 15 | 1 | | |
| Serum Creatinine (Low) | 1 | 0 | | |
| Serum Creatinine (Normal) | 11 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Participants with Vital Signs Abnormalities Shift from Baseline to Worst During Treatment

| | |
|-----------------|--|
| End point title | Incidence of Participants with Vital Signs Abnormalities Shift from Baseline to Worst During Treatment |
|-----------------|--|

End point description:

Incidence of participant with vital signs abnormalities shift from baseline to worst during treatment. Assessment is based on shift from normal and abnormal baseline categories. Normal range= ; 90 <= Systolic Blood pressure <= 120 (mmHg) ; 60 <= Diastolic Blood Pressure <= 80 (mmHg) ; 60 <= Pulse <= 100 (beats/min) ; 36.6 <= Temperature < 37.3 (°C)

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 44 months

| End point values | Lenalidomide | Placebo | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 17 | | |
| Units: Participants | | | | |
| Diastolic Blood Pressure (Normal) | 15 | 8 | | |
| Diastolic Blood Pressure (Abnormal) | 2 | 0 | | |
| Systolic Blood Pressure (Normal) | 9 | 3 | | |
| Systolic Blood Pressure (Abnormal) | 1 | 0 | | |
| Pulse (Normal) | 12 | 2 | | |
| Pulse (Abnormal) | 1 | 0 | | |
| Temperature (Normal) | 6 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Participants with Second Primary Malignancies (SPMs)

| | |
|-----------------|---|
| End point title | Incidence of Participants with Second Primary Malignancies (SPMs) |
|-----------------|---|

End point description:

Incidence of participants with second primary malignancies (SPMs) including all SPMs, Invasive SPMs (hematologic malignancies and solid tumors), and non-invasive SPMs (non-melanoma skin cancers).

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 76 months | |

| End point values | Lenalidomide | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 17 | | |
| Units: Participants | | | | |
| All SPMs | 6 | 1 | | |
| Invasive SPMs | 5 | 1 | | |
| Non-Invasive SPMs | 1 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose to up to 28 days post last dose (Up to 44 months)

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|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

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|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo PO from Days 1 to 21 (given in 28-day cycles) until documented progression disease

| | |
|-----------------------|--------------|
| Reporting group title | Lenalidomide |
|-----------------------|--------------|

Reporting group description:

10mg/day PO from Days 1 to 21 (given in 28-day cycles) until documented progression disease

| Serious adverse events | Placebo | Lenalidomide | |
|---|-----------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 15 / 29 (51.72%) | |
| number of deaths (all causes) | 8 | 17 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon neoplasm | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic bronchial carcinoma | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal cancer metastatic | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |

| | | | |
|--|----------------|----------------|--|
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| 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 | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial prostatitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine infection | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 1 / 29 (3.45%) | |
| 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 | Placebo | Lenalidomide | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 17 (82.35%) | 27 / 29 (93.10%) | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 3 / 29 (10.34%) | |
| occurrences (all) | 1 | 3 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 29 (10.34%) | |
| occurrences (all) | 0 | 3 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 5 / 29 (17.24%) | |
| occurrences (all) | 4 | 7 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 13 / 29 (44.83%) | |
| occurrences (all) | 0 | 22 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 29 (13.79%) | |
| occurrences (all) | 3 | 5 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 3 / 29 (10.34%) | |
| occurrences (all) | 4 | 3 | |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 29 (6.90%) | |
| occurrences (all) | 0 | 2 | |

| | | | |
|--|---|--|--|
| Prostatitis subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 29 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Productive cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 2 / 17 (11.76%) 2 5 / 17 (29.41%) 5 | 2 / 29 (6.90%) 2 2 / 29 (6.90%) 4 5 / 29 (17.24%) 8 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 2 / 29 (6.90%) 3 | |
| Investigations Blood pressure increased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 2 1 / 17 (5.88%) 1 1 / 17 (5.88%) 2 | 0 / 29 (0.00%) 0 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 | |
| Nervous system disorders Cervicobrachial syndrome subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Paraesthesia | 1 / 17 (5.88%) 1 0 / 17 (0.00%) 0 | 0 / 29 (0.00%) 0 4 / 29 (13.79%) 4 | |

| | | | |
|---|----------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 3 | 0 / 29 (0.00%) 0 | |
| Restless legs syndrome subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 29 (0.00%) 0 | |
| Sciatica subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 29 (6.90%) 2 | |
| Somnolence subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 2 / 29 (6.90%) 2 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 4 | 3 / 29 (10.34%) 4 | |
| Neutropenia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 11 / 29 (37.93%) 27 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 29 (6.90%) 4 | |
| Eye disorders Diabetic retinopathy subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 29 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 2 / 29 (6.90%) 2 | |
| Diverticulum subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | 0 / 29 (0.00%) 0 | |
| Dry mouth subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 29 (3.45%) 1 | |
| Enterocolitis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 8 / 29 (27.59%) | |
| occurrences (all) | 1 | 10 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Gastrointestinal angiectasia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 7 / 29 (24.14%) | |
| occurrences (all) | 6 | 19 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 29 (13.79%) | |
| occurrences (all) | 1 | 4 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 29 (10.34%) | |
| occurrences (all) | 0 | 3 | |
| Rash | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 3 / 29 (10.34%) | |
| occurrences (all) | 0 | 6 | |
| Ingrowing nail | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 3 / 29 (10.34%) | |
| occurrences (all) | 5 | 4 | |
| Erythema | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 2 / 29 (6.90%) | |
| occurrences (all) | 2 | 2 | |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 2 / 29 (6.90%) | |
| occurrences (all) | 2 | 3 | |
| Bone pain | | | |
| subjects affected / exposed | 4 / 17 (23.53%) | 0 / 29 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Back pain | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 5 / 29 (17.24%) | |
| occurrences (all) | 4 | 7 | |
| Muscle contracture | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 4 / 29 (13.79%) | |
| occurrences (all) | 2 | 9 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 29 (6.90%) | |
| occurrences (all) | 1 | 2 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Spinal pain | | | |

| | | | |
|--|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 3 | 1 / 29 (3.45%) 1 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 8 / 29 (27.59%) | |
| occurrences (all) | 4 | 13 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 29 (6.90%) | |
| occurrences (all) | 1 | 2 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 4 / 29 (13.79%) | |
| occurrences (all) | 2 | 4 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 4 / 29 (13.79%) | |
| occurrences (all) | 1 | 5 | |
| Influenza | | | |
| subjects affected / exposed | 3 / 17 (17.65%) | 6 / 29 (20.69%) | |
| occurrences (all) | 3 | 6 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 2 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | 2 / 29 (6.90%) | |
| occurrences (all) | 0 | 3 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 29 (6.90%) | |
| occurrences (all) | 1 | 2 | |
| Metabolism and nutrition disorders | | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 17 (5.88%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Decreased appetite | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 17 (5.88%) | 2 / 29 (6.90%) | |
| occurrences (all) | 1 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 27 November 2013 | Study Design Update |
| 06 March 2014 | Study Endpoints Update |
| 31 October 2014 | Exclusion and Inclusion Criteria Update |
| 30 August 2015 | Study Design Update |
| 22 November 2017 | Study Design and Endpoints Update |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported