



Clinical trial results:

A Randomised, Double-blind, Multicentre Phase III Study to Assess the Efficacy and Safety of RGB-14-P Compared to Prolia® in Women with Postmenopausal Osteoporosis

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2020-006017-38 |
| Trial protocol | PL CZ HU BG ES IT |
| Global end of trial date | 15 November 2023 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 25 October 2024 |
| First version publication date | 25 October 2024 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | RGB-14-101 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05087030 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND: 146025 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Gedeon Richter Plc. |
| Sponsor organisation address | 1103 Budapest, Gyömrői út 19-21, Budapest, Hungary, |
| Public contact | Medical Information Service, Gedeon Richter Plc., medinfo@richter.hu |
| Scientific contact | Medical Information Service, Gedeon Richter Plc., medinfo@richter.hu |

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 | 13 February 2024 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 November 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Efficacy

To demonstrate similar efficacy and effect of RGB 14 P with US licensed Prolia® on BMD at the lumbar spine at Week 52 in female subjects with postmenopausal osteoporosis

Pharmacodynamics

To demonstrate similar pharmacodynamics (AUEC of %CfB in sCTX) of RGB 14 P with US licensed Prolia® in female subjects with postmenopausal osteoporosis (only required for EMA)

Protection of trial subjects:

This study was conducted in accordance with the principles laid down in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidance – ICH E6(R2), and in accordance with the Declaration of Helsinki and in accordance with applicable national laws and regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 21 September 2021 |
| 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 | Poland: 225 |
| Country: Number of subjects enrolled | Spain: 35 |
| Country: Number of subjects enrolled | Bulgaria: 67 |
| Country: Number of subjects enrolled | Czechia: 61 |
| Country: Number of subjects enrolled | Hungary: 39 |
| Country: Number of subjects enrolled | Italy: 23 |
| Country: Number of subjects enrolled | United States: 20 |
| Country: Number of subjects enrolled | Ukraine: 3 |
| Worldwide total number of subjects | 473 |
| EEA total number of subjects | 450 |

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) | 186 |
| From 65 to 84 years | 287 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 21-September-2021 (first subject first visit) to 15-November-2023 (last subject last visit).

Pre-assignment

Screening details:

Subjects who met the inclusion criteria and none of the exclusion criteria were enrolled to the study. All study assessments were performed as per the schedule of assessment.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Main 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 | RGB-14-P |

Arm description:

Subjects received RGB-14-P as subcutaneous (SC) injection on Day 1 of treatment period 1 (week 0) and treatment period 2 (week 26).

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RGB-14-P |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

RGB-14-P was provided as a single-dose (1 mL solution) pre-filled syringe for subcutaneous injection administration.

| | |
|------------------|---------|
| Arm title | Prolia® |
|------------------|---------|

Arm description:

Subjects received Prolia® as SC injection on Day 1 of treatment period 1 (week 0) and treatment period 2 (week 26).

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Prolia® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Prolia® was provided as a single-dose (1 mL solution) pre-filled syringe for subcutaneous injection administration.

| Number of subjects in period 1 | RGB-14-P | Prolia® |
|--------------------------------|----------|---------|
| Started | 242 | 231 |
| Completed | 225 | 211 |
| Not completed | 17 | 20 |
| Exclusion criteria met | 1 | - |
| Adverse event, serious fatal | - | 1 |
| Consent withdrawn by subject | 8 | 13 |
| Adverse event, non-fatal | 2 | 2 |
| Unspecified | 1 | 2 |
| Lost to follow-up | 3 | - |
| Study objective confounded | 1 | - |
| Subject's personal reason | - | 2 |
| Protocol deviation | 1 | - |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Transition period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | RGB-14-P to RGB-14-P |

Arm description:

Subjects who received RGB-14-P during the main period were re-randomized and received Prolia® as SC injection on day 1 of treatment period 3 (week 52).

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | RGB-14-P |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

RGB-14-P was provided as a single-dose (1 mL solution) pre-filled syringe for subcutaneous injection administration.

| | |
|------------------|---------------------|
| Arm title | Prolia® to RGB-14-P |
|------------------|---------------------|

Arm description:

Subjects who received Prolia® during the main period were re-randomized and received RGB-14-P as SC injection on Day 1 of treatment period 3 (week 52).

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

| | |
|--|------------------|
| Investigational medicinal product name | Prolia® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Prolia® was provided as a single-dose (1 mL solution) pre-filled syringe for subcutaneous injection administration.

| | |
|------------------|--------------------|
| Arm title | Prolia® to Prolia® |
|------------------|--------------------|

Arm description:

Subjects who received Prolia® during the main period were re-randomized and received Prolia® as SC injection on Day 1 of treatment period 3 (week 52).

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Prolia® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Prolia® was provided as a single-dose (1 mL solution) pre-filled syringe for subcutaneous injection administration.

| Number of subjects in period 2^[1] | RGB-14-P to RGB-14-P | Prolia® to RGB-14-P | Prolia® to Prolia® |
|---|----------------------|---------------------|--------------------|
| Started | 63 | 62 | 63 |
| Completed | 63 | 62 | 62 |
| Not completed | 0 | 0 | 1 |
| Consent withdrawn by subject | - | - | 1 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only a subset of patients continued the study in the Transition period (as outlined in the clinical study protocol).

Baseline characteristics

Reporting groups

| | |
|---|----------|
| Reporting group title | RGB-14-P |
| Reporting group description: | |
| Subjects received RGB-14-P as subcutaneous (SC) injection on Day 1 of treatment period 1 (week 0) and treatment period 2 (week 26). | |
| Reporting group title | Prolia® |
| Reporting group description: | |
| Subjects received Prolia® as SC injection on Day 1 of treatment period 1 (week 0) and treatment period 2 (week 26). | |

| Reporting group values | RGB-14-P | Prolia® | Total |
|--|----------|---------|-------|
| Number of subjects | 242 | 231 | 473 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 100 | 86 | 186 |
| From 65-84 years | 142 | 145 | 287 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 66.7 | 66.8 | |
| standard deviation | ± 5.20 | ± 4.91 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 242 | 231 | 473 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|---|----------------------|
| Reporting group title | RGB-14-P |
| Reporting group description: Subjects received RGB-14-P as subcutaneous (SC) injection on Day 1 of treatment period 1 (week 0) and treatment period 2 (week 26). | |
| Reporting group title | Prolia® |
| Reporting group description: Subjects received Prolia® as SC injection on Day 1 of treatment period 1 (week 0) and treatment period 2 (week 26). | |
| Reporting group title | RGB-14-P to RGB-14-P |
| Reporting group description: Subjects who received RGB-14-P during the main period were re-randomized and received Prolia® as SC injection on day 1 of treatment period 3 (week 52). | |
| Reporting group title | Prolia® to RGB-14-P |
| Reporting group description: Subjects who received Prolia® during the main period were re-randomized and received RGB-14-P as SC injection on Day 1 of treatment period 3 (week 52). | |
| Reporting group title | Prolia® to Prolia® |
| Reporting group description: Subjects who received Prolia® during the main period were re-randomized and received Prolia® as SC injection on Day 1 of treatment period 3 (week 52). | |

Primary: Percentage Change from Baseline (%CfB) in Lumbar Spine Bone Mineral Density (BMD)

| | |
|---|---|
| End point title | Percentage Change from Baseline (%CfB) in Lumbar Spine Bone Mineral Density (BMD) |
| End point description: Percentage change from baseline in lumbar bone BMD was assessed. BMD at the lumbar spine was measured by dual-energy x-ray absorptiometry (DXA). This outcome measure was assessed for main period. The Full analysis set (FAS) included all subjects to whom the investigational medicinal product (IMP) has been randomized. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure. | |
| End point type | Primary |
| End point timeframe: Week 52 | |

| End point values | RGB-14-P | Prolia® | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 222 | 206 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 5.68 (± 3.535) | 5.19 (± 4.118) | | |

Statistical analyses

| | |
|--|----------------------------|
| Statistical analysis title | RGB-14-P v/s Prolia® |
| Statistical analysis description: | |
| The analysis was performed with an ANCOVA model with %CfB in lumbar spine BMD at Week 52 as the dependent variable; covariates were treatment Arm (RGB-14-P and US licenced Prolia), stratification factors at randomization (Previous use of bisphosphonates [yes/no] and geographical region [Europe, US], Baseline BMD value in lumbar spine, machine type and machine type*baseline BMD value interaction. | |
| Comparison groups | RGB-14-P v Prolia® |
| Number of subjects included in analysis | 428 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[1] |
| Parameter estimate | Estimated Difference |
| Point estimate | 0.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.402 |
| upper limit | 1.09 |

Notes:

[1] - Comparison between Study Treatment Groups

Primary: Area Under the Effective Curve (AUEC) After the First Dose Until Day 183 of %CfB in serum Type I Collagen C-telopeptide (sCTX)

| | |
|-----------------|--|
| End point title | Area Under the Effective Curve (AUEC) After the First Dose Until Day 183 of %CfB in serum Type I Collagen C-telopeptide (sCTX) |
|-----------------|--|

End point description:

The AUEC of %CfB in sCTX of RGB-14-P was assessed as part of pharmacodynamics parameter with US-licensed Prolia® in female subjects was demonstrated with postmenopausal osteoporosis. This outcome measure was assessed for main period only.

The pharmacodynamic analysis set (PDS) included all subjects in the safety population with at least one evaluable pharmacodynamic (PD) parameter (%CfB and AUEC) and not had any protocol deviations that have a relevant impact on sCTX or serum procollagen type 1 N-terminal propeptide (P1NP) results included in the pharmacodynamic parameter calculation. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Week 26 | |

| End point values | RGB-14-P | Prolia® | | |
|--|---------------------------------------|---------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 241 | 229 | | |
| Units: milligram(s)/deciliter(dL)*day | | | | |
| geometric mean (confidence interval 95%) | 13501.300 (12737.814 to 14264.794) | 13344.650 (12583.291 to 14106.002) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | RGB-14-P v/s Prolia® |
| Statistical analysis description: | |
| The analysis was performed with a mixed-effects model ANCOVA on natural log-transformed AUEC data as the dependent variable and the following model covariates: Treatment Arm, Stratification factors (Previous use of bisphosphonates [yes/no] and Geographical region [Europe, US], Log of baseline sCTX. | |
| Comparison groups | RGB-14-P v Prolia® |
| Number of subjects included in analysis | 470 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[2] |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.978 |
| upper limit | 1.046 |
| Notes: | |
| [2] - Comparison between Study Treatment Groups | |

Secondary: Percentage Change from Baseline (%CfB) in Total Hip BMD

| | |
|---|---|
| End point title | Percentage Change from Baseline (%CfB) in Total Hip BMD |
| End point description: | |
| Percentage Change from Baseline in total hip BMD was assessed. The FAS included all subjects to whom the IMP has been randomized. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure. Here, 9999 indicates that the data were not available due to insufficient number of subjects. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 26, 52 and 78 | |

| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
|--------------------------------------|-----------------|----------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 225 | 63 | 211 | 62 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 26 (n = 225, 62, 211, 58, 62) | 2.42 (± 2.659) | 2.46 (± 2.712) | 2.69 (± 2.519) | 2.81 (± 2.607) |
| Week 52 (n = 220, 63, 205, 60, 63) | 3.42 (± 2.916) | 3.03 (± 3.103) | 3.49 (± 2.872) | 3.36 (± 2.696) |
| Week 78 (n = 0, 62, 0, 62, 60) | 9999 (± 9999) | 4.24 (± 3.381) | 9999 (± 9999) | 4.12 (± 3.128) |

| End point values | Prolia® to Prolia® | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 63 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 26 (n = 225, 62, 211, 58, 62) | 3.35 (± 2.559) | | | |

| | | | | |
|------------------------------------|---------------------|--|--|--|
| Week 52 (n = 220, 63, 205, 60, 63) | 4.21 (\pm 3.452) | | | |
| Week 78 (n = 0, 62, 0, 62, 60) | 4.95 (\pm 3.849) | | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | RGB-14-P v/s Prolia® at Week 26 |
| Statistical analysis description: at Week 26 | |
| Comparison groups | RGB-14-P v Prolia® |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| Parameter estimate | Estimated Difference |
| Point estimate | -0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.792 |
| upper limit | 0.165 |

Notes:

[3] - Mixed Model Repeated Measures

| | |
|---|---------------------------------|
| Statistical analysis title | RGB-14-P v/s Prolia® at Week 52 |
| Statistical analysis description: at Week 52 | |
| Comparison groups | RGB-14-P v Prolia® |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| Parameter estimate | Estimated Difference |
| Point estimate | -0.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.68 |
| upper limit | 0.358 |

Notes:

[4] - Mixed model repeated measures

Secondary: Percentage Change from Baseline (%CfB) in Lumbar Spine BMD

| | |
|--|--|
| End point title | Percentage Change from Baseline (%CfB) in Lumbar Spine BMD |
| End point description: Percentage Change from Baseline in lumbar spine BMD was assessed. The Full analysis set (FAS) included all subjects to whom the IMP has been randomized. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure. Here, 9999 indicates that the data were not available due to insufficient number of subjects. | |
| End point type | Secondary |

End point timeframe:

Weeks 26 and 78

| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
|--------------------------------------|-----------------|----------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 227 | 63 | 218 | 62 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 26 (n= 227, 62, 218, 61, 63) | 3.56 (± 3.747) | 3.98 (± 3.185) | 3.45 (± 4.227) | 3.39 (± 3.848) |
| Week 78 (n= 0, 63, 0, 62, 60) | 9999 (± 9999) | 7.03 (± 3.828) | 9999 (± 9999) | 7.06 (± 4.327) |

| End point values | Prolia® to Prolia® | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 63 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 26 (n= 227, 62, 218, 61, 63) | 3.68 (± 4.979) | | | |
| Week 78 (n= 0, 63, 0, 62, 60) | 7.09 (± 4.240) | | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | RGB-14-P v/s Prolia® at Week 26 |
| Statistical analysis description: | |
| Week 26 | |
| Comparison groups | RGB-14-P v Prolia® |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| Parameter estimate | Estimated Difference |
| Point estimate | 0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.703 |
| upper limit | 0.769 |

Notes:

[5] - mixed model for repeated measures

Secondary: Percentage Change from Baseline (%CfB) in Femoral Neck BMD

| | |
|--|--|
| End point title | Percentage Change from Baseline (%CfB) in Femoral Neck BMD |
| End point description: | |
| Percentage Change from Baseline in femoral neck BMD was assessed by DXA. | |

The FAS included all subjects to whom the IMP has been randomized. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure.

Here, 9999 indicates that the data were not available due to insufficient number of subjects.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Weeks 26, 52 and 78 | |

| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
|--------------------------------------|-----------------|----------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 225 | 63 | 211 | 62 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 26 (n= 225, 62, 211, 58, 62) | 1.88 (± 3.040) | 1.60 (± 2.833) | 1.94 (± 3.610) | 2.21 (± 3.296) |
| Week 52 (n= 220, 63, 205, 60, 63) | 2.42 (± 3.687) | 1.95 (± 3.621) | 2.64 (± 3.751) | 2.60 (± 3.127) |
| Week 78 (n= 0, 63, 0, 62, 60) | 9999 (± 9999) | 3.08 (± 4.259) | 9999 (± 9999) | 3.06 (± 3.337) |

| End point values | Prolia® to Prolia® | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 63 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 26 (n= 225, 62, 211, 58, 62) | 2.35 (± 4.057) | | | |
| Week 52 (n= 220, 63, 205, 60, 63) | 3.24 (± 4.549) | | | |
| Week 78 (n= 0, 63, 0, 62, 60) | 4.04 (± 4.764) | | | |

Statistical analyses

| | |
|---|---------------------------------|
| Statistical analysis title | RGB-14-P v/s Prolia® at Week 26 |
| Statistical analysis description: | |
| The analysis was performed with a mixed model repeated measures with observed %CfB in femoral neck BMD as the dependent variable; covariates were treatment arm (RGB-14-P and US licenced Prolia), stratification factors at randomization (Previous use of bisphosphonates [yes/no] and geographical region [Europe, US], Baseline BMD value in femoral neck, machine type and machine type*baseline BMD value interaction, study week and study week*treatment arm interaction. | |
| Comparison groups | RGB-14-P v Prolia® |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| Parameter estimate | Estimated Difference |
| Point estimate | -0.12 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.727 |
| upper limit | 0.478 |

Notes:

[6] - Mixed model repeated measures

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | RGB-14-P v/s Prolia® at Week 52 |
|-----------------------------------|---------------------------------|

Statistical analysis description:

The analysis was performed with a mixed model repeated measures with observed %CfB in femoral neck BMD as the dependent variable; covariates were treatment arm (RGB-14-P and US licenced Prolia), stratification factors at randomization (Previous use of bisphosphonates [yes/no] and geographical region [Europe, US], Baseline BMD value in femoral neck, machine type and machine type*baseline BMD value interaction, study week and study week*treatment arm interaction.

| | |
|---|----------------------|
| Comparison groups | RGB-14-P v Prolia® |
| Number of subjects included in analysis | 436 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| Parameter estimate | Estimated Difference |
| Point estimate | -0.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.006 |
| upper limit | 0.359 |

Notes:

[7] - Mixed model repeated measures

Secondary: Number of Subjects with Vertebral Fragility Fracture

| | |
|-----------------|--|
| End point title | Number of Subjects with Vertebral Fragility Fracture |
|-----------------|--|

End point description:

Number of subjects with vertebral fragility fracture were assessed. Information on vertebral fractures was centrally collected through the evaluation of lateral thoraco-lumbar spine X-ray. The Full analysis set (FAS) included all subjects to whom the IMP has been randomized. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure. Here, 9999 indicates that the data were not available due to insufficient number of subjects.

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

End point timeframe:

Weeks 52 and 78

| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
|--------------------------------|-----------------|----------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 242 | 63 | 231 | 62 |
| Units: Subjects | | | | |
| Week 52 (n= 242, 0, 231, 0, 0) | 4 | 9999 | 8 | 9999 |
| Week 78 (n= 0, 63, 0, 62, 63) | 9999 | 3 | 9999 | 4 |

| | | | | |
|--------------------------------|--------------------|--|--|--|
| End point values | Prolia® to Prolia® | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 63 | | | |
| Units: Subjects | | | | |
| Week 52 (n= 242, 0, 231, 0, 0) | 9999 | | | |
| Week 78 (n= 0, 63, 0, 62, 63) | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Non-Vertebral Fragility Fracture

| | |
|---|--|
| End point title | Number of Subjects with Non-Vertebral Fragility Fracture |
| End point description: | |
| Number of subjects with non-vertebral fragility fracture were assessed. Information on non-vertebral fractures was centrally collected through the evaluation of lateral thoraco-lumbar spine X-ray. The FAS included all subjects to whom the IMP has been randomized. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure. Here, 9999 indicates that the data were not available due to insufficient number of subjects. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 52 and 78 | |

| | | | | |
|--------------------------------|-----------------|----------------------|-----------------|---------------------|
| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 242 | 63 | 231 | 62 |
| Units: Subjects | | | | |
| Week 52 (n= 242, 0, 231, 0, 0) | 4 | 9999 | 10 | 9999 |
| Week 78 (n= 0, 63, 0, 62, 63) | 9999 | 2 | 9999 | 5 |

| | | | | |
|--------------------------------|--------------------|--|--|--|
| End point values | Prolia® to Prolia® | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 63 | | | |
| Units: Subjects | | | | |
| Week 52 (n= 242, 0, 231, 0, 0) | 9999 | | | |
| Week 78 (n= 0, 63, 0, 62, 63) | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline (%CfB) in Serum Procollagen Type 1 N Terminal Propeptide (P1NP)

| | |
|-----------------|---|
| End point title | Percentage Change from Baseline (%CfB) in Serum Procollagen Type 1 N Terminal Propeptide (P1NP) |
|-----------------|---|

End point description:

Percentage Change from Baseline in serum P1NP was assessed as part of pharmacodynamics parameter with US-licensed Prolia® in female subjects with postmenopausal osteoporosis.

The PDS included all subjects in safety population with at least one evaluable PD parameter (%CfB and AUEC) and not had any protocol deviations that have a relevant impact on sCTX or serum P1NP results included in PD parameter calculation. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure.

Here, 9999 indicates that the data were not available due to insufficient number of subjects.

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

End point timeframe:

Weeks 4, 26, 52 and 78

| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
|--------------------------------------|------------------|----------------------|------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 234 | 60 | 220 | 60 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n= 234, 60, 220, 59, 62) | 22.10 (± 14.905) | 19.85 (± 13.939) | 20.22 (± 15.091) | 18.45 (± 15.835) |
| Week 26 (n= 216, 57, 211, 59, 60) | 65.92 (± 17.828) | 68.42 (± 11.693) | 62.89 (± 29.294) | 63.41 (± 42.677) |
| Week 52 (n= 204, 60, 198, 60, 61) | 65.04 (± 19.131) | 64.86 (± 16.902) | 63.82 (± 21.712) | 66.05 (± 20.428) |
| Week 78 (n= 0, 54, 0, 59, 58) | 9999 (± 9999) | 64.12 (± 18.845) | 9999 (± 9999) | 66.91 (± 16.816) |

| End point values | Prolia® to Prolia® | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 62 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n= 234, 60, 220, 59, 62) | 17.31 (± 15.524) | | | |
| Week 26 (n= 216, 57, 211, 59, 60) | 66.08 (± 16.098) | | | |
| Week 52 (n= 204, 60, 198, 60, 61) | 65.89 (± 17.651) | | | |
| Week 78 (n= 0, 54, 0, 59, 58) | 63.08 (± 21.364) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline (%CfB) in serum Type I Collagen C-telopeptide (sCTX)

| | |
|-----------------|--|
| End point title | Percentage Change from Baseline (%CfB) in serum Type I Collagen C-telopeptide (sCTX) |
|-----------------|--|

End point description:

Percentage Change from Baseline in sCTX was assessed as part of pharmacodynamics parameter with US-licensed Prolia® was assessed in female subjects with postmenopausal osteoporosis.

PDS included all subjects in safety population with at least one evaluable PD parameter (%CfB and AUEC) and not had any protocol deviations that have a relevant impact on sCTX or serum P1NP results included in PD parameter calculation. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure.

Here, 9999 indicates that the data were not available due to insufficient number of subjects.

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

End point timeframe:

Weeks 4, 26, 52 and 78

| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
|--------------------------------------|------------------|----------------------|------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 234 | 60 | 220 | 60 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n= 234, 60, 220, 59, 62) | 85.87 (± 9.567) | 84.96 (± 11.206) | 85.38 (± 15.501) | 84.71 (± 23.071) |
| Week 26 (n= 216, 57, 211, 59, 60) | 69.74 (± 23.212) | 67.29 (± 23.572) | 61.51 (± 83.764) | 53.23 (± 147.679) |
| Week 52 (n= 204, 60, 198, 60, 61) | 62.90 (± 28.995) | 60.41 (± 31.958) | 58.26 (± 63.927) | 53.89 (± 94.853) |
| Week 78 (n= 0, 54, 0, 59, 59) | 9999 (± 9999) | 58.70 (± 34.117) | 9999 (± 9999) | 53.32 (± 42.855) |

| End point values | Prolia® to Prolia® | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 62 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n= 234, 60, 220, 59, 62) | 88.08 (± 5.832) | | | |

| | | | | |
|-----------------------------------|------------------|--|--|--|
| Week 26 (n= 216, 57, 211, 59, 60) | 71.27 (± 17.483) | | | |
| Week 52 (n= 204, 60, 198, 60, 61) | 66.79 (± 24.151) | | | |
| Week 78 (n= 0, 54, 0, 59, 59) | 57.38 (± 30.562) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|--|
| End point title | Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|--|

End point description:

The safety and tolerability of RGB-14-P with US-licensed Prolia® in female subjects with postmenopausal osteoporosis was assessed.

Safety analysis set (SAF) included all subjects who received at least one full or partial dose of IMP.

Here, disc = discontinuation, IMP = Investigational Medicinal Product, s/ws = severe or worse severity

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

End point timeframe:

Main Period: From screening (Weeks -5 to 0) to Week 52; Transition Period: From Week 52 to Week 78

| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
|--|-----------------|----------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 242 | 63 | 231 | 62 |
| Units: Subjects | | | | |
| Any AE | 161 | 0 | 158 | 0 |
| Any TEAEs | 158 | 30 | 152 | 25 |
| Any TEAEs s/ws | 8 | 0 | 9 | 1 |
| Any treatment related TEAE | 36 | 2 | 32 | 5 |
| Any treatment related TEAE s/ws | 1 | 0 | 0 | 0 |
| Any serious TEAEs | 7 | 0 | 16 | 0 |
| Any serious TEAEs s/ws | 5 | 0 | 9 | 0 |
| Any non-serious TEAEs | 158 | 30 | 149 | 25 |
| Any AEs leading to subject disc | 2 | 0 | 3 | 0 |
| Any TEAEs leading to subject disc | 2 | 0 | 3 | 0 |
| Any treatment related TEAE leading to subject disc | 1 | 0 | 0 | 0 |
| Any TEAEs leading to disc of IMP | 2 | 0 | 2 | 0 |
| Any treatment related TEAE leading to disc of IMP | 1 | 0 | 0 | 0 |
| Any fracture TEAE | 9 | 4 | 18 | 3 |
| Any fracture TEAE s/ws | 2 | 0 | 1 | 0 |
| Any serious fracture TEAEs | 1 | 0 | 1 | 0 |
| Any serious fracture TEAEs s/ws | 1 | 0 | 1 | 0 |
| Deaths | 0 | 0 | 1 | 0 |
| Any AE leading to death | 0 | 0 | 1 | 0 |

| | | | | |
|--|---|---|---|---|
| Any TEAE leading to death | 0 | 0 | 1 | 0 |
| Any injection site reactions | 0 | 0 | 2 | 3 |
| Any treatment related serious TEAE | 0 | 0 | 0 | 0 |
| Any treatment related serious TEAE s/ws | 0 | 0 | 0 | 0 |
| Any treatment related fracture TEAE | 0 | 0 | 0 | 0 |
| Any treatment related fracture TEAE s/ws | 0 | 0 | 0 | 0 |
| Any treatment related serious fracture TEAE | 0 | 0 | 0 | 0 |
| Any treatment related serious fracture TEAE s/ws | 0 | 0 | 0 | 0 |
| Any treatment related fatal serious TEAEs | 0 | 0 | 0 | 0 |
| Any injection site reactions of CTCAE grade ≥ 3 | 0 | 0 | 0 | 0 |
| Any injection site reactions s/ws | 0 | 0 | 0 | 0 |

| End point values | Prolia® to Prolia® | | | |
|--|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 63 | | | |
| Units: Subjects | | | | |
| Any AE | 0 | | | |
| Any TEAEs | 25 | | | |
| Any TEAEs s/ws | 0 | | | |
| Any treatment related TEAE | 1 | | | |
| Any treatment related TEAE s/ws | 0 | | | |
| Any serious TEAEs | 0 | | | |
| Any serious TEAEs s/ws | 0 | | | |
| Any non-serious TEAEs | 25 | | | |
| Any AEs leading to subject disc | 0 | | | |
| Any TEAEs leading to subject disc | 0 | | | |
| Any treatment related TEAE leading to subject disc | 0 | | | |
| Any TEAEs leading to disc of IMP | 0 | | | |
| Any treatment related TEAE leading to disc of IMP | 0 | | | |
| Any fracture TEAE | 1 | | | |
| Any fracture TEAE s/ws | 0 | | | |
| Any serious fracture TEAEs | 0 | | | |
| Any serious fracture TEAEs s/ws | 0 | | | |
| Deaths | 0 | | | |
| Any AE leading to death | 0 | | | |
| Any TEAE leading to death | 0 | | | |
| Any injection site reactions | 1 | | | |
| Any treatment related serious TEAE | 0 | | | |
| Any treatment related serious TEAE s/ws | 0 | | | |
| Any treatment related fracture TEAE | 0 | | | |
| Any treatment related fracture TEAE s/ws | 0 | | | |

| | | | | |
|--|---|--|--|--|
| Any treatment related serious fracture TEAE | 0 | | | |
| Any treatment related serious fracture TEAE s/ws | 0 | | | |
| Any treatment related fatal serious TEAEs | 0 | | | |
| Any injection site reactions of CTCAE grade ≥ 3 | 0 | | | |
| Any injection site reactions s/ws | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Anti-Drug Antibodies (ADAs)

| | |
|-----------------|---|
| End point title | Number of Subjects with Anti-Drug Antibodies (ADAs) |
|-----------------|---|

End point description:

Number of subjects with positive ADAs were assessed.

Immunogenicity analysis set (IAS) included all subjects in the safety population who had the pre-dose immunogenicity result and at least one available postbaseline immunogenicity assessment. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure. Here, 9999 indicates that data was not available due to insufficient number of subjects.

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

End point timeframe:

Weeks 0, 2, 4, 26, 28, 30, 52, 54, 56 and 78

| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
|-----------------------------------|-----------------|----------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 239 | 63 | 228 | 62 |
| Units: Subjects | | | | |
| Week 0 (n= 239, 63, 228, 62, 62) | 0 | 0 | 1 | 0 |
| Week 2 (n= 236, 63, 224, 60, 61) | 2 | 0 | 0 | 0 |
| Week 4 (n= 237, 63, 226, 60, 62) | 0 | 0 | 0 | 0 |
| Week 26 (n= 227, 63, 219, 62, 62) | 0 | 0 | 0 | 0 |
| Week 28 (n= 218, 60, 206, 58, 59) | 0 | 0 | 1 | 0 |
| Week 30 (n= 220, 63, 215, 62, 62) | 0 | 0 | 1 | 0 |
| Week 52 (n= 225, 63, 208, 62, 61) | 0 | 0 | 0 | 0 |
| Week 54 (n= 0, 62, 0, 61, 62) | 9999 | 0 | 9999 | 0 |
| Week 56 (n= 0, 63, 0, 62, 61) | 9999 | 0 | 9999 | 0 |
| Week 78 (n= 0, 63, 0, 62, 61) | 9999 | 0 | 9999 | 0 |

| End point values | Prolia® to Prolia® | | | |
|-----------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 62 | | | |
| Units: Subjects | | | | |

| | | | | |
|-----------------------------------|---|--|--|--|
| Week 0 (n= 239, 63, 228, 62, 62) | 0 | | | |
| Week 2 (n= 236, 63, 224, 60, 61) | 0 | | | |
| Week 4 (n= 237, 63, 226, 60, 62) | 0 | | | |
| Week 26 (n= 227, 63, 219, 62, 62) | 0 | | | |
| Week 28 (n= 218, 60, 206, 58, 59) | 1 | | | |
| Week 30 (n= 220, 63, 215, 62, 62) | 1 | | | |
| Week 52 (n= 225, 63, 208, 62, 61) | 0 | | | |
| Week 54 (n= 0, 62, 0, 61, 62) | 1 | | | |
| Week 56 (n= 0, 63, 0, 62, 61) | 1 | | | |
| Week 78 (n= 0, 63, 0, 62, 61) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Neutralizing Antibodies

| | |
|--|---|
| End point title | Number of Subjects with Neutralizing Antibodies |
| End point description: | |
| Number of subjects with positive neutralizing antibodies were assessed. IAS included all subjects in the safety population who had the pre-dose immunogenicity result and at least one available postbaseline immunogenicity assessment. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for this outcome measure. Here, 9999 indicates that the data were not available due to insufficient number of subjects. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 0, 2, 4, 26, 28, 30, 52, 54, 56 and 78 | |

| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
|-----------------------------|-----------------|----------------------|-----------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2 | 0 ^[8] | 2 | 0 ^[9] |
| Units: Subjects | | | | |
| Week 0 (n= 0, 0, 1, 0, 0) | 9999 | | 9999 | |
| Week 2 (n= 2, 0, 0, 0, 0) | 1 | | 9999 | |
| Week 4 (n= 0, 0, 0, 0, 0) | 9999 | | 9999 | |
| Week 26 (n= 0, 0, 0, 0, 0) | 9999 | | 9999 | |
| Week 28 (n= 0, 0, 1, 0, 1) | 9999 | | 1 | |
| Week 30 (n= 0, 0, 1, 0, 1) | 9999 | | 9999 | |
| Week 52 (n= 0, 0, 0, 0, 0) | 9999 | | 9999 | |
| Week 54 (n= 0, 0, 0, 0, 1) | 9999 | | 9999 | |
| Week 56 (n= 0, 0, 0, 0, 1) | 9999 | | 9999 | |
| Week 78 (n= 0, 0, 0, 0, 0) | 9999 | | 9999 | |

Notes:

[8] - Number of subjects analyzed were 0 due to no positive ADA response.

[9] - Number of subjects analyzed were 0 due to no positive ADA response.

| | | | | |
|------------------|--------------------|--|--|--|
| End point values | Prolia® to Prolia® | | | |
|------------------|--------------------|--|--|--|

| | | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 1 | | | |
| Units: Subjects | | | | |
| Week 0 (n= 0, 0, 1, 0, 0) | 9999 | | | |
| Week 2 (n= 2, 0, 0, 0, 0) | 9999 | | | |
| Week 4 (n= 0, 0, 0, 0, 0) | 9999 | | | |
| Week 26 (n= 0, 0, 0, 0, 0) | 9999 | | | |
| Week 28 (n= 0, 0, 1, 0, 1) | 1 | | | |
| Week 30 (n= 0, 0, 1, 0, 1) | 9999 | | | |
| Week 52 (n= 0, 0, 0, 0, 0) | 9999 | | | |
| Week 54 (n= 0, 0, 0, 0, 1) | 1 | | | |
| Week 56 (n= 0, 0, 0, 0, 1) | 1 | | | |
| Week 78 (n= 0, 0, 0, 0, 0) | 9999 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Titre of ADAs

| | |
|--|---------------|
| End point title | Titre of ADAs |
| End point description: | |
| <p>The immunogenicity of RGB -14- P with US-licensed Prolia® in female subjects with postmenopausal osteoporosis was assessed.</p> <p>IAS included all subjects in the safety population who had the pre-dose immunogenicity result and at least one available postbaseline immunogenicity assessment. Here, 'number of subjects analyzed' specifies all subjects who were evaluated for ADA.</p> <p>The outcome measure in this table is the titer, N refers to all subjects analyzed for ADA. (Only 7 samples, from 4 subjects were evaluated for titer).</p> <p>Here, '99999' indicates that titer was not evaluable due to no positive ADA response and '9999' indicates that data was not available due to insufficient number of subjects.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 0, 2, 4, 26, 28, 30, 52, 54, 56 and 78 | |

| End point values | RGB-14-P | RGB-14-P to RGB-14-P | Prolia® | Prolia® to RGB-14-P |
|-----------------------------------|------------------------|------------------------|------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 239 | 63 | 228 | 62 |
| Units: titre | | | | |
| median (full range (min-max)) | | | | |
| Week 0 (n= 239, 63, 228, 62, 62) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 302.0 (302 to 302) | 99999 (99999 to 99999) |
| Week 2 (n= 236, 63, 224, 60, 61) | 761.0 (60 to 1462) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 99999 (99999 to 99999) |
| Week 4 (n= 237, 63, 226, 60, 62) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 99999 (99999 to 99999) |
| Week 26 (n= 227, 63, 219, 62, 62) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 99999 (99999 to 99999) |
| Week 28 (n= 218, 60, 206, 58, 59) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 172.0 (172 to 172) | 99999 (99999 to 99999) |

| | | | | |
|-----------------------------------|------------------------|------------------------|------------------------|------------------------|
| Week 30 (n= 220, 63, 215, 62, 62) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 211.0 (211 to 211) | 99999 (99999 to 99999) |
| Week 52 (n= 225, 63, 208, 62, 61) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 99999 (99999 to 99999) |
| Week 54 (n= 0, 62, 0, 61, 62) | 9999 (9999 to 9999) | 99999 (99999 to 99999) | 9999 (9999 to 9999) | 99999 (99999 to 99999) |
| Week 56 (n= 0, 63, 0, 62, 61) | 9999 (9999 to 9999) | 99999 (99999 to 99999) | 9999 (9999 to 9999) | 99999 (99999 to 99999) |
| Week 78 (n= 0, 63, 0, 62, 61) | 9999 (9999 to 9999) | 99999 (99999 to 99999) | 9999 (9999 to 9999) | 99999 (99999 to 99999) |

| End point values | Prolia® to Prolia® | | | |
|-----------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 62 | | | |
| Units: titre | | | | |
| median (full range (min-max)) | | | | |
| Week 0 (n= 239, 63, 228, 62, 62) | 99999 (99999 to 99999) | | | |
| Week 2 (n= 236, 63, 224, 60, 61) | 99999 (99999 to 99999) | | | |
| Week 4 (n= 237, 63, 226, 60, 62) | 99999 (99999 to 99999) | | | |
| Week 26 (n= 227, 63, 219, 62, 62) | 99999 (99999 to 99999) | | | |
| Week 28 (n= 218, 60, 206, 58, 59) | 172.0 (172 to 172) | | | |
| Week 30 (n= 220, 63, 215, 62, 62) | 211.0 (211 to 211) | | | |
| Week 52 (n= 225, 63, 208, 62, 61) | 99999 (99999 to 99999) | | | |
| Week 54 (n= 0, 62, 0, 61, 62) | 224.0 (224 to 224) | | | |
| Week 56 (n= 0, 63, 0, 62, 61) | 152.0 (152 to 152) | | | |
| Week 78 (n= 0, 63, 0, 62, 61) | 99999 (99999 to 99999) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Main Period: From screening (Weeks -5 to 0) to Week 52; Transition Period: From Week 52 to Week 78

Adverse event reporting additional description:

Safety analysis set included all subjects who received at least one full or partial dose of IMP.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | RGB-14-P |
|-----------------------|----------|

Reporting group description:

Subjects received RGB-14-P as subcutaneous (SC) injection on Day 1 of treatment period 1 (week 0) and treatment period 2 (week 26).

| | |
|-----------------------|---------|
| Reporting group title | Prolia® |
|-----------------------|---------|

Reporting group description:

Subjects received Prolia® as SC injection on Day 1 of treatment period 1 (week 0) and treatment period 2 (week 26).

| | |
|-----------------------|----------------------|
| Reporting group title | RGB-14-P to RGB-14-P |
|-----------------------|----------------------|

Reporting group description:

Subjects who received RGB-14-P during the main period were re-randomized and received Prolia® as SC injection on day 1 of treatment period 3 (week 52).

| | |
|-----------------------|---------------------|
| Reporting group title | Prolia® to RGB-14-P |
|-----------------------|---------------------|

Reporting group description:

Subjects who received Prolia® during the main period were re-randomized and received RGB-14-P as SC injection on Day 1 of treatment period 3 (week 52).

| | |
|-----------------------|--------------------|
| Reporting group title | Prolia® to Prolia® |
|-----------------------|--------------------|

Reporting group description:

Subjects who received Prolia® during the main period were re-randomized and received Prolia® as SC injection on Day 1 of treatment period 3 (week 52).

| Serious adverse events | RGB-14-P | Prolia® | RGB-14-P to RGB-14-P |
|---|-----------------|------------------|----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 242 (2.89%) | 16 / 231 (6.93%) | 0 / 63 (0.00%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | | | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Breast cancer | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Clear cell renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Follicular lymphoma | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Renal neoplasm | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Thyroid cancer | | | |
| subjects affected / exposed | 1 / 242 (0.41%) | 0 / 231 (0.00%) | 0 / 63 (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 | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 242 (0.41%) | 0 / 231 (0.00%) | 0 / 63 (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 |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 242 (0.41%) | 1 / 231 (0.43%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 disorder | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 failure chronic | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 infarction | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Nervous system disorders | | | |
| Lumbosacral radiculopathy | | | |
| subjects affected / exposed | 1 / 242 (0.41%) | 0 / 231 (0.00%) | 0 / 63 (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 |
| Gastrointestinal disorders | | | |
| Chronic gastritis | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Reproductive system and breast disorders | | | |
| Endometrial disorder | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 242 (0.41%) | 1 / 231 (0.43%) | 0 / 63 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 1 / 242 (0.41%) | 0 / 231 (0.00%) | 0 / 63 (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 |
| Panic attack | | | |
| subjects affected / exposed | 1 / 242 (0.41%) | 0 / 231 (0.00%) | 0 / 63 (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 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 242 (0.41%) | 0 / 231 (0.00%) | 0 / 63 (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 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 242 (0.00%) | 1 / 231 (0.43%) | 0 / 63 (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 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 242 (0.41%) | 0 / 231 (0.00%) | 0 / 63 (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 |

| Serious adverse events | Prolia® to RGB-14-P | Prolia® to Prolia® | |
|---|---------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clear cell renal cell carcinoma | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Follicular lymphoma | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Invasive ductal breast carcinoma | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (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 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid cancer | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (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 | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorder | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Lumbosacral radiculopathy | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Chronic gastritis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Endometrial disorder | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 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 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Panic attack | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | RGB-14-P | Prolia® | RGB-14-P to RGB-14-P |
|---|--------------------|-------------------|----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 100 / 242 (41.32%) | 85 / 231 (36.80%) | 4 / 63 (6.35%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 8 / 242 (3.31%) | 13 / 231 (5.63%) | 0 / 63 (0.00%) |
| occurrences (all) | 9 | 14 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 14 / 242 (5.79%) | 4 / 231 (1.73%) | 0 / 63 (0.00%) |
| occurrences (all) | 15 | 5 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 12 / 242 (4.96%) | 10 / 231 (4.33%) | 0 / 63 (0.00%) |
| occurrences (all) | 16 | 13 | 0 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 25 / 242 (10.33%) | 24 / 231 (10.39%) | 0 / 63 (0.00%) |
| occurrences (all) | 25 | 25 | 0 |
| Nasopharyngitis | | | |

| | | | |
|---|------------------------|------------------------|---------------------|
| subjects affected / exposed occurrences (all) | 23 / 242 (9.50%) 29 | 21 / 231 (9.09%) 28 | 1 / 63 (1.59%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 23 / 242 (9.50%) 34 | 11 / 231 (4.76%) 13 | 0 / 63 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 11 / 242 (4.55%) 13 | 11 / 231 (4.76%) 17 | 0 / 63 (0.00%) 0 |
| Metabolism and nutrition disorders Hypocalcaemia subjects affected / exposed occurrences (all) | 22 / 242 (9.09%) 31 | 22 / 231 (9.52%) 27 | 3 / 63 (4.76%) 3 |

| Non-serious adverse events | Prolia® to RGB-14-P | Prolia® to Prolia® | |
|---|---------------------|---------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 3 / 62 (4.84%) | 6 / 63 (9.52%) | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 0 / 62 (0.00%) 0 | 0 / 63 (0.00%) 0 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 62 (0.00%) 0 | 0 / 63 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 62 (0.00%) 0 | 0 / 63 (0.00%) 0 | |
| Infections and infestations COVID-19 subjects affected / exposed occurrences (all) | 0 / 62 (0.00%) 0 | 0 / 63 (0.00%) 0 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 62 (3.23%) 2 | 4 / 63 (6.35%) 4 | |
| Upper respiratory tract infection | | | |

| | | | |
|------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 0 / 63 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Metabolism and nutrition disorders | | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 2 / 63 (3.17%) | |
| occurrences (all) | 1 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 03 August 2021 | The protocol was amended to Substantial Amendment 1, dated 03 Aug 2021, to incorporate and implement responses and suggestions made by the USFDA. |
| 10 January 2022 | The protocol was amended to Substantial Amendment 2, dated 10 Jan 2022, to incorporate and implement changes for statistical analysis, consistency with supporting study documents and suggestions made based on Investigator experiences. |
| 19 January 2023 | The protocol was amended to Substantial Amendment 3, dated 19 Jan 2023, to incorporate and implement 10% increase in the number of subjects to be enrolled for the Transition Period to meet the requirements of USFDA, considering the drop-out was higher than expected. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported