



Clinical trial results:

A Study in Japan and Ex-Japan to Characterize the Pharmacokinetic and Pharmacodynamic Response to Orteronel (TAK-700) in Chemotherapy-Naïve Patients With Castration-Resistant Prostate Cancer

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2012-001539-30 |
| Trial protocol | IE GR GB NL |
| Global end of trial date | 01 September 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 06 February 2018 |
| First version publication date | 06 February 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | C21013 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01666314 |
| WHO universal trial number (UTN) | U1111-1179-5750 |

Notes:

Sponsors

| | |
|------------------------------|---------------------------------------------------------------------------------------------|
| Sponsor organisation name | Takeda |
| Sponsor organisation address | One Takeda Parkway, Deerfield, IL, Japan, 60015 |
| Public contact | Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com |
| Scientific contact | Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.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 | 01 September 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 September 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine whether orteronel plus prednisone more effectively reduces serum testosterone levels, compared to placebo plus prednisone when administered to subjects in Japan.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|----------------|
| Actual start date of recruitment | 20 August 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Japan: 65 |
| Country: Number of subjects enrolled | Australia: 8 |
| Country: Number of subjects enrolled | Greece: 10 |
| Country: Number of subjects enrolled | Ireland: 13 |
| Country: Number of subjects enrolled | Netherlands: 13 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | United States: 25 |
| Worldwide total number of subjects | 137 |
| EEA total number of subjects | 39 |

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) | 32 |
| From 65 to 84 years | 101 |
| 85 years and over | 4 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 43 investigative sites in Japan, United States, Greece, Australia, Netherlands, Ireland and United Kingdom from 20 August 2012 to 01 September 2016.

Pre-assignment

Screening details:

Male participants with a diagnosis of adenocarcinoma of the prostate were enrolled in the study. In Japan, participants were randomized to 200 mg orteronel, Placebo, 300 mg orteronel, or Placebo, BID, in a ratio of 2:1:2:1; ex-Japan participants were randomized to 200 mg orteronel, Placebo, 400 mg orteronel, or Placebo, BID, in a ratio of 2:1:2:1.

Period 1

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

Arms

| | |
|------------------------------|------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo + Orteronel 200 mg (Japan) |

Arm description:

Orteronel placebo-matching tablets or Orteronel 200 mg, tablets, orally, twice daily (BID) in Cycle 1 (28 days) followed by orteronel 200 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 3 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily continuously throughout the study.

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

Dosage and administration details:

Orteronel placebo-matching 200 mg tablets, orally, twice daily in Cycle 1 (28 days) in Japan for up to 2.5 years.

| | |
|----------------------------------------|-----------|
| Investigational medicinal product name | Orteronel |
| Investigational medicinal product code | TAK-700 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Orteronel 200 mg, tablets, orally, twice daily in 28-day cycles in Japan for up to 2.5 years.

| | |
|------------------|------------------------------------|
| Arm title | Placebo + Orteronel 300 mg (Japan) |
|------------------|------------------------------------|

Arm description:

Orteronel placebo-matching tablets or Orteronel 300 mg, tablets, orally, twice daily in Cycle 1 followed by orteronel 300 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 2.8 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|----------------------------------------|-----------|
| Investigational medicinal product name | Orteronel |
| Investigational medicinal product code | TAK-700 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Orteronel 300 mg tablets, orally, twice daily in Cycle 1 in 28-day cycles in Japan for up to 2.5 years.

| | |
|----------------------------------------|----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Orteronel placebo-matching 300 mg tablets, orally, twice daily in Cycle 1 in 28-day cycles in Japan for up to 2.5 years.

| | |
|------------------|---------------------------------------|
| Arm title | Placebo + Orteronel 200 mg (Ex-Japan) |
|------------------|---------------------------------------|

Arm description:

Orteronel placebo-matching tablets, or Orteronel 200 mg, tablets, orally, twice daily in Cycle 1 followed by orteronel 200 mg, tablets, orally, twice daily in 28 day cycles outside of Japan (Ex-Japan) for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|----------------------------------------|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Orteronel |
| Investigational medicinal product code | TAK-700 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Orteronel 200 mg tablets, orally, twice daily in 28-day cycles outside of Japan (Ex-Japan) for up to 2.5 years.

| | |
|----------------------------------------|----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Orteronel placebo-matching 200 mg tablets, orally, twice daily in Cycle 1 outside of Japan (Ex-Japan) for up to 2.5 years.

| | |
|------------------|---------------------------------------|
| Arm title | Placebo + Orteronel 400 mg (Ex-Japan) |
|------------------|---------------------------------------|

Arm description:

Orteronel placebo-matching tablets, or Orteronel 400 mg, tablets, orally, twice daily in Cycle 1 followed by orteronel 400 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

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

Dosage and administration details:

Orteronel placebo-matching 400 mg tablets, orally, twice daily in Cycle 1 Ex-Japan for up to 2.5 years.

| | |
|----------------------------------------|-----------|
| Investigational medicinal product name | Orteronel |
| Investigational medicinal product code | TAK-700 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Orteronel 400 mg, tablets, orally, twice daily in 28-day cycles Ex-Japan for up to 2.5.years.

| Number of subjects in period 1 | Placebo + Orteronel 200 mg (Japan) | Placebo + Orteronel 300 mg (Japan) | Placebo + Orteronel 200 mg (Ex-Japan) |
|---------------------------------------|---------------------------------------|---------------------------------------|------------------------------------------|
| Started | 33 | 32 | 36 |
| Completed | 0 | 0 | 0 |
| Not completed | 33 | 32 | 36 |
| Unsatisfactory Therapeutic Response | 7 | 2 | 1 |
| Consent withdrawn by subject | 1 | 1 | 2 |
| Adverse event, non-fatal | 3 | 13 | 7 |
| Progressive Disease | 11 | 9 | 19 |
| Symptomatic Deterioration | 1 | - | 2 |
| Reason not Specified | 10 | 7 | 5 |

| Number of subjects in period 1 | Placebo + Orteronel 400 mg (Ex-Japan) |
|---------------------------------------|------------------------------------------|
| Started | 36 |
| Completed | 0 |
| Not completed | 36 |
| Unsatisfactory Therapeutic Response | 1 |
| Consent withdrawn by subject | 3 |
| Adverse event, non-fatal | 7 |
| Progressive Disease | 20 |
| Symptomatic Deterioration | - |
| Reason not Specified | 5 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|-------------------------------------------------------|---------------|-------|--|
| Number of subjects | 137 | 137 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 32 | 32 | |
| From 65-84 years | 101 | 101 | |
| 85 years and over | 4 | 4 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 70.6 | | |
| full range (min-max) | 49 to 88 | - | |
| Gender, Male/Female | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 137 | 137 | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | |
| Not Hispanic or Latino | 136 | 136 | |
| Unknown or Not Reported | 0 | 0 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 70 | 70 | |
| Black or African American | 2 | 2 | |
| Asian - Japanese | 65 | 65 | |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Japan | 65 | 65 | |
| Australia | 8 | 8 | |
| Greece | 10 | 10 | |
| Ireland | 13 | 13 | |
| Netherlands | 13 | 13 | |
| United Kingdom | 3 | 3 | |
| United States | 25 | 25 | |

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------|--------------------------|---|--|
| Study Specific Characteristic Height Units: cm arithmetic mean full range (min-max) | 169.29 151.0 to 189.0 | - | |
| Study Specific Characteristic Weight Units: kg arithmetic mean full range (min-max) | 77.77 44.7 to 134.6 | - | |
| Study Specific Characteristic Body Mass Index (BMI) Units: kg/m ² arithmetic mean full range (min-max) | 26.96 16.7 to 40.3 | - | |

End points

End points reporting groups

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| Reporting group title | Placebo + Orteronel 200 mg (Japan) |
| Reporting group description: Orteronel placebo-matching tablets or Orteronel 200 mg, tablets, orally, twice daily (BID) in Cycle 1 (28 days) followed by orteronel 200 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 3 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily continuously throughout the study. | |
| Reporting group title | Placebo + Orteronel 300 mg (Japan) |
| Reporting group description: Orteronel placebo-matching tablets or Orteronel 300 mg, tablets, orally, twice daily in Cycle 1 followed by orteronel 300 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 2.8 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Reporting group title | Placebo + Orteronel 200 mg (Ex-Japan) |
| Reporting group description: Orteronel placebo-matching tablets, or Orteronel 200 mg, tablets, orally, twice daily in Cycle 1 followed by orteronel 200 mg, tablets, orally, twice daily in 28 day cycles outside of Japan (Ex-Japan) for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Reporting group title | Placebo + Orteronel 400 mg (Ex-Japan) |
| Reporting group description: Orteronel placebo-matching tablets, or Orteronel 400 mg, tablets, orally, twice daily in Cycle 1 followed by orteronel 400 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 200 mg (Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 3 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 300 mg (Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel 300 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 2.8 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 200 mg (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 400 mg (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel 400 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Placebo (Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel placebo-matching tablets, orally, twice daily in Cycle 1. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Subject analysis set title | Placebo (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel placebo-matching tablets, orally, twice daily in Cycle 1. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Placebo (Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel placebo-matching tablets, orally, twice daily in Cycle 1 (28 days). Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Placebo (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel placebo-matching tablets, orally, twice daily in Cycle 1. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 200 mg (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 400 mg (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel 400 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 200 mg (Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 3 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 300 mg (Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel 300 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 2.8 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 200 mg (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 400 mg (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Orteronel 400 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study. | |
| Subject analysis set title | Orteronel 200 mg (Japan) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 3 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Orteronel 300 mg (Japan) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Orteronel 300 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 2.8 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Orteronel 200 mg (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Orteronel 400 mg (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Orteronel 400 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Orteronel 200 mg (Ex-Japan) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|----------------------------|---------------------------------------|
| Subject analysis set title | Orteronel 200 mg (Japan and ex-Japan) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles in Japan and ex-Japan for up to 3 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

Primary: Percentage of Participants with Serum Testosterone Levels Reduced to ≤ 2 ng/dL After 4 Weeks of Treatment in Japan

| | |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with Serum Testosterone Levels Reduced to ≤ 2 ng/dL After 4 Weeks of Treatment in Japan |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

Serum Ultra-sensitive testosterone was measured by liquid chromatography at a central laboratory.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and Week 4

| End point values | Orteronel 300 mg (Japan) | Placebo (Japan) | | |
|-----------------------------------|--------------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 22 | 21 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 100.0 (84.6 to 100.0) | 86.0 (63.7 to 97.0) | | |

Statistical analyses

| | |
|-----------------------------------------|--------------------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Placebo (Japan) v Orteronel 300 mg (Japan) |
| Number of subjects included in analysis | 43 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1078 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Serum Testosterone Levels Reduced to ≤ 2 ng/dL in Ex-Japan

| | |
|------------------------|---------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with Serum Testosterone Levels Reduced to ≤ 2 ng/dL in Ex-Japan |
| End point description: | Serum Ultra-sensitive testosterone was measured by liquid chromatography at a central laboratory. |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 4 |

| | | | | |
|-----------------------------------|-----------------------------|----------------------|--|--|
| End point values | Orteronel 400 mg (Ex-Japan) | Placebo (Ex-Japan) | | |
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 24 | 23 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 79.0 (57.8 to 92.9) | 48.0 (26.8 to 69.4) | | |

Statistical analyses

| | |
|-----------------------------------------|--------------------------------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo (Ex-Japan) v Orteronel 400 mg (Ex-Japan) |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0355 |
| Method | Fisher exact |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 4.145 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9895 |
| upper limit | 18.7606 |

Secondary: Percent Change from Baseline in Serum Testosterone Level after 4 Weeks of Treatment

| | |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| End point title | Percent Change from Baseline in Serum Testosterone Level after 4 Weeks of Treatment |
| End point description: Serum Ultra-sensitive testosterone was measured by liquid chromatography at a central laboratory. | |
| End point type | Secondary |
| End point timeframe: Baseline and Week 4 | |

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|--------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 21 | 22 |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -97.245 (± 1.2548) | -96.812 (± 2.7055) | -86.268 (± 37.2015) | -53.954 (± 118.8050) |

| End point values | Placebo (Japan) | Placebo (Ex-Japan) | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 20 | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -87.666 (± 10.4250) | -63.702 (± 43.3941) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Serum Testosterone Level after 12 Weeks of Treatment

| | |
|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| End point title | Percent Change from Baseline in Serum Testosterone Level after 12 Weeks of Treatment |
| End point description: Serum Ultra-sensitive testosterone was measured by liquid chromatography at a central laboratory. | |
| End point type | Secondary |

End point timeframe:
Baseline and Week 12

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|--------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 31 | 26 | 28 | 31 |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -95.804 (\pm 5.3367) | -95.703 (\pm 5.7468) | -91.311 (\pm 17.5217) | -14.442 (\pm 406.3116) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Prostate-Specific Antigen Reduction \geq 50% (PSA50) after 4 Weeks of Treatment

| | |
|------------------------|-------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with Prostate-Specific Antigen Reduction \geq 50% (PSA50) after 4 Weeks of Treatment |
| End point description: | A 50% PSA response rate (PSA50) was defined as PSA reduction \geq 50% from Baseline. |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 4 |

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-----------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 50.0 (28.2 to 71.8) | 41.0 (20.7 to 63.6) | 48.0 (27.8 to 68.7) | 46.0 (25.6 to 67.2) |

| End point values | Placebo (Japan) | Placebo (Ex-Japan) | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 23 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 48.0 (25.7 to 70.2) | 17.0 (5.0 to 38.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with PSA50 after 12 Weeks of Treatment

| | |
|------------------------|----------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with PSA50 after 12 Weeks of Treatment |
| End point description: | A 50% PSA response rate (PSA50) was defined as PSA reduction \geq 50% from Baseline. |
| End point type | Secondary |
| End point timeframe: | Baseline and Week 12 |

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-----------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 33 | 32 | 36 | 36 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 55.0 (36.4 to 71.9) | 47.0 (29.1 to 65.3) | 56.0 (38.1 to 72.1) | 44.0 (27.9 to 61.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Values for Testosterone

| | |
|------------------------|---------------------------------------------------------------------------------------------------|
| End point title | Absolute Values for Testosterone |
| End point description: | Serum Ultra-sensitive testosterone was measured by liquid chromatography at a central laboratory. |
| End point type | Secondary |
| End point timeframe: | Baseline, Cycle 1 Day 8 and Cycle 2 Day 1 |

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: ng/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 9.079 (\pm 4.4581) | 10.148 (\pm 4.6504) | 9.263 (\pm 5.6572) | 14.588 (\pm 13.9833) |
| Cycle 1 Day 8 (n=22, 22, 20, 21, 20, 19) | 0.213 (\pm 0.0449) | 0.251 (\pm 0.1727) | 0.345 (\pm 0.2770) | 6.658 (\pm 20.4347) |
| Cycle 2 Day 1 (n=22, 22, 21, 22, 21, 20) | 0.203 (\pm 0.0145) | 0.270 (\pm 0.2311) | 0.266 (\pm 0.1837) | 11.720 (\pm 45.1753) |

| End point values | Placebo (Japan) | Placebo (Ex-Japan) | | |
|------------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 23 | | |
| Units: ng/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 9.749 (± 3.8460) | 9.173 (± 5.6123) | | |
| Cycle 1 Day 8 (n=22, 22, 20, 21, 20, 19) | 1.957 (± 2.2843) | 3.509 (± 4.3471) | | |
| Cycle 2 Day 1 (n=22, 22, 21, 22, 21, 20) | 1.096 (± 0.7751) | 3.095 (± 3.7254) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Values for Dehydroepiandrosterone Sulfate (DHEA-S)

| | |
|-----------------|-------------------------------------------------------------|
| End point title | Absolute Values for Dehydroepiandrosterone Sulfate (DHEA-S) |
|-----------------|-------------------------------------------------------------|

End point description:

Serum Ultra low level quantification of DHEA-S was measured by liquid chromatography and mass spectrometry (LC/MS) at a central laboratory.

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

End point timeframe:

Baseline, Cycle 1 Day 8 and Cycle 2 Day 1

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 2529.0 (± 1309.39) | 2340.9 (± 1606.36) | 1783.0 (± 1554.76) | 2155.7 (± 1591.51) |
| Cycle 1 Day 8 (n=22, 22, 23, 22, 21, 20) | 63.4 (± 55.11) | 71.8 (± 80.23) | 116.9 (± 161.01) | 226.6 (± 328.70) |
| Cycle 2 Day 1 (n=22, 22, 22, 22, 21, 20) | 14.5 (± 21.83) | 36.3 (± 123.48) | 21.5 (± 25.68) | 180.6 (± 527.03) |

| End point values | Placebo (Japan) | Placebo (Ex-Japan) | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 23 | | |

| | | | | |
|------------------------------------------|--------------------|--------------------|--|--|
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 1928.0 (± 1306.59) | 2601.7 (± 3009.41) | | |
| Cycle 1 Day 8 (n=22, 22, 23, 22, 21, 20) | 414.9 (± 392.63) | 973.8 (± 1677.95) | | |
| Cycle 2 Day 1 (n=22, 22, 22, 22, 21, 20) | 268.9 (± 357.32) | 815.7 (± 1918.88) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Values for Adrenocorticotrophic Hormone (ACTH)

| | |
|------------------------|--------------------------------------------------------------------------|
| End point title | Absolute Values for Adrenocorticotrophic Hormone (ACTH) |
| End point description: | Serum ACTH was measured by immunometric assay at the central laboratory. |
| End point type | Secondary |
| End point timeframe: | Baseline, Cycle 1 Day 8 and Cycle 2 Day 1 |

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 5.5 (± 2.54) | 8.3 (± 4.98) | 6.0 (± 4.05) | 6.4 (± 4.04) |
| Cycle 1 Day 8 (n=22, 22, 21, 18, 21, 22) | 2.3 (± 1.55) | 3.0 (± 2.70) | 3.8 (± 3.04) | 3.2 (± 2.56) |
| Cycle 2 Day 1 (n=22, 22, 24, 22, 21, 22) | 1.7 (± 1.08) | 2.7 (± 2.17) | 3.7 (± 4.38) | 3.6 (± 2.26) |

| End point values | Placebo (Japan) | Placebo (Ex-Japan) | | |
|------------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 23 | | |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 5.0 (± 1.66) | 4.7 (± 2.06) | | |
| Cycle 1 Day 8 (n=22, 22, 21, 18, 21, 22) | 3.1 (± 2.68) | 3.1 (± 2.62) | | |
| Cycle 2 Day 1 (n=22, 22, 24, 22, 21, 22) | 1.7 (± 1.19) | 3.0 (± 1.73) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Values for Corticosterone

| | |
|-----------------|------------------------------------|
| End point title | Absolute Values for Corticosterone |
|-----------------|------------------------------------|

End point description:

Serum Corticosterone was measured by high pressure liquid chromatography with mass spectrometry at the central laboratory.

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

End point timeframe:

Baseline, Cycle 1 Day 8 and Cycle 2 Day 1

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 6.515 (± 4.8246) | 7.768 (± 6.8625) | 10.030 (± 7.7341) | 17.975 (± 35.0695) |
| Cycle 1 Day 8 (n=22, 22, 23, 21, 21, 20) | 11.067 (± 14.4220) | 9.709 (± 13.4538) | 48.668 (± 66.3904) | 60.301 (± 77.5434) |
| Cycle 2 Day 1 (n=22, 22, 23, 22, 21, 20) | 11.108 (± 9.0708) | 14.654 (± 9.2064) | 29.929 (± 35.5565) | 47.204 (± 53.4566) |

| End point values | Placebo (Japan) | Placebo (Ex-Japan) | | |
|------------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 23 | | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 5.946 (± 3.4433) | 6.317 (± 4.1467) | | |
| Cycle 1 Day 8 (n=22, 22, 23, 21, 21, 20) | 1.530 (± 1.6404) | 5.598 (± 7.1366) | | |
| Cycle 2 Day 1 (n=22, 22, 23, 22, 21, 20) | 0.758 (± 0.5108) | 4.321 (± 6.4063) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Values for Cortisol

| | |
|--------------------------------------------------------------------------------------------------------|------------------------------|
| End point title | Absolute Values for Cortisol |
| End point description: Serum Cortisol was measured by immunometric assay at the central laboratory. | |
| End point type | Secondary |
| End point timeframe: Baseline, Cycle 1 Day 8 and Cycle 2 Day 1 | |

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 371.3 (± 119.38) | 383.4 (± 125.98) | 449.0 (± 131.54) | 446.8 (± 193.09) |
| Cycle 1 Day 8 (n=22, 22, 24, 22, 21, 23) | 49.5 (± 25.53) | 55.5 (± 55.97) | 100.9 (± 87.38) | 122.0 (± 88.70) |
| Cycle 2 Day 1 (n=22, 22, 24, 23, 20, 21) | 49.2 (± 21.71) | 54.3 (± 39.93) | 97.2 (± 85.66) | 109.1 (± 83.19) |

| End point values | Placebo (Japan) | Placebo (Ex-Japan) | | |
|------------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 23 | | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 366.5 (± 116.69) | 384.8 (± 117.14) | | |
| Cycle 1 Day 8 (n=22, 22, 24, 22, 21, 23) | 82.3 (± 46.16) | 175.8 (± 107.82) | | |
| Cycle 2 Day 1 (n=22, 22, 24, 23, 20, 21) | 53.9 (± 24.92) | 149.6 (± 122.91) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Values for Prostate-Specific Antigen (PSA)

| | |
|-----------------------------------------------------------------------------|-----------------------------------------------------|
| End point title | Absolute Values for Prostate-Specific Antigen (PSA) |
| End point description: Serum PSA was measured at the central laboratory. | |
| End point type | Secondary |

End point timeframe:

Baseline and Cycle 2 Day 1

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 27.227 (± 24.8821) | 97.504 (± 293.9496) | 165.992 (± 368.5016) | 100.237 (± 210.5675) |
| Cycle 2 Day 1 (n=22, 22, 24, 23, 20, 21) | 18.005 (± 16.9858) | 38.892 (± 95.0124) | 117.257 (± 286.1870) | 56.437 (± 97.1621) |

| End point values | Placebo (Japan) | Placebo (Ex-Japan) | | |
|------------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 23 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=22, 22, 25, 24, 21, 23) | 37.588 (± 48.9413) | 133.238 (± 189.9345) | | |
| Cycle 2 Day 1 (n=22, 22, 24, 23, 20, 21) | 24.325 (± 46.9725) | 152.940 (± 261.9735) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Plasma Concentration for Orteronel and M-I Metabolite

| | |
|-----------------|------------------------------------------------------------------------------|
| End point title | Cmax: Maximum Observed Plasma Concentration for Orteronel and M-I Metabolite |
|-----------------|------------------------------------------------------------------------------|

End point description:

Maximum observed plasma concentration (Cmax) is the peak plasma concentration of a drug after administration, obtained directly from the plasma concentration-time curve.

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

End point timeframe:

Cycle 1 Day 1 Predose, 0.5, 1, 2, 3, 5, 8, 12 hours post-dose

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-----------------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Orteronel | 1520 (± 23.9) | 2210 (± 33.9) | 1300 (± 59.7) | 1610 (± 50.3) |
| Orteronel Metabolite M-I | 272 (± 33.1) | 422 (± 37.0) | 199 (± 61.9) | 261 (± 47.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-12): Area Under the Plasma Concentration-Time Curve From Time 0 to 12 Hours Post-dose for Orteronel and M-I Metabolite

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| End point title | AUC(0-12): Area Under the Plasma Concentration-Time Curve From Time 0 to 12 Hours Post-dose for Orteronel and M-I Metabolite |
| End point description: | |
| AUC(0-12) is measure of area under the curve over the dosing interval where the length of the dosing interval is time 0 to 12 hours in this study. | |
| End point type | Secondary |
| End point timeframe: | |
| Cycle 1 Day 1 Predose, 0.5, 1, 2, 3, 5, 8, 12 hours post-dose | |

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-----------------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Orteronel | 8810 (± 16.4) | 12800 (± 31.2) | 7830 (± 51.1) | 10200 (± 41.4) |
| Orteronel Metabolite M-I | 2130 (± 28.3) | 3290 (± 33.8) | 1570 (± 65.5) | 2080 (± 44.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Orteronel and M-I Metabolite

| | |
|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| End point title | Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Orteronel and M-I Metabolite |
| End point description: | |
| Tmax: Time to reach the maximum plasma concentration (Cmax), equal to time (hours) to Cmax. | |
| End point type | Secondary |

End point timeframe:

Cycle 1 Day 1 Predose, 0.5, 1, 2, 3, 5, 8, 12 hours post-dose

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: hours | | | | |
| median (full range (min-max)) | | | | |
| Orteronel | 2.97 (1.00 to 5.10) | 2.43 (1.00 to 4.97) | 2.00 (0.500 to 7.93) | 1.92 (0.500 to 5.00) |
| Orteronel Metabolite M-I | 5.00 (2.03 to 8.10) | 4.98 (2.00 to 8.23) | 5.05 (1.03 to 11.1) | 4.98 (1.22 to 11.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: AE (0-24) Cumulative Amount of Drug Excreted into the Urine for Orteronel and MI-Metabolite

| | |
|-----------------|---------------------------------------------------------------------------------------------|
| End point title | AE (0-24) Cumulative Amount of Drug Excreted into the Urine for Orteronel and MI-Metabolite |
|-----------------|---------------------------------------------------------------------------------------------|

End point description:

Cumulative amount of urine excreted time 0 to 24 hour.

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

End point timeframe:

Cycle 1 Day 1 Predose, 0.5, 1, 2, 3, 5, 8, 12 hours post-dose

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-----------------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: mg | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Orteronel | 115.0 (± 26.0) | 164.0 (± 26.2) | 95.3 (± 31.9) | 161.0 (± 41.4) |
| Orteronel Metabolite M-I | 39.6 (± 31.5) | 62.5 (± 26.6) | 30.0 (± 40.1) | 52.8 (± 46.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: C_{max,ss}: Maximum Observed Plasma Concentration at Steady State for

Orteronel and MI-Metabolite

| | |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| End point title | C _{max,ss} : Maximum Observed Plasma Concentration at Steady State for Orteronel and MI-Metabolite |
|-----------------|-------------------------------------------------------------------------------------------------------------|

End point description:

Maximum observed steady-state plasma concentration during a dosing interval.

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

End point timeframe:

Cycle 1 Day 8 Predose, 0.5, 1, 2, 3, 5, 8, 12 hours post-dose

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-----------------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Orteronel | 2180 (± 22.4) | 3210 (± 31.5) | 1840 (± 37.1) | 3100 (± 45.0) |
| Orteronel Metabolite M-I | 565 (± 32.4) | 864 (± 39.5) | 485 (± 75.4) | 761 (± 81.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: T_{max,ss}: Time to reach the maximum plasma concentration (C_{max}), equal to time (hours) to C_{max} at Steady State for Orteronel and M-I Metabolite

| | |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | T _{max,ss} : Time to reach the maximum plasma concentration (C _{max}), equal to time (hours) to C _{max} at Steady State for Orteronel and M-I Metabolite |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Time to reach the maximum plasma concentration (C_{max}), equal to time (hours) to C_{max} at steady state.

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

End point timeframe:

Cycle 1 Day 8 Predose, 0.5, 1, 2, 3, 5, 8, 12 hours post-dose

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|----------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: hours | | | | |
| median (confidence interval 95%) | | | | |
| Orteronel | 2.05 (1.00 to 5.08) | 2.96 (1.00 to 5.17) | 2.00 (0.550 to 5.17) | 1.98 (0.500 to 3.08) |
| Orteronel Metabolite M-I | 3.08 (2.00 to 5.17) | 4.78 (2.00 to 8.13) | 3.00 (1.00 to 5.07) | 3.00 (0 to 8.00) |

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-tau): Area Under the Plasma Concentration-time Curve from Time 0 to Time tau Over the Dosing Interval for Orteronel and M-I Metabolite

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | AUC(0-tau): Area Under the Plasma Concentration-time Curve from Time 0 to Time tau Over the Dosing Interval for Orteronel and M-I Metabolite |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Area under the plasma concentration-time curve during a dosing interval, where tau is the length of the dosing interval.

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

End point timeframe:

Cycle 1 Day 8 Predose, 0.5, 1, 2, 3, 5, 8, 12 hours post-dose

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-----------------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Orteronel | 13300 (± 20.4) | 20400 (± 36.1) | 12600 (± 36.2) | 20000 (± 55.0) |
| Orteronel Metabolite M-I | 4840 (± 35.0) | 7460 (± 46.3) | 4340 (± 69.4) | 6590 (± 78.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Rac: Accumulation index for Orteronel and M-I metabolite

| | |
|-----------------|----------------------------------------------------------|
| End point title | Rac: Accumulation index for Orteronel and M-I metabolite |
|-----------------|----------------------------------------------------------|

End point description:

Rac was calculated as the ratio of AUCtau to AUC12hr.

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

End point timeframe:

Cycle 1 Day 8 Predose, 0.5, 1, 2, 3, 5, 8, 12 hours post-dose

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-----------------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 25 | 24 |
| Units: ratio | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Orteronel | 1.51 (± 9.1) | 1.59 (± 46.6) | 1.62 (± 39.3) | 1.97 (± 90.5) |
| Orteronel Metabolite M-I | 2.27 (± 17.5) | 2.26 (± 43.0) | 2.76 (± 45.0) | 3.17 (± 77.7) |

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough,ss: Observed Predose Plasma Concentration at Steady State for Orteronel and M-I Metabolite

| | |
|------------------------|----------------------------------------------------------------------------------------------------|
| End point title | Ctrough,ss: Observed Predose Plasma Concentration at Steady State for Orteronel and M-I Metabolite |
| End point description: | Observed predose plasma concentration at steady state. |
| End point type | Secondary |
| End point timeframe: | Cycle 1 Day 8 Predose |

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-----------------------------------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 22 | 22 | 24 | 22 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Orteronel | 710 (± 28.1) | 1060 (± 63.7) | 807 (± 45.4) | 899 (± 59.8) |
| Orteronel Metbolite M-I | 291 (± 47.1) | 444 (± 66.7) | 314 (± 68.6) | 417 (± 58.0) |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent Adverse events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|-------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Treatment-Emergent Adverse events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|-------------------------------------------------------------------------------------------------------|

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether

or not it is considered related to the drug. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant.

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

End point timeframe:

From signing of the informed consent form through 30 days after the last dose of study drug, approximately 3.2 years

| End point values | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) | Orteronel 200 mg (Ex-Japan) | Orteronel 400 mg (Ex-Japan) |
|-----------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 33 | 32 | 36 | 36 |
| Units: participants | | | | |
| AE | 33 | 32 | 36 | 36 |
| SAE | 8 | 18 | 16 | 12 |

| End point values | Placebo (Japan) | Placebo (Ex-Japan) | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 23 | | |
| Units: participants | | | | |
| AE | 7 | 18 | | |
| SAE | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of the informed consent form through 30 days after the last dose of study drug, approximately 3.2 years for serious adverse events and up to data-cut-off 12-Sep-2013 for non-serious adverse events.

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment. Adverse events were summarized as per the treatment received.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Orteronel placebo-matching tablets, orally, twice daily in Cycle 1 (28 days). Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|-----------------------|--------------------------|
| Reporting group title | Orteronel 200 mg (Japan) |
|-----------------------|--------------------------|

Reporting group description:

Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles in for up to 2.8 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|-----------------------|--------------------------|
| Reporting group title | Orteronel 300 mg (Japan) |
|-----------------------|--------------------------|

Reporting group description:

Orteronel 300 mg, tablets, orally, twice daily in 28 day cycles in Japan for up to 2.8 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Orteronel 200 mg (Ex-Japan) |
|-----------------------|-----------------------------|

Reporting group description:

Orteronel 200 mg, tablets, orally, twice daily in 28 day cycles in for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| | |
|-----------------------|----------------------------|
| Reporting group title | Orteronel 400mg (Ex-Japan) |
|-----------------------|----------------------------|

Reporting group description:

Orteronel 400 mg, tablets, orally, twice daily in 28 day cycles Ex-Japan for up to 3.1 years. Study drug will be administered concomitantly with prednisone (or commercially available equivalent) 5 mg twice daily (BID) continuously throughout the study.

| Serious adverse events | Placebo | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) |
|---------------------------------------------------------------------|------------------|--------------------------|--------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 44 (22.73%) | 8 / 33 (24.24%) | 18 / 32 (56.25%) |
| number of deaths (all causes) | 0 | 0 | 2 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal neoplasm | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung Neoplasm Malignant | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic Carcinoma | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastatic Pain | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |

| | | | |
|------------------------------------------------------|----------------|----------------|----------------|
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Pancreatic enzymes increased | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar Vertebral Fracture | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal Compression Fracture | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thoracic Vertebral Fracture | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial Bones Fracture | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac disorder | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary Artery Stenosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial Ischaemia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aphasia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Altered State Of Consciousness | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parkinsonism | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parkinson's disease | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| Anaemia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 33 (3.03%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 33 (3.03%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| Large Intestine Polyp | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomitting | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal Angiodysplasia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bile Duct Stone | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Dermatitis exfoliative subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 44 (2.27%) 0 / 1 0 / 0 | 0 / 33 (0.00%) 0 / 0 0 / 0 | 0 / 32 (0.00%) 0 / 0 0 / 0 |
| Renal and urinary disorders | | | |
| Haematuria subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 44 (2.27%) 0 / 1 0 / 0 | 0 / 33 (0.00%) 0 / 0 0 / 0 | 0 / 32 (0.00%) 0 / 0 0 / 0 |
| Urinary tract obstruction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 44 (2.27%) 0 / 1 0 / 0 | 0 / 33 (0.00%) 0 / 0 0 / 0 | 0 / 32 (0.00%) 0 / 0 0 / 0 |
| Acute Kidney Injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 44 (0.00%) 0 / 0 0 / 0 | 0 / 33 (0.00%) 0 / 0 0 / 0 | 0 / 32 (0.00%) 0 / 0 0 / 0 |
| Renal Colic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 44 (0.00%) 0 / 0 0 / 0 | 0 / 33 (0.00%) 0 / 0 0 / 0 | 0 / 32 (0.00%) 0 / 0 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Rotator Cuff Syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 44 (0.00%) 0 / 0 0 / 0 | 0 / 33 (0.00%) 0 / 0 0 / 0 | 1 / 32 (3.13%) 0 / 1 0 / 0 |
| Spinal Ligament Ossification subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 44 (0.00%) 0 / 0 0 / 0 | 0 / 33 (0.00%) 0 / 0 0 / 0 | 1 / 32 (3.13%) 0 / 1 0 / 0 |
| Lumbar Spinal Stenosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 44 (0.00%) 0 / 0 0 / 0 | 0 / 33 (0.00%) 0 / 0 0 / 0 | 1 / 32 (3.13%) 0 / 1 0 / 0 |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| Pathological Fracture | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device Related Infection | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Orteronel 200 mg (Ex-Japan) | Orteronel 400mg (Ex-Japan) | |
|---------------------------------------------------------------------|--------------------------------|-------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 36 (44.44%) | 12 / 36 (33.33%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung adenocarcinoma | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal neoplasm | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------|----------------|----------------|--|
| Lung Neoplasm Malignant subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic Carcinoma subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic Pain subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders Deep vein thrombosis subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis limb subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic Hypotension subjects affected / exposed | 0 / 36 (0.00%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions General physical health deterioration subjects affected / exposed | 0 / 36 (0.00%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| Asthenia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Pancreatic enzymes increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 36 (2.78%) | |
| 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 / 36 (0.00%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar Vertebral Fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Compression Fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic Vertebral Fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial Bones Fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac disorder | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary Artery Stenosis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial Ischaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Altered State Of Consciousness | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parkinsonism | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parkinson's disease | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large Intestine Polyp | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomitting | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal Angiodysplasia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |

| | | | |
|-------------------------------------------------------------------------------------------------|----------------|----------------|--|
| Hepatic function abnormal subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile Duct Stone subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders Dermatitis exfoliative subjects affected / exposed | 0 / 36 (0.00%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders Haematuria subjects affected / exposed | 2 / 36 (5.56%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute Kidney Injury subjects affected / exposed | 1 / 36 (2.78%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Colic subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| Musculoskeletal and connective tissue disorders | | | |
| Rotator Cuff Syndrome | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Ligament Ossification | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar Spinal Stenosis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological Fracture | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 2 / 36 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device Related Infection | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 36 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 3 / 36 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Orteronel 200 mg (Japan) | Orteronel 300 mg (Japan) |
|----------------------------------------------------------------------------|-------------------|-----------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 44 / 44 (100.00%) | 33 / 33 (100.00%) | 32 / 32 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 33 (3.03%) | 3 / 32 (9.38%) |
| occurrences (all) | 2 | 1 | 4 |
| Metastatic pain | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |

| | | | |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| Hot flush | | | |
| subjects affected / exposed | 7 / 44 (15.91%) | 3 / 33 (9.09%) | 5 / 32 (15.63%) |
| occurrences (all) | 7 | 3 | 5 |
| Hypertension | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 3 / 33 (9.09%) | 3 / 32 (9.38%) |
| occurrences (all) | 4 | 3 | 3 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flushing | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 44 (18.18%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 9 | 0 | 3 |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 8 / 33 (24.24%) | 6 / 32 (18.75%) |
| occurrences (all) | 4 | 10 | 7 |
| Malaise | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 4 / 33 (12.12%) | 6 / 32 (18.75%) |
| occurrences (all) | 5 | 5 | 7 |
| Face Oedema | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 2 | 3 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 0 | 2 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |

| | | | |
|------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| Seasonal allergy subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 3 / 32 (9.38%) 3 |
| Cough subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Productive cough subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 2 / 33 (6.06%) 2 | 2 / 32 (6.25%) 2 |
| Depression subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Restlessness subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Investigations | | | |
| Lipase increased subjects affected / exposed occurrences (all) | 19 / 44 (43.18%) 36 | 25 / 33 (75.76%) 46 | 19 / 32 (59.38%) 32 |
| Amylase increased subjects affected / exposed occurrences (all) | 16 / 44 (36.36%) 21 | 21 / 33 (63.64%) 35 | 19 / 32 (59.38%) 27 |

| | | | |
|---------------------------------------|-----------------|-----------------|-----------------|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 44 (13.64%) | 7 / 33 (21.21%) | 7 / 32 (21.88%) |
| occurrences (all) | 7 | 7 | 11 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 6 / 44 (13.64%) | 7 / 33 (21.21%) | 7 / 32 (21.88%) |
| occurrences (all) | 8 | 7 | 11 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 6 / 44 (13.64%) | 5 / 33 (15.15%) | 8 / 32 (25.00%) |
| occurrences (all) | 6 | 6 | 14 |
| Weight decreased | | | |
| subjects affected / exposed | 5 / 44 (11.36%) | 2 / 33 (6.06%) | 6 / 32 (18.75%) |
| occurrences (all) | 5 | 2 | 9 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 5 / 44 (11.36%) | 8 / 33 (24.24%) | 4 / 32 (12.50%) |
| occurrences (all) | 5 | 8 | 4 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 33 (0.00%) | 5 / 32 (15.63%) |
| occurrences (all) | 2 | 0 | 5 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 33 (3.03%) | 6 / 32 (18.75%) |
| occurrences (all) | 1 | 1 | 7 |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 4 / 32 (12.50%) |
| occurrences (all) | 2 | 0 | 8 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 3 / 33 (9.09%) | 3 / 32 (9.38%) |
| occurrences (all) | 5 | 4 | 5 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 4 / 33 (12.12%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 3 / 33 (9.09%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Glycosylated haemoglobin increased | | | |

| | | | |
|------------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 2 | 1 |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 1 | 2 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 3 / 33 (9.09%) | 5 / 32 (15.63%) |
| occurrences (all) | 2 | 4 | 8 |
| Contusion | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 3 / 32 (9.38%) |
| occurrences (all) | 0 | 1 | 3 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 2 | 1 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 0 | 2 |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 0 | 2 |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 33 (3.03%) | 2 / 32 (6.25%) |
| occurrences (all) | 2 | 1 | 2 |
| Nervous system disorders | | | |

| | | | |
|--------------------------------------|----------------|-----------------|-----------------|
| Dysgeusia | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 2 / 33 (6.06%) | 4 / 32 (12.50%) |
| occurrences (all) | 3 | 2 | 4 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 2 / 33 (6.06%) | 4 / 32 (12.50%) |
| occurrences (all) | 1 | 2 | 5 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 33 (0.00%) | 3 / 32 (9.38%) |
| occurrences (all) | 1 | 0 | 4 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 5 / 33 (15.15%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 2 | 1 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 1 | 2 |
| Increased tendency to bruise | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |

| | | | |
|------------------------------------------------------------------------------------------------|------------------------|----------------------|------------------------|
| Ear pain subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 3 / 33 (9.09%) 3 | 1 / 32 (3.13%) 1 |
| Lacrimation increased subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 3 / 33 (9.09%) 3 | 0 / 32 (0.00%) 0 |
| Glaucoma subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 7 / 44 (15.91%) 7 | 8 / 33 (24.24%) 9 | 10 / 32 (31.25%) 12 |
| Diarrhoea subjects affected / exposed occurrences (all) | 11 / 44 (25.00%) 12 | 4 / 33 (12.12%) 4 | 5 / 32 (15.63%) 6 |
| Nausea subjects affected / exposed occurrences (all) | 7 / 44 (15.91%) 12 | 5 / 33 (15.15%) 6 | 7 / 32 (21.88%) 10 |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 44 (6.82%) 3 | 4 / 33 (12.12%) 4 | 3 / 32 (9.38%) 11 |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 4 / 44 (9.09%) 4 | 4 / 33 (12.12%) 4 | 2 / 32 (6.25%) 3 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 33 (3.03%) 1 | 2 / 32 (6.25%) 3 |
| Abdominal pain subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 2 / 33 (6.06%) 2 | 0 / 32 (0.00%) 0 |
| Stomatitis | | | |

| | | | |
|----------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 4 / 44 (9.09%) | 2 / 33 (6.06%) | 2 / 32 (6.25%) |
| occurrences (all) | 4 | 2 | 2 |
| Chronic Gastritis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 1 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 1 | 2 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 0 | 3 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 3 / 32 (9.38%) |
| occurrences (all) | 0 | 0 | 4 |
| Skin and subcutaneous tissue disorders | | | |
| Rash macular | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Rash maculo-papular | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 3 / 33 (9.09%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 3 / 32 (9.38%) |
| occurrences (all) | 0 | 1 | 4 |
| Purpura | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 2 | 2 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 1 | 2 |
| Eczema | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 1 | 2 |
| Haemorrhage subcutaneous | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 0 | 2 |
| Skin atrophy | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash papular | | | |

| | | | |
|--------------------------------------------------------------------------|------------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Renal and urinary disorders | | | |
| Haematuria subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 1 / 33 (3.03%) 1 | 2 / 32 (6.25%) 2 |
| Nocturia subjects affected / exposed occurrences (all) | 3 / 44 (6.82%) 4 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Dysuria subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 2 / 33 (6.06%) 2 | 1 / 32 (3.13%) 1 |
| Pollakiuria subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 3 / 33 (9.09%) 3 | 0 / 32 (0.00%) 0 |
| Renal failure subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Hydronephrosis subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Urinary retention subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Endocrine disorders | | | |
| Cushingoid subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 3 / 33 (9.09%) 3 | 1 / 32 (3.13%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms subjects affected / exposed occurrences (all) | 11 / 44 (25.00%) 16 | 3 / 33 (9.09%) 3 | 8 / 32 (25.00%) 9 |
| Back pain | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 3 / 44 (6.82%) | 2 / 33 (6.06%) | 3 / 32 (9.38%) |
| occurrences (all) | 3 | 2 | 3 |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 2 | 0 | 2 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 3 / 33 (9.09%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 1 | 2 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 2 | 1 |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Groin pain | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |

| | | | |
|-----------------------------------|-----------------|-----------------|-----------------|
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 44 (15.91%) | 8 / 33 (24.24%) | 8 / 32 (25.00%) |
| occurrences (all) | 7 | 10 | 13 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 3 / 33 (9.09%) | 4 / 32 (12.50%) |
| occurrences (all) | 4 | 4 | 5 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 33 (3.03%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 1 | 3 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 3 / 33 (9.09%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 1 / 32 (3.13%) |
| occurrences (all) | 0 | 2 | 1 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all) | 0 | 0 | 2 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 33 (6.06%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---------------------------------------------------------------------------------------------|----------------------|-----------------------|----------------------|
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus subjects affected / exposed occurrences (all) | 5 / 44 (11.36%) 5 | 9 / 33 (27.27%) 10 | 6 / 32 (18.75%) 8 |
| Decreased appetite subjects affected / exposed occurrences (all) | 5 / 44 (11.36%) 7 | 1 / 33 (3.03%) 1 | 5 / 32 (15.63%) 8 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 4 / 44 (9.09%) 4 | 2 / 33 (6.06%) 3 | 2 / 32 (6.25%) 2 |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 3 / 44 (6.82%) 3 | 1 / 33 (3.03%) 1 | 2 / 32 (6.25%) 2 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 2 / 44 (4.55%) 2 | 2 / 33 (6.06%) 2 | 0 / 32 (0.00%) 0 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 33 (0.00%) 0 | 3 / 32 (9.38%) 4 |
| Type 2 diabetes mellitus subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 33 (0.00%) 0 | 2 / 32 (6.25%) 2 |
| Hyperlipidaemia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 2 / 33 (6.06%) 2 | 0 / 32 (0.00%) 0 |
| Hypercholesterolaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 33 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Orteronel 200 mg (Ex-Japan) | Orteronel 400mg (Ex-Japan) | |
|---------------------------------------------------------------------|--------------------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 35 / 36 (97.22%) | 36 / 36 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Metastatic pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 10 / 36 (27.78%) | |
| occurrences (all) | 5 | 10 | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 8 / 36 (22.22%) | |
| occurrences (all) | 2 | 8 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 1 / 36 (2.78%) | |
| occurrences (all) | 3 | 1 | |
| Flushing | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 1 / 36 (2.78%) | |
| occurrences (all) | 3 | 1 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 36 (5.56%) | |
| occurrences (all) | 1 | 2 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 19 / 36 (52.78%) | 15 / 36 (41.67%) | |
| occurrences (all) | 22 | 17 | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------|----------------------|----------------------|--|
| Oedema peripheral subjects affected / exposed occurrences (all) | 7 / 36 (19.44%) 7 | 5 / 36 (13.89%) 6 | |
| Malaise subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 | 0 / 36 (0.00%) 0 | |
| Face Oedema subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Peripheral swelling subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | 2 / 36 (5.56%) 2 | |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | 2 / 36 (5.56%) 2 | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 5 / 36 (13.89%) 5 | 4 / 36 (11.11%) 5 | |
| Cough subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 | 2 / 36 (5.56%) 2 | |
| Productive cough subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 0 / 36 (0.00%) 0 | |
| Pulmonary embolism subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 0 / 36 (0.00%) 0 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 6 / 36 (16.67%) 6 | 4 / 36 (11.11%) 4 | |

| | | | |
|---------------------------------------|-----------------|-----------------|--|
| Depression | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 2 / 36 (5.56%) | |
| occurrences (all) | 3 | 2 | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 2 / 36 (5.56%) | |
| occurrences (all) | 2 | 2 | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Investigations | | | |
| Lipase increased | | | |
| subjects affected / exposed | 9 / 36 (25.00%) | 7 / 36 (19.44%) | |
| occurrences (all) | 10 | 9 | |
| Amylase increased | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 6 / 36 (16.67%) | |
| occurrences (all) | 7 | 10 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 4 | 1 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 4 | 1 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 3 / 36 (8.33%) | |
| occurrences (all) | 2 | 4 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 2 | 1 | |
| Blood alkaline phosphatase increased | | | |

| | | | |
|------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood urea increased | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 2 | 1 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 5 / 36 (13.89%) | |
| occurrences (all) | 4 | 6 | |
| Contusion | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 0 / 36 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin abrasion | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 3 / 36 (8.33%) | |
| occurrences (all) | 0 | 3 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 4 / 36 (11.11%) | |
| occurrences (all) | 4 | 4 | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 5 / 36 (13.89%) | |
| occurrences (all) | 3 | 5 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 2 | 1 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Headache | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 1 / 36 (2.78%) | |
| occurrences (all) | 4 | 2 | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 3 / 36 (8.33%) | |
| occurrences (all) | 3 | 3 | |
| Syncope | | | |

| | | | |
|----------------------------------------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | 2 / 36 (5.56%) 3 | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 1 / 36 (2.78%) 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 0 / 36 (0.00%) 0 | |
| Increased tendency to bruise subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | 2 / 36 (5.56%) 2 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 0 / 36 (0.00%) 0 | |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 1 | 2 / 36 (5.56%) 2 | |
| Eye disorders | | | |
| Cataract subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Lacrimation increased subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Glaucoma subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 2 / 36 (5.56%) 2 | |
| Gastrointestinal disorders | | | |
| Constipation subjects affected / exposed occurrences (all) | 10 / 36 (27.78%) 13 | 12 / 36 (33.33%) 13 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 15 / 36 (41.67%) 30 | 13 / 36 (36.11%) 16 | |
| Nausea | | | |

| | | |
|----------------------------------|------------------|------------------|
| subjects affected / exposed | 13 / 36 (36.11%) | 12 / 36 (33.33%) |
| occurrences (all) | 17 | 16 |
| Vomiting | | |
| subjects affected / exposed | 9 / 36 (25.00%) | 3 / 36 (8.33%) |
| occurrences (all) | 12 | 3 |
| Abdominal discomfort | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 36 (5.56%) |
| occurrences (all) | 1 | 2 |
| Abdominal pain upper | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 4 / 36 (11.11%) |
| occurrences (all) | 1 | 4 |
| Abdominal pain | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 3 / 36 (8.33%) |
| occurrences (all) | 4 | 3 |
| Stomatitis | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 2 / 36 (5.56%) |
| occurrences (all) | 4 | 7 |
| Chronic Gastritis | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) |
| occurrences (all) | 0 | 0 |
| Dyspepsia | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 3 / 36 (8.33%) |
| occurrences (all) | 1 | 3 |
| Abdominal distension | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) |
| occurrences (all) | 0 | 0 |
| Dental caries | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) |
| occurrences (all) | 0 | 0 |
| Pancreatitis | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) |
| occurrences (all) | 0 | 0 |
| Gastrooesophageal reflux disease | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 2 / 36 (5.56%) |
| occurrences (all) | 2 | 2 |
| Mouth ulceration | | |

| | | | |
|----------------------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 4 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 3 | |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash macular | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 4 / 36 (11.11%) | |
| occurrences (all) | 4 | 4 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 2 | 1 | |
| Rash erythematous | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Purpura | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 36 (5.56%) | |
| occurrences (all) | 1 | 2 | |
| Eczema | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Haemorrhage subcutaneous | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin atrophy | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 3 / 36 (8.33%) | 1 / 36 (2.78%) | |
| occurrences (all) | 3 | 2 | |
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 36 (5.56%) | |
| occurrences (all) | 1 | 2 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 2 | 1 | |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 36 (5.56%) | |
| occurrences (all) | 1 | 2 | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 3 | |
| Rash papular | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 3 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 2 / 36 (5.56%) | |
| occurrences (all) | 4 | 2 | |
| Nocturia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 3 | 1 | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 3 / 36 (8.33%) | |
| occurrences (all) | 1 | 3 | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 2 | 1 | |

| | | | |
|----------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------|--|
| Hydronephrosis subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 0 / 36 (0.00%) 0 | |
| Urinary retention subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 2 / 36 (5.56%) 2 | |
| Endocrine disorders Cushingoid subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) | 8 / 36 (22.22%) 11 | 12 / 36 (33.33%) 22 | |
| Back pain subjects affected / exposed occurrences (all) | 5 / 36 (13.89%) 6 | 3 / 36 (8.33%) 3 | |
| Arthralgia subjects affected / exposed occurrences (all) | 5 / 36 (13.89%) 6 | 4 / 36 (11.11%) 5 | |
| Muscular weakness subjects affected / exposed occurrences (all) | 4 / 36 (11.11%) 4 | 4 / 36 (11.11%) 4 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 4 | 3 / 36 (8.33%) 4 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 4 | 3 / 36 (8.33%) 3 | |
| Lumbar spinal stenosis subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 36 (0.00%) 0 | |
| Osteoporosis subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 2 / 36 (5.56%) 2 | |
| Musculoskeletal discomfort | | | |

| | | | |
|-----------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 3 / 36 (8.33%) | 1 / 36 (2.78%) | |
| occurrences (all) | 3 | 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 36 (5.56%) | |
| occurrences (all) | 2 | 2 | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 4 | 1 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 36 (5.56%) | |
| occurrences (all) | 1 | 2 | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | 2 / 36 (5.56%) | |
| occurrences (all) | 7 | 2 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 36 (5.56%) | |
| occurrences (all) | 5 | 3 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 2 / 36 (5.56%) | |
| occurrences (all) | 2 | 2 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|-----------------------------------------|-----------------|-----------------|--|
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 2 / 36 (5.56%) | |
| occurrences (all) | 4 | 2 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 4 / 36 (11.11%) | |
| occurrences (all) | 0 | 6 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Tooth abscess | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 36 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 36 (5.56%) | |
| occurrences (all) | 0 | 2 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 4 / 36 (11.11%) | |
| occurrences (all) | 1 | 4 | |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 36 (25.00%) | 7 / 36 (19.44%) | |
| occurrences (all) | 10 | 8 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 4 / 36 (11.11%) | |
| occurrences (all) | 1 | 4 | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 4 / 36 (11.11%) | |
| occurrences (all) | 3 | 5 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 36 (5.56%) | |
| occurrences (all) | 3 | 2 | |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 36 (13.89%) | 1 / 36 (2.78%) | |
| occurrences (all) | 6 | 1 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 2 / 36 (5.56%) | |
| occurrences (all) | 4 | 2 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 4 / 36 (11.11%) | |
| occurrences (all) | 2 | 5 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 36 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 2 / 36 (5.56%) | |
| occurrences (all) | 2 | 2 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 36 (2.78%) | |
| occurrences (all) | 2 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported