

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761392Orig1s000**

**761392Orig2s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

## Summary Review Memorandum

|                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| <b>Date</b>                   | See Electronic Stamp Date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>From</b>                   | Sabiha Khan, MD (Clinical Reviewer, OTBB)<br>Michelle Luo, MD, PhD (CTL, CDTL, OTBB)<br>Theresa Kehoe, MD (Division Signatory, DGE)<br>Christy Osgood, MD (Division Signatory, DO1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Subject</b>                | Request for Approval for Interchangeability after Provisional Determination - Summary Review of Amendment to BLA 761392/Original 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Application Type</b>       | 351(k) BLA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>BLA/Supplement Number</b>  | 761392/Original 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Received Date</b>          | April 30, 2025                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Target Action Date</b>     | October 29, 2025                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Division/Office</b>        | Division of General Endocrinology/Office of Cardiology, Hematology, Endocrinology, and Nephrology<br>Division of Oncology 1/Office of Oncologic Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Proprietary Name</b>       | Ospomyv (proposed interchangeable biosimilar to US-licensed Prolia (US-Prolia)); and<br>Xbryk (proposed interchangeable biosimilar to US-licensed Xgeva (US-Xgeva))                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Proper Name</b>            | denosumab-dssb                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Product Code</b>           | SB16                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Reference Product</b>      | US-Prolia/Xgeva (denosumab)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Pharmacologic Class</b>    | Receptor Activator of Nuclear Factor Kappa B (RANK) Ligand (RANKL) Inhibitor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Applicant</b>              | Samsung Bioepis Co, Ltd                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Approved Indication(s)</b> | Ospomyv (proposed interchangeable biosimilar to US-Prolia): <ul style="list-style-type: none"> <li>• Treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures.</li> <li>• Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.</li> <li>• Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are</li> </ul> |

|                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                               | <p>either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.</p> <ul style="list-style-type: none"> <li>• Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures.</li> <li>• Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.</li> </ul> <p>Xbryk (proposed interchangeable biosimilar to US-Xgeva):</p> <ul style="list-style-type: none"> <li>• Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.</li> <li>• Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.</li> <li>• Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.</li> </ul> |
| <b>Purpose of the Submission</b>              | <p>Approval of Ospomyv (denosumab-dssb) as interchangeable with US-Prolia (denosumab) and Xbryk (denosumab-dssb) as interchangeable with US-Xgeva (denosumab) as follows per the provisional determination letter dated February 12, 2025:</p> <ul style="list-style-type: none"> <li>• Ospomyv (denosumab-dssb) 60 mg/mL injection for subcutaneous use in a single-dose prefilled syringe (PFS) as interchangeable with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS, and</li> <li>• Xbryk (denosumab-dssb) 120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a single-dose vial (vial) as interchangeable with US-Xgeva (denosumab) 120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a vial.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>New Indication(s) and/or Population(s)</b> | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>New Dosing Regimen(s)</b>                  | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Recommendation on Regulatory Action</b>    | Approval of:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <ul style="list-style-type: none"> <li>• Ospomyv (denosumab-dssb) 60 mg/mL injection for subcutaneous use in a PFS as interchangeable with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS, and</li> <li>• Xbryk (denosumab-dssb) 120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a vial as interchangeable with US-Xgeva (denosumab) 120 mg/1.7 mL (70mg/mL) injection for subcutaneous use in a vial.</li> </ul> |
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## 1. Background/Regulatory History

The subject of this review is the amendment submitted on September 18, 2025, to BLA 761392/Original 2 to seek approval for interchangeability of all products under the application that previously received a provisional determination on February 12, 2025.

On February 12, 2024, Samsung Bioepis Co., Ltd. (Applicant) submitted a Biologics License Application (BLA) 761392 under section 351(k) of the Public Health Service (PHS) Act seeking licensure of Ospomyv (denosumab-dssb) injection and Xbryk (denosumab-dssb) injection, product code SB16, as an interchangeable biosimilar product as follows:

- Ospomyv (denosumab-dssb) injection 60 mg/mL in a single-dose prefilled syringe (PFS) for subcutaneous use as an interchangeable biosimilar with US-Prolia (denosumab) 60 mg/mL in a PFS for subcutaneous use, and
- Xbryk (denosumab-dssb) injection 120 mg/1.7 mL (70mg/mL) in a single-dose vial (vial) for subcutaneous use as an interchangeable biosimilar with US-Xgeva (denosumab) 120 mg/1.7 mL (70mg/mL) in a single-dose vial for subcutaneous use.

The data and information submitted in the original BLA supported licensure of Ospomyv and Xbryk as biosimilar products. The Applicant included a scientific justification that Ospomyv and Xbryk will produce the same clinical result in any given patient for each condition of use for which licensure is sought and for which US-Prolia and US-Xgeva have been approved, a scientific justification for extrapolating data and information to support licensure of Ospomyv and Xbryk as interchangeable for each indication for which licensure is sought and for which US-Prolia and US-Xgeva have been previously approved, and use-related risk analyses and comparative analyses for the PFS platform. The data and information in the BLA demonstrated that Ospomyv and Xbryk can be expected to produce the same clinical result as US-Prolia and US-Xgeva, respectively, in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between the use of Ospomyv and US-Prolia or Xbryk and US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch.

After reviewing BLA 761392, FDA did not identify any deficiencies that would justify a complete response action. FDA considered whether any unexpired first interchangeable exclusivity precluded approval of any products in the BLA as interchangeable. Ospomyv and Xbryk could not be approved as interchangeable at that time due to unexpired first interchangeable exclusivity for Jubbonti (denosumab-bbdz) injection 60 mg/mL for subcutaneous use and Wyost (denosumab-bbdz) injection 120 mg/1.7 mL (70 mg/mL) for subcutaneous use. Refer to the Purple Book at <https://purplebooksearch.fda.gov> for more information about unexpired first interchangeable exclusivity.

Therefore, BLA 761392 was administratively split to facilitate the following:

- An approval action for BLA 761392/Original 1:
  - o Ospomyv (denosumab-dssb) 60 mg/mL injection for subcutaneous use in a PFS is biosimilar to US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS,
  - o Xbryk (denosumab-dssb) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial is biosimilar to US-Xgeva (denosumab) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.
- A provisional determination for BLA 761392/Original 2:
  - o Ospomyv (denosumab-dssb) 60 mg/mL injection for subcutaneous use in a PFS meets the applicable standards for interchangeability with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS,
  - o Xbryk (denosumab-dssb) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial meets the applicable standards for interchangeability with US-Xgeva (denosumab) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

The “Biosimilar Multidisciplinary Evaluation and Review” (BMER) documenting the Agency’s review of BLA 761392 dated February 12, 2025, is incorporated herein by reference.

BLA 761392/Original 1 received an approval letter dated February 13, 2025, and BLA 761392/Original 2 received a provisional determination letter dated February 12, 2025. The provisional determination letter instructed the Applicant to submit an amendment no more than six months prior to the date it believed that the application would be eligible for approval.

## **2. Request for Approval**

To obtain approval of Ospomyv (denosumab-dssb) 60 mg/mL injection for subcutaneous use in a PFS and Xbryk (denosumab-dssb) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a single dose vial as interchangeable products, the Applicant submitted an amendment, “Request for Approval of Provisional Determination of Interchangeability on BLA 761392/Original 2,” on April 30, 2025, which is the subject of this review.

## **3. Summary Recommendations**

The provisional determination letter issued February 12, 2025, states, “[i]n addition to a safety update, the amendment should also identify changes, if any, in the application, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS).”

In its Request for Approval dated April 30, 2025, the Applicant noted the submission of Supplement 1 - Changes Being Effectuated (CBE-0) on February 25, 2025, pertaining to chemistry, manufacturing, and controls data. Supplement 1 was approved on August 25, 2025. The Applicant submitted three additional CMC supplements (Supplements 2, 3, and 4) after submitting its request for approval on April 30, 2025. Supplement 2 (CBE-30) pertains to (b) (4). Supplement 3 (CMC-Prior Approval Supplement [PAS]) pertains to (b) (4). (b) (4); and Supplement 4 (CMC-PAS) pertains to (b) (4). Review of Supplements 2, 3, and 4 is ongoing.

There have been no changes to the REMS since the approval of the original BLA.

All manufacturing facilities remain compliant since the approval of the original BLA.

On June 11, 2025, the Applicant submitted a Periodic Adverse Experience Report (PADER) for Ospomyv and Xbryk covering the safety reporting period from February 13, 2025, to May 12, 2025. On September 11, 2025, the Applicant submitted a PADER for Ospomyv and Xbryk covering the safety reporting period from May 13, 2025, to August 12, 2025. The review team identified no safety concerns in their review of both PADERs.

The review team considered the changes and updates to the application, including ongoing review of interim CMC supplements, and determined that they do not change our previous determination that BLA 761392/Original 2 meets the applicable standards for interchangeability.

#### **4. Labeling**

On May 22, 2025, FDA approved BLA 125320/S-219 for US-Prolia updating subsection 8.4 Pediatric Use in the USPI. On May 30, 2025, FDA approved BLA 125320/S-222 for US-Xgeva updating section 2 Dosage and Administration in the USPI as well as carton and container labeling. The Applicant submitted revised draft branded product and unbranded biological product labeling for Ospomyv and Xbryk that incorporated relevant information from the updated Prolia and Xgeva labeling, respectively, with appropriate modifications. The review team determined that the proposed labeling for Ospomyv and Xbryk is compliant with the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The final branded product and unbranded biological product labeling for both Ospomyv and Xbryk will be attached to the approval letter.

## 5. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, a biological product that is interchangeable with the reference product is not considered to have a “new active ingredient” for purposes of PREA.

At the time BLA 761392/Original 1 was approved on February 13, 2025, a PREA PMR was issued:

- 4799-1 Provide an assessment of Ospomyv (denosumab-dssb) for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age.

Final Report Submission: 06/2026

The Applicant submitted revised labeling to align with changes to the US-Prolia labeling updates approved on May 22, 2025, which updated subsection 8.4 Pediatric Use in the USPI. The updated labeling states that safety and effectiveness of Ospomyv have not been established in pediatric patients, including for patients aged 5-17 years with glucocorticoid-induced osteoporosis (GIOP). The Applicant fulfilled PREA requirements for this indication by including the relevant pediatric information in the labeling.

PeRC discussed this application on October 7, 2025, and agreed this product is assessed in pediatric patients 5 to 17 years of age for the GIOP indication and that PREA PMR 4799-1 is fulfilled.

## 6. REMS and Postmarketing Requirements and Commitments

### 6.1. Recommendations for Risk Evaluation and Mitigation Strategies

US-Prolia is approved with a REMS to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients. The US-Prolia REMS consists of a communication plan (CP) and timetable for submission of assessments.

Ospomyv was approved with a REMS on February 13, 2025. The Ospomyv REMS is comparable to the US-Prolia REMS and is designed to communicate the same key risk messages and achieve the same level of patient safety. The requirements of the Ospomyv REMS will also apply to any unbranded denosumab-dssb distributed by the

Applicant.

The Ospomyv REMS goal and objective are:

The goal of the Ospomyv REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Ospomyv.

Objective 1: Inform healthcare providers on:

- Risk of severe hypocalcemia in patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m<sup>2</sup>)
- Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Ospomyv in patients with advanced chronic kidney disease

The REMS elements consist of a Communication plan (CP) and timetable for submission of assessments.

The Communication Plan materials include:

- REMS Letter to Healthcare Providers
- REMS Letter to Professional Societies
- Patient Guide
- REMS website

Timetable for submission of assessments is at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS.

The currently approved REMS for Ospomyv will be attached to the approval letter.

## 6.2 Postmarketing Requirements and Commitments

The Applicant has fulfilled the following PMR:

- 4799-1 Provide an assessment of Ospomyv (denosumab-dssb) for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age.

## 7. Recommended Regulatory Action

The data and information in BLA 761392/Original 2, including the information submitted by the Applicant with this amendment, are sufficient to maintain FDA's determination

that Ospomyv and Xbryk can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Ospomyv and Xbryk is not greater than the use of US-Prolia and US-Xgeva without such alternation or switch. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that:

- Ospomyv (denosumab-dssb) 60 mg/mL injection for subcutaneous use in a PFS is interchangeable with US-Prolia 60 mg/mL injection for subcutaneous use in a PFS, and
- Xbryk (denosumab-dssb) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial is interchangeable with US-Xgeva 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

These Ospomyv and Xbryk (denosumab-dssb) products have met the statutory interchangeability requirements for the following indications for which US-Prolia and US-Xgeva have been previously approved:

Ospomyv:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

Xbryk:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.

- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

As noted in the Purple Book (<https://purplebooksearch.fda.gov>), the applicable first interchangeable exclusivity expiration dates are:

- Jubbonti (denosumab-bbdz) 60 mg/mL injection for subcutaneous use: October 29, 2025
- Wyost (denosumab-bbdz) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use: October 29, 2025

The recommended regulatory action is approval of:

- Ospomyv (denosumab-dssb) 60 mg/mL injection for subcutaneous use in a PFS is interchangeable with US-Prolia (denosumab) 60 mg/mL injection for subcutaneous use in a PFS, and
- Xbryk (denosumab-dssb) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial is interchangeable with US-Xgeva (denosumab) 120 mg/1.7 mL (70 mg/mL) injection for subcutaneous use in a vial.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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CHAU Q NGUYEN  
10/23/2025 11:48:09 AM

SABIHA KHAN  
10/23/2025 12:00:03 PM

MICHELLE T LUO  
10/23/2025 12:04:09 PM

THERESA E KEHOE  
10/24/2025 07:30:49 AM

CHRISTY L OSGOOD  
10/24/2025 10:29:42 AM

## BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

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|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>                         | BLA 351(k)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Application Number</b>                       | BLA 761392                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Received Date</b>                            | February 12, 2024                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>BsUFA Goal Date</b>                          | February 12, 2025                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Division/Office</b>                          | Division of General Endocrinology/Office of Cardiology, Hematology, Endocrinology and Nephrology<br>Division of Oncology 1/ Office of Oncologic Diseases                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Review Completion Date</b>                   | See DARRTS stamped date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Product Code Name</b>                        | SB16                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Proposed Nonproprietary Name<sup>1</sup></b> | denosumab-dssb                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Proposed Proprietary Name<sup>1</sup></b>    | Ospomyv (proposed interchangeable biosimilar to US-Prolia);<br>Xbryk (proposed interchangeable biosimilar to US-Xgeva)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Pharmacologic Class</b>                      | Receptor Activator Of Nuclear Factor Kappa B (RANK) Ligand (RANKL) Inhibitor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Applicant</b>                                | Samsung Bioepis Co, Ltd                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Applicant Proposed Indication(s)</b>         | Ospomyv (proposed interchangeable biosimilar to US-Prolia): <ul style="list-style-type: none"> <li>• Treatment of postmenopausal women with osteoporosis at high risk for fracture.</li> <li>• Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.</li> <li>• Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months.</li> <li>• Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.</li> <li>• Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.</li> </ul> Xbryk (proposed interchangeable biosimilar to US-Xgeva): |

<sup>1</sup>Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

Biosimilar Multidisciplinary Evaluation and Review (BMER) 351(k) BLA, BLA 761392, SB16, a proposed biosimilar to U.S.-licensed Prolia and U.S.-licensed Xgeva

|                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                            | <ul style="list-style-type: none"> <li>• Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.</li> <li>• Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.</li> <li>• Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.</li> </ul> |
| <b>Recommendation on Regulatory Action</b> | Approval of SB16 as a biosimilar to US-Prolia and US-Xgeva. Provisional determination that SB16 is interchangeable with US-Prolia and US-Xgeva. Approval as interchangeable is precluded due to unexpired first interchangeable exclusivity for Jubbonti and Wyost.                                                                                                                                                                                                    |

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OBP = Office of Biotechnology Products

OPMA = Office of Pharmaceutical Manufacturing Assessment

OPDP = Office of Prescription Drug Promotion

OSI = Office of Scientific Investigations

OSE = Office of Surveillance and Epidemiology

DEPI = Division of Epidemiology

DMEPA = Division of Medication Error and Prevention Analysis

DRISK = Division of Risk Management

DPMH = Division of Pediatric and Maternal Health

## Glossary

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|           |                                                                            |
|-----------|----------------------------------------------------------------------------|
| AC        | Advisory Committee                                                         |
| ADA       | Anti-drug Antibodies                                                       |
| AE        | Adverse Event                                                              |
| BLA       | Biologics License Application                                              |
| BMER      | Biosimilar Multidisciplinary Evaluation and Review                         |
| BMI       | Body Mass Index                                                            |
| BPD       | Biosimilar Biological Product Development                                  |
| BsUFA     | Biosimilar User Fee Agreements                                             |
| CDER      | Center for Drug Evaluation and Research                                    |
| CDRH      | Center for Devices and Radiological Health                                 |
| CDTL      | Cross-Discipline Team Leader                                               |
| CFR       | Code of Federal Regulations                                                |
| CI        | Confidence Interval                                                        |
| CMC       | Chemistry, Manufacturing, and Controls                                     |
| CRF       | Case Report Form                                                           |
| CRO       | Contract Research Organization                                             |
| CRP       | C-reactive Protein                                                         |
| CSC       | Computational Science Center                                               |
| CTD       | Common Technical Document                                                  |
| CV        | Coefficient of Variation                                                   |
| DEPI      | Division of Epidemiology                                                   |
| DGE       | Division of General Endocrinology                                          |
| DIA       | Division of Inspectional Assessment                                        |
| DMC       | Data Monitoring Committee                                                  |
| DMA       | Division of Microbiology Assessment                                        |
| DMEPA     | Division of Medication Error Prevention and Analysis                       |
| DPMH      | Division of Pediatric and Maternal Health                                  |
| DRISK     | Division of Risk Management                                                |
| eCTD      | Electronic Common Technical Document                                       |
| FDA       | Food and Drug Administration                                               |
| FISH      | Fluorescence In Situ Hybridization                                         |
| GCP       | Good Clinical Practice                                                     |
| GMR       | Geometric Mean Ratio                                                       |
| ICH       | International Conference on Harmonization                                  |
| IND       | Investigational New Drug                                                   |
| ITT       | Intention to Treat                                                         |
| LLOQ      | Lower Limit of Quantitation                                                |
| MAPP      | Manual of Policy and Procedure                                             |
| mITT      | Modified Intention to Treat                                                |
| MOA       | Mechanism of Action                                                        |
| NAb       | Neutralizing Antibody                                                      |
| NCI-CTCAE | National Cancer Institute – Common Terminology Criteria for Adverse Events |
| NCT       | National Clinical Trial                                                    |

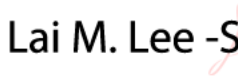
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|-------------|-----------------------------------------------------|
| OBP         | Office of Biotechnology Products                    |
| OCP         | Office of Clinical Pharmacology                     |
| OOD         | Office of Oncology Drugs                            |
| OPDP        | Office of Prescription Drug Promotion               |
| OSE         | Office of Surveillance and Epidemiology             |
| OSI         | Office of Scientific Investigations                 |
| OSIS        | Office of Study Integrity and Surveillance          |
| PD          | Pharmacodynamics                                    |
| PeRC        | Pediatric Review Committee                          |
| PFS         | Pre-filled syringe                                  |
| PK          | Pharmacokinetics                                    |
| PMC         | Postmarketing Commitments                           |
| PMR         | Postmarketing Requirements                          |
| PREA        | Pediatric Research Equity Act                       |
| PHS         | Public Health Service                               |
| PLR         | Physician Labeling Rule                             |
| PLLR        | Pregnancy and Lactation Labeling Rule               |
| RANKL       | Receptor activator of nuclear factor kappa B ligand |
| REMS        | Risk Evaluation and Mitigation Strategies           |
| ROA         | Route of Administration                             |
| SAE         | Serious Adverse Event                               |
| SAP         | Statistical Analysis Plan                           |
| SC          | subcutaneous                                        |
| SOC         | System Organ Class                                  |
| SOP         | Standard Operating Procedures                       |
| TEAE        | Treatment-Emergent Adverse Events                   |
| ULOQ        | Upper Limit of Quantitation                         |
| U.S.-Prolia | U.S.-licensed Prolia                                |
| U.S.-Xgeva  | U.S.-licensed Xgeva                                 |

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Biosimilar Multidisciplinary Evaluation and Review (BMER)

|                                    |                                                                                                                                                                        |           |              |
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## 1. Executive Summary

---

### 1.1. Product Introduction

Denosumab is a human monoclonal IgG2 antibody that targets the receptor activator of nuclear factor kappa B ligand (RANKL). It is marketed in the United States under the tradenames Prolia (60 mg/1 mL in a pre-filled syringe [PFS]) and Xgeva (120 mg/1.7 mL or 70 mg/mL in a single-dose vial). The indications and strength of US-Prolia are different from the indications and strength of US-Xgeva.

The Applicant proposes SB16 as an interchangeable biosimilar product to US-Prolia and US-Xgeva; the Applicant's proposed proprietary names are Ospomyv and Xbryk, respectively.

The Applicant seeks the same indications for SB16 as those which are approved for US-Prolia and US-Xgeva. The strengths, dosage form, route of administration, indications, and dosing regimens for SB16 will be the same as those of US-Prolia and US-Xgeva. They are listed below:

Ospomyv:

- Strength: 60 mg/1 mL
- Dosage form: injection
- Route of administration: subcutaneous (SC)
- Dosing regimen: 60 mg injected SC every six months.
- Indications
  - Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures.
  - Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
  - Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
  - Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures

- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

Xbryk:

- Strength: 120 mg/1.7 mL (70 mg/mL)
- Dosage form: injection
- Route of administration: subcutaneous (SC)
- Indications and associated dosing regimen:
  - Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors (120 mg injected SC every 4 weeks)
  - Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (120 mg injected SC every 5 weeks with addition 120 mg doses on Days 8 and 15 of the first month of therapy)
  - Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy (120 mg injected SC every 5 weeks with addition 120 mg doses on Days 8 and 15 of the first month of therapy)

## **1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act**

Not applicable

## **1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment**

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to receptor activator of the nuclear factor kappa-B ligand (RANKL), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclast, the cells responsible for bone resorption thereby modulating calcium release from bone.

This BLA contains sufficient data and information to demonstrate that SB16 has the same mechanism(s) of action as those of US-Prolia and US-Xgeva. The Applicant performed a comparative analytical assessment of SB16 and US-Prolia and US-Xgeva. The data provided support the conclusion that SB16 is highly similar to US-Prolia and US-Xgeva.

US-Prolia is licensed in 60 mg/1 mL in a pre-filled syringe (PFS) and US-Xgeva is licensed in 120 mg/1.7 mL or 70 mg/mL in a single-dose vial.

SB16 is proposed as below:

For subcutaneous injection:

- Single-dose prefilled syringe containing 60 mg denosumab-dssb in a 1 mL solution.
- Single-dose glass vial containing 120 mg denosumab-dssb in 1.7 mL solution (70 mg/mL).

SB16 has the same route of administration, dosage form, and strengths as those of US-Prolia and of US-Xgeva. Refer to Section 1.1 for details.

Additionally, the conditions of use which the Applicant is seeking licensure have been previously approved for US-Prolia and US-Xgeva.

#### **1.4. Inspection of Manufacturing Facilities**

Pre-license on-site inspections (PLI) were conducted at Samsung Biologics, Incheon, Republic of Korea (FEI: 3010479596), listed in this application as the SB16 drug substance (DS) and SB16 drug product (vial DP presentation) manufacturing facility, as well as at (b) (4) (FEI (b) (4)), listed as the SB16 DP (PFS DP presentation) manufacturing facility. At the conclusion of the inspections, FDA conveyed deficiencies to the respective representatives of the facilities along with the initial “withhold” classification of both firms by the Agency. Samsung Biologics and (b) (4) responded and provided adequate response and descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy to address the deficiencies communicated in Form FDA 483. The initial “withhold” classification was revised and approval was recommended for the DS and DP manufacturing facilities. Moreover, based on a CGMP inspection of Samsung Bioepis Co., Ltd., Korea (FEI 3010031951), listed as site for in-process testing for the SB16 DS, the facility compliance status was changed to a potential Official Action Indicated (pOAI). Samsung Bioepis provided responses and thus the initial pOAI was changed to Voluntary Action Indicated (VAI). Overall, all proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

#### **1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product**

The Applicant provided adequate data to establish the scientific bridge to justify the relevance of data generated from the study SB16-3001, which used EU-Prolia as the non-U.S.-licensed comparator product, to the assessment of biosimilarity:

- The Office of Pharmaceutical Products (OPQ), CDER has determined, and I agree, that based on the data provided by the Applicant, the analytical component of the scientific bridge between SB16, US-Prolia, and EU-Prolia was established.
- The Office of Clinical Pharmacology (OCP) has determined, and I agree, that based on the data provided by the Applicant, the PK component of the scientific bridge was established between SB16, US-Prolia and EU-Prolia.

## 1.6. Biosimilarity and Interchangeability Assessment

**Table 1: Summary and Assessment of Biosimilarity and Interchangeability**

| <b>Comparative Analytical Studies<sup>2</sup></b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Summary of Evidence                               | <ul style="list-style-type: none"> <li>The comparative analytical assessment included comparisons between SB16 and US-Prolia, US-Xgeva, and EU-Prolia.</li> <li>SB16 is highly similar to US-Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components.</li> <li>SB16 has the same strengths, dosage form, and route of administration as US-Prolia and US-Xgeva.</li> <li>The analytical component of the scientific bridge was established to support the use of EU-Prolia as a comparator in the comparative clinical study.</li> </ul> |
| Assessment of Residual Uncertainties              | <ul style="list-style-type: none"> <li>There are no residual uncertainties from the product quality assessment</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Animal/Nonclinical Studies</b>                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Summary of Evidence                               | <ul style="list-style-type: none"> <li>The information in the pharmacology/toxicology assessment supports the demonstration of biosimilarity</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Assessment of Residual Uncertainties              | <ul style="list-style-type: none"> <li>No residual uncertainties from the pharmacology/toxicology assessment</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Clinical Studies</b>                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b><i>Clinical Pharmacology Studies</i></b>       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Summary of Evidence                               | <ul style="list-style-type: none"> <li>PK similarity between SB16 and US-Prolia was demonstrated in healthy male subjects (Study SB16-1001) and supports a demonstration of no clinically meaningful differences between SB16 and US-Prolia.</li> <li>Because analytical similarity between SB16, US-Prolia and US-Xgeva is demonstrated, PK data from Study SB16-1001 also support that</li> </ul>                                                                                                                                                                       |

<sup>2</sup>Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

|                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      | <p>SB16 is expected to have similar PK as US-Xgeva.</p> <ul style="list-style-type: none"> <li>The PK similarity between SB16, EU-Prolia and US-Prolia demonstrated in Study SB16-1001 established the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Prolia for the assessment of biosimilarity in comparative clinical study in postmenopausal women with osteoporosis (Study SB16-3001).</li> <li>The anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were very low and comparable between SB16 and US-Prolia in healthy male subjects in Study SB16-1001, and between SB16 and EU-Prolia in female subjects with postmenopausal osteoporosis in Study SB16-3001. Immunogenicity data from Study SB16-1001 and Study SB16-3001 support the demonstration that SB16 has no clinically meaningful differences from US-Prolia and US-Xgeva.</li> </ul> |
| Assessment of Residual Uncertainties | <ul style="list-style-type: none"> <li>There are no residual uncertainties</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Additional Clinical Studies</b>   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Summary of Evidence                  | <ul style="list-style-type: none"> <li>The Applicant conducted a randomized, double-blind, comparative clinical study in 457 postmenopausal women with osteoporosis, comparing the efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity of SB16 and EU-Prolia (Study SB16-3001). Subjects were randomized to receive SB16 or EU-Prolia 60 mg injected SC every six months for one year (Treatment period 1). At Month 12, subjects initially assigned to EU-Prolia in Treatment period 1 were re-randomized to either continue EU-Prolia or transition to SB16, whereas subjects who were randomized to SB16 continued the drug. Subjects were then followed for additional 6 months.</li> <li>An adequate scientific bridge was established in the comparative analytical studies and the PK similarity study in healthy male subjects (Study</li> </ul>                                              |

|                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      | <p>SB16-1001) to justify the relevance of EU-Prolia used in Study SB16-3001.</p> <ul style="list-style-type: none"> <li>• This study demonstrated that SB16 and EU-Prolia have similar efficacy with respect to the percent change in lumbar spine BMD at Week 52 from baseline. The 90% confidence interval was within the <math>\pm 1.45\%</math> equivalence margin.</li> <li>• The safety profile of SB16 was comparable to that of EU-Prolia. No meaningful differences in the incidence of specific adverse events were identified, and the small differences in incidences of some of the treatment emergent adverse events were likely due to chance.</li> <li>• The study also demonstrated similarity of SB16 and EU-Prolia with respect to pharmacokinetics of denosumab, the pharmacodynamic effect on biomarker of bone turnover, and immunogenicity.</li> </ul> |
| Assessment of Residual Uncertainties | <ul style="list-style-type: none"> <li>• There are no residual uncertainties</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Switching Study</b>               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Summary of Evidence                  | <ul style="list-style-type: none"> <li>• FDA determined that a switching study is unnecessary to support a demonstration of interchangeability for SB16</li> <li>• The Applicant has provided adequate data and information to support a demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of SB16 and US-Prolia or SB16 and US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch</li> </ul>                                                                                                                                                                                                                                                                                                                                                                   |
| Assessment of Residual Uncertainties | <ul style="list-style-type: none"> <li>• There are no residual uncertainties from the clinical perspective.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Any Given Patient Evaluation</b>  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Summary of Evidence                  | <ul style="list-style-type: none"> <li>• The Applicant has provided adequate data and information, including the analytical and clinical data, to support a demonstration that SB16 can be expected to produce the same clinical result as that of US-Prolia and US-Xgeva in any given patient.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

|                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Assessment of Residual Uncertainties | <ul style="list-style-type: none"> <li>There are no residual uncertainties from the clinical perspective.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Extrapolation</b>                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Summary of Evidence                  | <ul style="list-style-type: none"> <li>Division of General Endocrinology (DGE) and the Office of Oncology Drugs (OOD) have determined that the Applicant has provided adequate scientific justification and agrees with the Applicant's justification for extrapolation to the other indications listed in the US-Prolia and US-Xgeva USPIs being sought for licensure based on: 1) the mechanism of action of denosumab, 2) the analysis of the known safety and immunogenicity profiles of denosumab across each of the indications being sought and 3) the assessment of any differences in expected toxicities for each indication.</li> <li>The data and information submitted by the Applicant, including the justification for extrapolation, supports licensure of SB16 as an interchangeable biosimilar to US-Prolia and US-Xgeva for the following indications for which US-Prolia and US-Xgeva have been previously approved: <ul style="list-style-type: none"> <li>Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures.</li> <li>Treatment to increase bone mass in men with osteoporosis, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.</li> <li>Treatment of glucocorticoid-induced osteoporosis who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of</li> </ul> </li> </ul> |

|                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      | <p>osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.</p> <ul style="list-style-type: none"> <li>○ Treatment to increase bone mass in men at high for fracture receiving androgen deprivation therapy for prostate cancer</li> <li>○ Treatment to increase bone mass in women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer</li> <li>○ Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors</li> <li>○ Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity</li> <li>○ Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy</li> </ul> |
| Assessment of Residual Uncertainties | <ul style="list-style-type: none"> <li>• There are no residual uncertainties regarding the extrapolation of data and information to support licensure of SB16 as an interchangeable biosimilar to US-Prolia and US-Xgeva for the above indications.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

### 1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that SB16 is highly similar to U.S.-Prolia and U.S.-Xgeva, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between SB16 and U.S.-Prolia, or between SB16 and U.S.-Xgeva, in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that SB16 can be expected to produce the same clinical result as U.S.-licensed Prolia and U.S.-licensed Xgeva in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of SB16 and U.S.-Prolia or between SB16 and U.S.-Xgeva is not greater than the risk of using U.S.-Prolia or U.S.-Xgeva without alternation or switch. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that SB16 is biosimilar to U.S.-Prolia and to U.S.-Xgeva and meets the statutory criteria to be interchangeable with U.S.-Prolia and U.S.-Xgeva as follows:

- SB16, 60 mg/mL injection for SC use in a single-dose PFS as an interchangeable biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- SB16, 120 mg/1.7 mL injection for SC use in a single-dose vial as an interchangeable biosimilar to US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial,

for each of the following indications for which U.S.-Prolia and U.S.-Xgeva have been previously approved and for which the Applicant is seeking licensure of SB16:

US-Prolia:

- Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

US-Xgeva:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

FDA has not identified any deficiencies that would justify a complete response action and has provisionally determined that SB16 meets the statutory interchangeability criteria for any condition of use as described above. However, pursuant to section 351(k)(6) of the PHS Act, FDA is unable to approve SB16 as interchangeable because of unexpired first interchangeable exclusivity (FIE) for US-licensed Jubbonti and Wyost. FDA has previously determined that FIE for Jubbonti and Wyost will

expire on October 29, 2025. (Refer to the Purple Book at <https://purplebooksearch.fda.gov/>.)

Therefore, BLA 761392 will be administratively split to facilitate an approval action for SB16 as biosimilar to US-Prolia and US-Xgeva (“Original 1”) and a provisional determination that SB16 would be interchangeable with US-Prolia and US-Xgeva (“Original 2”).

The review team recommends approval of SB16 as a biosimilar product as follows:

- SB16, 60 mg/mL injection for SC use in a single-dose PFS is biosimilar to US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS,
- SB16, 120 mg/1.7 mL injection for SC use in a single-dose vial is biosimilar to US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial.

The review team also recommends a Provisional Determination that:

- SB16, 60 mg/mL injection for SC use in a single-dose PFS meets the applicable standards for interchangeability with US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS, and
- SB16, 120 mg/1.7 mL injection for SC use in a single-dose vial meets the applicable standards for interchangeability with US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial,

BLA 761392/Original 2 will receive a Provisional Determination letter. The Applicant is expected to submit an amendment seeking approval no more than six months prior to the expiration of such exclusivity or when the Applicant believes that BLA 761392 Original 2 will become eligible for approval.

The CDTL and Division Signatory agree with the above assessment and recommendation.

**Author:**

Shivangi Vachhani, MD  
Cross Disciplinary Team Leader, DGE

## **2. Introduction and Regulatory Background**

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### **2.1. Summary of Presubmission Regulatory History Related to Submission**

On February 20, 2019, a pre-IND Biosimilar Product Development (BPD) Type 2 meeting occurred between FDA and the Applicant. To support a 351(k) application, the Applicant proposed to conduct a comparative pharmacokinetic (PK) study in healthy male subjects comparing safety, tolerability, and immunogenicity profiles of SB16 and European Union (EU)-Prolia, and a comparative clinical study in postmenopausal

female subjects with osteoporosis to compare the efficacy, safety, pharmacodynamics (PD), PK, and immunogenicity of SB16 and EU-Prolia. FDA informed the Applicant that they would need to justify the relevance of clinical data generated using EU-Prolia to support a demonstration of no clinically meaningful differences between SB16 and US-licensed Prolia and between SB16 US-licensed Xgeva. The Applicant agreed to conduct a 3-way comparative PK clinical study in healthy adult males using SB16, US-licensed Prolia, and EU-approved Prolia.

On March 29, 2021, the Applicant opened IND 141802 with submission of protocol SB16-1001 for a single dose, PK similarity study of SB16 and US-licensed Prolia and EU-approved Prolia, assessing PK, PD, safety, tolerability, and immunogenicity of SB16 in healthy adult males. FDA considered the study safe to proceed.

On October 29, 2021, a BPD Type 2 meeting occurred between FDA and the Applicant to discuss analytical comparability and similarity assessment protocols. The Applicant agreed to establish an indirect quality bridge between SB16 and US-Xgeva, using four-way quality, *in vitro* comparability studies and comparative similarity data between SB16 (60 PFS and 120 mg vial), US-Prolia, EU-Prolia and US-Xgeva, *in lieu* of a clinical study comparing SB16 and US-Xgeva.

The Applicant proposed to establish a scientific bridge to justify the relevance of the comparative clinical data obtained using EU-approved Prolia and support the assessment of biosimilarity between SB16 and US-Prolia and US-Xgeva as follows:

- Establish three-way PK similarity between SB16 and US-licensed Prolia and EU-approved Prolia in the PK similarity study SB16-1001.
- Conduct comparative analytical assessments (CAA) including a three-way comparison of SB16 60 mg/mL PFS with US-Prolia and EU-Prolia, and a CAA comparing SB16 120 mg vial with US-Xgeva

Subsequent interactions between FDA and the Applicant are shown [Table 2](#).

**Table 2: Regulatory Milestones**

| Date              | Event                        | Comments                                                                                                                 |
|-------------------|------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| February 20, 2019 | Pre-IND (BPD Type 2 meeting) | Discussed product quality, non-clinical, clinical, and extrapolation plan for SB16.                                      |
| March 29, 2021    | IND 141802 opened            | Submission of protocol SB16-1001 for a PK similarity study to compare SB16 to US-licensed Prolia and EU-approved Prolia. |

| Date               | Event                       | Comments                                                                                                                                          |
|--------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| October 21, 2021   | BPD Type 2 meeting          | Discussed product quality development for SB16                                                                                                    |
| November 09, 2022  | Advice letter from FDA      | FDA communicated to the Applicant that a switching study would not be necessary to support interchangeability.                                    |
| April 21, 2023     | Agreed iPSP letter from FDA | initial pediatric study plan (iPSP) agreement letter sent to the sponsor                                                                          |
| June 01, 2023      | Advice letter from FDA      | FDA communicated the necessity of addressing statutory requirements in the application to support a demonstration of interchangeability for SB16. |
| September 22, 2023 | BPD Type 4 meeting          | Discuss planned 351(k) BLA submission.                                                                                                            |

## 2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

No *in vivo* nonclinical studies were submitted for SB16.

**Table 3: Relevant Clinical Studies**

| Study Identity             | National Clinical Trial (NCT) no. | Study Objective                                                                                                   | Study Design                                                                                     | Study Population            | Treatment Groups                                                            |
|----------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------------------|-----------------------------------------------------------------------------|
| <b>PK Similarity Study</b> |                                   |                                                                                                                   |                                                                                                  |                             |                                                                             |
| Study SB16-1001            | EudraCT No. 2020-002592-35        | Compare the pharmacokinetics, pharmacodynamics, safety, and immunogenicity between SB16, US-Prolia, and EU-Prolia | Randomized, multicenter (France and US) double blind, three-arm, parallel group, active control, | Healthy adult male Subjects | SB16 60 mg SC once: 56 subjects<br><br>US-Prolia 60 mg SC once: 56 subjects |

| Study Identity                         | National Clinical Trial (NCT) no. | Study Objective                                                                                           | Study Design                                                                                                                                                                      | Study Population                       | Treatment Groups                                                                                                                                                                                                                                                 |
|----------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                        |                                   |                                                                                                           | single-dose study                                                                                                                                                                 |                                        | EU-Prolia 60 mg SC once: 56 subjects                                                                                                                                                                                                                             |
| <b>Comparative Clinical Study(ies)</b> |                                   |                                                                                                           |                                                                                                                                                                                   |                                        |                                                                                                                                                                                                                                                                  |
| Study SB16-3001                        | EudraCT No. 2020-001479-34        | Compare the efficacy, safety, immunogenicity, pharmacokinetics and pharmacodynamics of SB16 and EU-Prolia | Randomized, multicenter (Czech Republic, Denmark, Republic of Korea, Lithuania, Poland) double blind, active control, comparative clinical study involving two treatment periods. | Women with postmenopausal osteoporosis | <b>Main Period</b> (52 weeks):<br>EU-Prolia 60 mg SC q6 months: 231 subjects<br><br>SB16 60 mg SC q6 months: 225 subjects<br><br><b>Transition Period</b> (26 weeks):<br>EU-Prolia 60 mg SC q6 months: 101 subjects<br><br>SB16 60 mg SC q6 months: 306 subjects |

**Authors:**

Nicholas Heiniger, MD  
Clinical Reviewer, DGE

Shivangi Vachhani, MD  
Clinical Team Leader

### 3. Summary of Conclusions of Other Review Disciplines

#### 3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761392 for SB16 manufactured by Samsung Bioepis Co., Ltd. The data submitted in this application are adequate to support the conclusion that the manufacture of SB16 is well-

controlled and leads to a product that is safe, pure, and potent. The comparative analytical data support a demonstration that SB16 is highly similar to US-licensed Prolia and US-licensed Xgeva, notwithstanding minor differences in clinically inactive components. The analytical component of the scientific bridge was established to support the use of EU-approved Prolia (EU Prolia) as a comparator in clinical studies supporting this application. It is recommended that this product be approved for human use under conditions specified in the package insert.

### **3.2. Devices**

Ospomyv is supplied as a drug-device combination product, and each prefilled syringe contains 60 mg of SB16. Xbryk is supplied as a single-dose vial, and hence, is not considered a drug-device combination product.

#### **3.2.1. Center for Devices and Radiological Health (CDRH)**

The Center for Devices and Radiological Health (CDRH) was consulted for review of the device constituent part of the Ospomyv combination product. The device constituent parts consist of a prefilled syringe (PFS) with a Needle Safety Device (NSD).

SB16 drug product is a clear, colorless to slightly yellow, sterile, and preservative-free solution for injection that is presented as a single-use vial and a pre-filled syringe (PFS). The SB16 PFS container closure system consists of a glass syringe with staked needle, rigid needle shield, a plunger stopper, and this is assembled with needle safety device. Approval is recommended for the device component of the combination product. Refer to the CDRH consult dated October 3, 2024, in DARRTS.

#### **3.2.2. Division of Medication Error Prevention and Analysis 1 (DMEPA 1)**

The Applicant submitted a comparative analyses and use-related risk analysis (URRA) under BLA 761392, a proposed interchangeable biosimilar to US-licensed Prolia. DMEPA 1 reviewed the comparative analyses and URRA and determined that no additional data (e.g., data from a comparative use human factors (CUHF) study) is needed to support their marketing application. DMEPA 1 has no HF recommendations for this marketing application. Refer to the DMEPA1 review dated July 8, 2024, in DARRTS.

### **3.3. Office of Study Integrity and Surveillance (OSIS)**

OSIS audits were requested for one bioanalytical site: (b) (4). (b) (4) and three clinical sites: PPD Development, L.P. (Austin, TX), Biotrial Inc. (Newark, NJ) and Biotrial Rennes (Rennes Cedex, France). The inspections were requested due to the PK similarity study SB16-1001 under BLA 761392 was conducted and analyzed at these sites. Refer to the Bioequivalence Establishment Inspection Report Review dated on May 9, 2024 and December 19, 2024, in DARRTS.

OSIS determined that inspections are not needed for the analytical site (b) (4) (b) (4) and the clinical site PPD Development L.P. (Austin, TX), and concluded that data from the studies were reliable.

OSIS conducted inspections for the clinical sites at Biotrial Inc. (Newark NJ) and Biotrial Rennes (France) for the study SB16-1001 under BLA 761392. No Form FDA 483 was issued. However, there was one identified concern regarding Subject (b) (6) at Biotrial Inc., which OSIS defers to the review division to determine whether the inclusion of the data from this subject impacts the reliability of the data. The review division concluded that the protocol deviation for Subject (b) (6) does not significantly affect the final study results. Specifically, Subject (b) (6) failed to maintain the required minimum 8-hour fast prior to the Day 43 fasting PK blood sample collection. Despite this deviation, the division determined that the overall integrity and validity of the study outcomes remain intact.

### 3.4. Office of Scientific Investigations (OSI)

OSI audit was not requested for this BLA, as no data integrity issues were identified. The statistical reviewer did not note any discrepancies in the datasets that raised concern. The clinical reviewer assessed protocol deviations that occurred during the comparative clinical Study SB16-3001, and concluded that these protocol deviations were unlikely to have impacted the overall results.

A comparable proportion of subjects in each group had protocol deviations. A total of 112/225 (49.8%) subjects in SB16 arm and 105/232 (45.3%) subjects in EU-Prolia had at least 1 protocol deviation, with 103/225 (45.8%) and 94/232 (40.5%) subjects, respectively, reporting major protocol deviations. The most commonly reported major deviations (i.e., observed in  $\geq 10\%$  of subjects in either treatment arm) were comparable between the two groups and were related to 1) blood sampling for CTX and P1NP either not be performed or performed outside of the visit window (17.8% vs. 16.4% for the SB16 and EU-Prolia arms, respectively); 2) timing of total hip/femoral neck BMD assessment (14.2% vs. 10.8% for the SB16 and EU-Prolia arms, respectively); and 3) timing of the LS BMD assessment (12.9% vs. 9.5% for the SB16 and EU-Prolia arms, respectively). These were unlikely to have impacted the biosimilarity assessment.

Of potential concern related to evaluation of efficacy of SB16 and EU-Prolia were protocol deviations related to “Use of (1) Xgeva (Denosumab) or (2) drugs used for osteoporosis or (3) drugs that affect bone metabolism, or (4) any kind of monoclonal antibodies or fusion receptor protein”, especially considering that treatment with denosumab or other osteoporosis treatment may impact BMD. This protocol deviation was reported in a comparable proportion between the two groups: 19/225 (8.4%) and 12/232 (5.2%) subjects originally randomized to SB16 and EU-Prolia, respectively. Further, the proportion of subjects in each arm who received products that may impact BMD, i.e., bisphosphonates or denosumab, was small and balanced between the two groups: 4/225 (1.8%) and 3/232 (1.3%) subjects in the SB16 and EU-Prolia groups, respectively, received bisphosphates and only 1/232 (0.4%) subject, in the EU-Prolia

group, received denosumab outside of the assigned study drug. Therefore, it is unlikely this protocol deviation had an impact on the results of the study.

Additionally, no single study site reported protocol deviations in more than 10% of the total study population or an unbalanced incidence of protocol deviations between the two arms. The study site reporting protocol deviations in the highest proportion of total subjects (Site SB161002) reported protocol deviations in 21/225 (9.3%) and 20/232 (8.7%) subjects in the SB16 and EU-Prolia groups, respectively. The majority of these (16/225 [7.1%] and 13/232 [5.6%], respectively) were related to the protocol deviation “other major GCP non-compliance that might affect data integrity or safety of the subject.” However, these were specifically related to a failure to obtain re-consent with an informed consent form at the earliest next visit after the effective date of the revised informed consent. Hence, it is unlikely that this deviation had a significant impact on the results of the study.

In conclusion, the overall integrity and validity of the outcomes of the comparative clinical study SB16-3001 remain intact, and it was determined that no OSI audits or study site inspections related to Study SB16-3001 were necessary.

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Clinical Team Leader

## **4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations**

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### **4.1. Nonclinical Executive Summary and Recommendation**

Samsung Bioepis Co., Ltd. is developing an injectable solution of SB16 as a proposed interchangeable biosimilar biological product to US Prolia and US Xgeva. The SB16 product is presented as a single use pre-filled syringe (PFS) containing 60 mg/mL of denosumab for the same indications as US Prolia and a single use vial of 120 mg of denosumab for the same indications as US Xgeva. Thus, the two presentations only differed in strength and container closure system.

Animal studies were not conducted in support of the application, and none were considered necessary as agreed in a BPD type 2 meeting on February 20, 2019. From a nonclinical perspective, the toxicity of denosumab products is related to their affinity to RANKL and related activity. The in vitro structural characterization and functional analyses are considered sufficient and more sensitive than animal studies to detect any functional differences (e.g., in affinity to RANKL and related receptor activity) between SB16 and US-Prolia and US-Xgeva. The applicant conducted corroborative in vitro biological activity studies and functional assays to assess the similarity of SB16 and US-Prolia or EU Prolia, and US-Xgeva that was reviewed by the Office of

Pharmaceutical Products (OPQ). RANKL binding activity, anti-differentiation activity, RANKL neutralization potency, and FcRn binding affinity for SB16 were compared with the US-Prolia and US-Xgeva in vitro. In addition, the relative FcγR1a binding, and the potential for antibody-dependent cell-mediated and complement-dependent cytotoxicity were assessed for SB16 relative to US/EU Prolia and US-Xgeva. Results of these studies demonstrated similar pharmacological activity between SB16 and US-Prolia and US-Xgeva. Refer to OPQ Quality Executive Summary dated November 13, 2024 in DARRTS.

In conclusion, no animal studies with SB16 and US-Prolia or US-Xgeva were needed to support this 351(k) application and the results of the in vitro studies support a demonstration of biosimilarity.

#### **4.1.1. Nonclinical Residual Uncertainties Assessment**

There are no nonclinical residual uncertainties.

## **4.2. Product Information**

### **Product Formulation**

The SB16 is presented as a single-dose pre-filled syringe (SB16 PFS DP) containing 60 mg/1.0 mL sterile solution as a biosimilar to US-Prolia and as a single-dose vial (SB16 Vial DP) containing 120 mg/1.7 mL sterile solution as a biosimilar to US -Xgeva. Both PFS and vial presentations are for subcutaneous injection and contain the same drug product ingredients (Table 4). All excipients are compendial and qualitatively similar between the drug product formulations.

**Table 4: Composition of SB16 Pre-Filled Syringe and Vial Drug Products****Composition of SB16 PFS DP**

| Component                           | Nominal Quantity/PFS <sup>a</sup> | Function         | Quality Standard <sup>b</sup> |
|-------------------------------------|-----------------------------------|------------------|-------------------------------|
| Denosumab                           | 60 mg                             | Active substance | In-house <sup>c</sup>         |
| Histidine                           | 0.28 mg                           | (b) (4)          | Ph. Eur., USP                 |
| Histidine hydrochloride monohydrate | 3.81 mg                           |                  | Ph. Eur.                      |
| Polysorbate 20                      | 0.10 mg                           |                  | Ph. Eur., NF                  |
| Sorbitol                            | 44.00 mg                          |                  | Ph. Eur., NF                  |
| Water for injections                | <i>q.s.</i>                       |                  | Ph. Eur., USP                 |

<sup>a</sup> Although the nominal quantity per syringe for each component may be adjusted when deemed necessary, the proportion of the components remains constant.

<sup>b</sup> The quality standards of the compendial components are described as USP or Ph. Eur. as representative pharmacopoeia, and each component may also comply with pharmacopoeia of other regions than those specified.

<sup>c</sup> Specification of SB16 drug substance (denosumab) is provided in CTD Section 3.2.S.4.1.

**Composition of SB16 Vial DP**

| Component                           | Nominal Quantity/Vial <sup>a</sup> | Function         | Quality Standard <sup>b</sup> |
|-------------------------------------|------------------------------------|------------------|-------------------------------|
| Denosumab                           | 120 mg                             | Active substance | In-house <sup>c</sup>         |
| Histidine                           | 0.44 mg                            | (b) (4)          | Ph. Eur., USP                 |
| Histidine hydrochloride monohydrate | 6.53 mg                            |                  | Ph. Eur.                      |
| Polysorbate 20                      | 0.17 mg                            |                  | Ph. Eur., NF                  |
| Sorbitol                            | 74.8 mg                            |                  | Ph. Eur., USP                 |
| Water for injections                | <i>q.s.</i>                        |                  | Ph. Eur., USP                 |

<sup>a</sup> Although the nominal quantity per vial for each component may be adjusted when deemed necessary, the proportion of the components remains constant.

<sup>b</sup> The quality standards of the compendial components are described as USP or Ph. Eur. as representative pharmacopoeia, and each component may also comply with pharmacopoeia of other regions than those specified.

<sup>c</sup> Specification of SB16 drug substance (denosumab) is provided in CTD Section 3.2.S.4.1.

[Source: Applicant submission]

**Comments on Excipients**

There are minor differences in the (b) (4) and levels of excipients between SB16 PFS or vial and the US reference products. The slight variations in the composition of excipients in the SB16 drug product between US-Prolia and US-Xgeva

are not expected to alter the safety profile of the proposed drug products. There are no nonclinical safety concerns with the drug product composition.

### Comments on Impurities of Concern

The applicant has reported that the process- and product-related impurities are similar in the drug substance and drug product. The levels of each of these impurities were consistently low among the batches of drug substances and are not expected to affect the safety of the product. No extractable or leachable compounds of concern were identified in assessments of container closure systems. Overall, no impurities or degradants of toxicologic concern were identified.

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## 5. Clinical Pharmacology Evaluation and Recommendations

### 5.1. Clinical Pharmacology Executive Summary and Recommendation

**Table 5: Clinical Pharmacology Major Review Issues and Recommendations**

| Review Issue            | Recommendations and Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pharmacokinetics</b> | <ul style="list-style-type: none"> <li>• PK similarities between SB16 and US-Prolia, between SB16 and EU-Prolia, and between US-Prolia and EU-Prolia were demonstrated in healthy male subjects (Study SB16-1001).</li> <li>• The PK similarity between EU-Prolia and US-Prolia demonstrated in Study SB16-1001 provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Prolia for the assessment of biosimilarity in Study SB16-3001.</li> <li>• Comparable denosumab product exposure between SB16 and EU-Prolia was demonstrated in postmenopausal women with osteoporosis (Study SB16-3001).</li> <li>• PK data from Study SB16-1001 also support the conclusion that SB16 would be expected to have similar PK as US-Xgeva because comparative PK</li> </ul> |

| Review Issue          | Recommendations and Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                       | <p>data generated with the 60 mg/1 mL strength are relevant for conclusions about PK similarity for the 120 mg/1.7 mL strength.</p> <ul style="list-style-type: none"> <li>• The results support a demonstration that SB16 has no clinically meaningful differences from US-Prolia and US-Xgeva.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Immunogenicity</b> | <p>Immunogenicity data from Study SB16-1001 (healthy male subjects) and Study SB16-3001 (female subjects with postmenopausal osteoporosis) support the demonstration that SB16 has no meaningful differences from US-Prolia and EU-Prolia. This conclusion is based on the very low and comparable incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NABs) observed across treatment arms in both studies.</p> <ul style="list-style-type: none"> <li>• There was no apparent impact of ADA and NAb on study drugs' PK, PD, safety and efficacy. Therefore, the immunogenicity data also support that SB16 has no clinically meaningful differences from US-Prolia and US-Xgeva.</li> </ul> |

The clinical development program of SB16 included two clinical studies:

1. Study SB16-1001, a randomized, double-blind, 3-arm, parallel-group, single-dose, PK similarity study in healthy male subjects comparing SB16, US-Prolia and EU-Prolia.
2. Study SB16-3001, a randomized, double-blind, active-controlled comparative clinical study comparing efficacy, safety, and immunogenicity in female subjects with postmenopausal osteoporosis. This study utilized EU-Prolia and SB16.

The Clinical Pharmacology review for this BLA primarily focused on the PK similarity study (Study SB16-1001) and additional PK and immunogenicity data from the comparative clinical study (Study SB16-3001).

PK similarity between SB16, EU-Prolia and US-Prolia was demonstrated given that the 90% confidence intervals (CIs) for the ratios (SB16/EU-Prolia, SB16/US-Prolia and EU-Prolia/US-Prolia) of geometric means for AUC<sub>0-inf</sub>, AUC<sub>0-last</sub> and C<sub>max</sub> were all completely contained within the pre-specified equivalence limits [0.80; 1.25] ([Table 6](#)).

The results also established the PK component of the scientific bridge that justifies the relevance of EU-Prolia to the assessment of biosimilarity. This 3-way PK assessment, together with the 3-way analytical and functional assessment (refer to Section 1.5), justified the relevance of clinical data obtained using EU-Prolia as the comparator (Study SB16-3001) to the assessment of biosimilarity.

**Table 6: Summary of statistical analyses for assessment of PK similarity (Study SB16-1001)**

| Parameter                          | Geometric Mean (%CV)        |                             |                             | Geometric Mean Ratio* (90% CI) |                     |                           |
|------------------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------------|---------------------|---------------------------|
|                                    | SB16                        | U.S.- Prolia                | EU-Prolia                   | SB16 vs U.S.- Prolia           | SB16 vs EU-Prolia   | EU-Prolia vs U.S.- Prolia |
| <b>Primary</b>                     |                             |                             |                             |                                |                     |                           |
| AUC <sub>0-inf</sub><br>(h*mcg/mL) | 6477.6<br>(26.09)<br>(N=55) | 6577.2<br>(28.98)<br>(N=55) | 6465.2<br>(41.7)<br>(N=52)  | 0.98(0.90,<br>1.07)            | 1.00(0.92,<br>1.09) | 0.98(0.90,<br>1.07)       |
| AUC <sub>last</sub><br>(h*mcg/mL)  | 6351.2<br>(25.28)<br>(N=55) | 6142.4<br>(40.54)<br>(N=56) | 6219.5<br>(55.23)<br>(N=54) | 1.03(0.94,<br>1.14)            | 1.02(0.92,<br>1.13) | 1.01(0.92,<br>1.12)       |
| C <sub>max</sub> (mcg/mL)          | 5.65<br>(23.68)<br>(N=55)   | 5.30<br>(26.13)<br>(N=56)   | 5.54<br>(23.72)<br>(N=54)   | 1.07(0.99,<br>1.15)            | 1.02(0.94,<br>1.10) | 1.04(0.97,<br>1.13)       |

\*Presented as percent. Source: FDA analysis

In addition to Study SB16-1001, the Applicant also assessed PK/PD similarity in Study SB16-3001, in which post-menopausal women with osteoporosis (PMO) received 60 mg SB16 or EU-Prolia by SC administration. Refer to Section 6.2 for more detailed information on the design of the study. The mean serum concentrations of study drugs were comparable between the SB16 and EU-Prolia treatment groups up to Month 12. Additionally, the incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NABs) was comparable between SB16, US-Prolia and EU-Prolia in both Study SB16-1001 and Study SB16-3001 (refer to Section 5.4.1 for details).

In conclusion, the clinical pharmacology data submitted supports the demonstration of no clinically meaningful differences between SB-16 and US-Prolia, and between SB16 and US-Xgeva. This evidence contributes to the overall totality of evidence supporting the biosimilarity between SB-16 and US-Prolia, and between SB16 and US-Xgeva. Based on these findings, the clinical pharmacology review team recommends approval of BLA 761392.

#### 5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

There are no residual uncertainties from the clinical pharmacology perspective.

## **5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product**

In the PK similarity study in healthy male subjects, SB16-1001, following subcutaneous administration of SB16, EU-Prolia, or U.S.-Prolia, the 90% CIs for the GMRs of SB16 to EU-Prolia, SB16 to U.S.-Prolia, and EU-Prolia to U.S.-Prolia for the tested PK parameters (i.e.,  $AUC_{0-inf}$ ,  $AUC_{last}$  and  $C_{max}$ ) were all within the PK similarity acceptance interval of 80%-125%. These pairwise comparisons met the pre-specified criteria for PK similarity between SB16, EU-Prolia, and U.S.-Prolia; thus, the PK portion of the scientific bridge was established to support the relevance of the clinical data generated using EU-Prolia.

In conclusion, the Applicant provided adequate clinical pharmacology data and information to establish a scientific bridge to justify the relevance of data generated with a non-U.S.- licensed comparator product in Study SB16-3001 to the demonstration of biosimilarity. See sections 1.5, 1.6, and 5.1 for details.

## **5.3. Human Pharmacokinetic and Pharmacodynamic Studies**

To support a demonstration that SB16 has no clinically meaningful differences from US-Prolia and US-Xgeva, the applicant submitted two clinical studies, Studies SB16-1001 and SB16-3001. The Clinical Pharmacology review for this BLA primarily focused on the PK similarity study (Study SB16-1001) and the additional PK and immunogenicity data from the comparative clinical study (Study SB16-3001). The Applicant collected and analyzed PD data in both clinical studies, for which the results have been presented for completeness. These data were only evaluated to ensure the findings did not conflict with any of the results from the primary endpoint results from other assessments considered as part of decision-making as it pertains to the assessment of biosimilarity.

### **5.3.1. STUDY SB16-1001**

#### **Clinical Pharmacology Study Design Features**

Study SB16-1001 was a double-blind, randomized, three-arm parallel group study to compare the PK, PD, safety, tolerability and immunogenicity of SB16, EU-Prolia and US-Prolia after a single s.c. injection of 60 mg in healthy male subjects.

#### **Study population and treatment**

The study was conducted in healthy male, aged 28-55 years and had a body weight between 60.0 - 95.0 kg and a body mass index (BMI) between 20.0 - 29.9 kg/m<sup>2</sup> at Screening and Day -1. Subjects were randomized in a 1:1:1 ratio (56 per treatment arm) to receive a single 60 mg s.c. dose of either SB16 or US-Prolia or EU-Prolia. All subjects were provided with calcium (at least 1000 mg) and vitamin D (at least 400 IU) daily during the treatment period. The study duration per subject was up to 32 weeks,

consisting of a screening period of up to 4 weeks, 1 treatment day and a post-dosing assessment period of 28 weeks.

### Clinical Pharmacology Study Endpoints

- **Primary PK endpoints:** area under the concentration curve from 0 to last observation/infinity (AUC0-last/AUC0-inf) and maximum observed study drug concentration (C<sub>max</sub>). To demonstrate PK similarity, the 90% CI of the geometric LS mean ratios needs to fall within 80-125%.
- **PD endpoints:** area under the effect-time curve (AUEC) of percent change from baseline (%CfB) in serum type 1 collagen carboxy terminal telopeptide (CTX). The 90% CI of the geometric LS mean ratios needs to fall within 80-125% to demonstrate PD similarity.
- **PK Datasets Analyzed:** A total of 166 subjects were included for PK analysis. Two subjects with a major protocol deviation were not included in the PK Analysis Set (1 subject each in the SB16 and EU-Prolia treatment groups).

### Bioanalytical PK Method and Performance

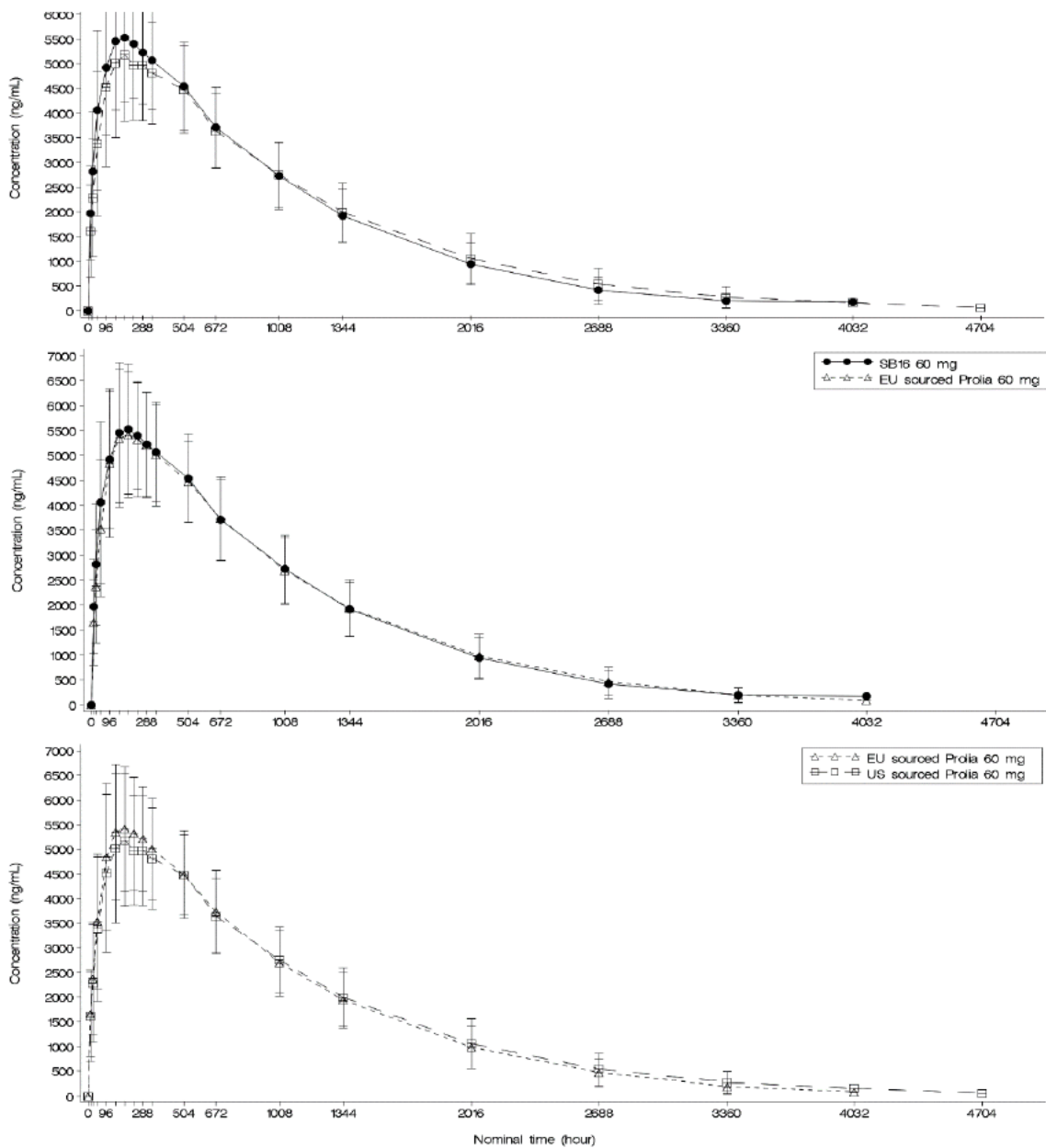
A Electrochemiluminescence (ECL) method was used to determine the free or partially bound denosumab concentration in human serum. A streptavidin coated plate is blocked and then coated with biotinylated anti-denosumab antibody. Denosumab present in samples is captured by biotinylated anti-denosumab antibodies. Sulfo-tagged anti-denosumab antibodies are then used to detect denosumab. In the presence of tripropylamine-containing read buffer, the Sulfo-Tag produces an electrochemiluminescent signal that is triggered when voltage is applied. Only samples that contain denosumab bound to both biotinylated anti-denosumab antibodies and sulfo-tagged anti-denosumab antibodies will generate an ECL signal.

The method was fully validated over a range of 20 to 2000 ng/mL for study drug in accordance with the Bioanalytical Method Validation Guidance from the agency. Refer to the Appendix 13.4.1 for more detailed information on method validation.

### PK Similarity Assessment

The mean study drug serum concentration-time profiles are similar for all treatment groups (Figure 1). For the primary PK parameters (AUC0-last, AUC0-inf, and C<sub>max</sub>), the similarity criterion (90% CI of the geometric least-square mean ratio for test/reference within the limits 80.00% and 125.00%) was met in all the comparisons ([Table 7](#)).

**Figure 1: Study drug serum concentrations vs. time profile (Study SB16-1001)**



Source: Section 5.3.3.1 CSR Study SB16-1001, Figure 11-1, Figure 11-2 and Figure 11-3

**Table 7: Geometric mean ratio and 90% CI for primary PK parameters to compare treatments (Study SB16-1001)****Table 11-4 Statistical Comparison of Primary Pharmacokinetic Parameters between SB16 and EU sourced Prolia (Pharmacokinetic Analysis Set)**

| PK Parameter                     | Treatment         | N  | n  | Geo-LSMean | Ratio A/B | 90% CI of Ratio |
|----------------------------------|-------------------|----|----|------------|-----------|-----------------|
| AUC <sub>inf</sub><br>(h·µg/mL)  | SB16              | 55 | 55 | 6403.1     | 1.01      | [0.93, 1.10]    |
|                                  | EU sourced Prolia | 55 | 52 | 6340.5     |           |                 |
| C <sub>max</sub><br>(µg/mL)      | SB16              | 55 | 55 | 5.651      | 1.02      | [0.95, 1.10]    |
|                                  | EU sourced Prolia | 55 | 54 | 5.541      |           |                 |
| AUC <sub>last</sub><br>(h·µg/mL) | SB16              | 55 | 55 | 6292.4     | 1.02      | [0.94, 1.12]    |
|                                  | EU sourced Prolia | 55 | 54 | 6156.2     |           |                 |

**Table 11-5 Statistical Comparison of Primary Pharmacokinetic Parameters between SB16 and US sourced Prolia (Pharmacokinetic Analysis Set)**

| PK Parameter                     | Treatment         | N  | n  | Geo-LSMean | Ratio A/B | 90% CI of Ratio |
|----------------------------------|-------------------|----|----|------------|-----------|-----------------|
| AUC <sub>inf</sub><br>(h·µg/mL)  | SB16              | 55 | 55 | 6403.1     | 0.99      | [0.91, 1.08]    |
|                                  | US sourced Prolia | 56 | 55 | 6484.8     |           |                 |
| C <sub>max</sub><br>(µg/mL)      | SB16              | 55 | 55 | 5.651      | 1.07      | [0.99, 1.15]    |
|                                  | US sourced Prolia | 56 | 56 | 5.305      |           |                 |
| AUC <sub>last</sub><br>(h·µg/mL) | SB16              | 55 | 55 | 6292.4     | 1.01      | [0.92, 1.10]    |
|                                  | US sourced Prolia | 56 | 56 | 6259.1     |           |                 |

**Table 11-6 Statistical Comparison of Primary Pharmacokinetic Parameters between EU sourced Prolia and US sourced Prolia (Pharmacokinetic Analysis Set)**

| PK Parameter                     | Treatment         | N  | n  | Geo-LSMean | Ratio A/B | 90% CI of Ratio |
|----------------------------------|-------------------|----|----|------------|-----------|-----------------|
| AUC <sub>inf</sub><br>(h·µg/mL)  | EU sourced Prolia | 55 | 52 | 6340.5     | 0.98      | [0.89, 1.07]    |
|                                  | US sourced Prolia | 56 | 55 | 6484.8     |           |                 |
| C <sub>max</sub><br>(µg/mL)      | EU sourced Prolia | 55 | 54 | 5.541      | 1.04      | [0.97, 1.13]    |
|                                  | US sourced Prolia | 56 | 56 | 5.305      |           |                 |
| AUC <sub>last</sub><br>(h·µg/mL) | EU sourced Prolia | 55 | 54 | 6156.2     | 0.98      | [0.89, 1.08]    |
|                                  | US sourced Prolia | 56 | 56 | 6259.1     |           |                 |

Source: Section 5.3.3.1 CSR Study SB16-1001, Table 11-4, Table 11-5 and Table 11-6

**Bioanalytical PD Method and Performance**

CTX in human serum was quantified using a validated ECL platform. In this assay, samples were incubated with biotinylated monoclonal anti-β-CrossLaps antibody. β-CrossLaps present in the samples was captured by biotinylated monoclonal anti-β-CrossLaps antibody. Ruthenium complex-labeled monoclonal anti-β-CrossLaps antibody was then used to detect β-CrossLaps. When voltage was applied, the ruthenium complex produced an ECL signal. The resulting ECL was measured by a

photomultiplier and the results were determined via master curve generated by the instrument.

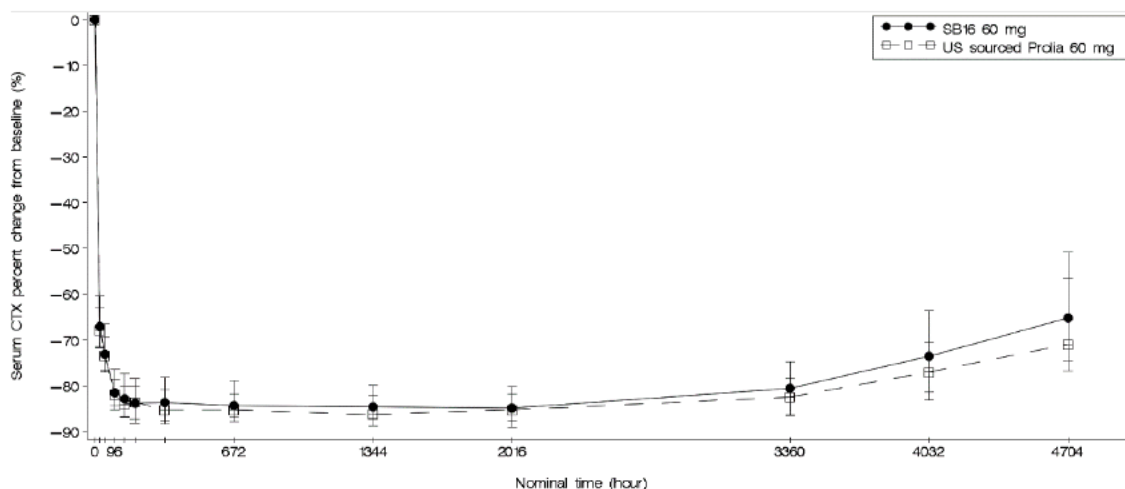
All validation parameters passed the acceptance criteria and the assays are considered appropriate for the quantification of CTX in human serum. The validated range of CTX measurement is 0.043 ng/mL to 1.21 ng/mL. A summary of the bioanalytical validation report to assess the PD marker can be found in the Clinical Pharmacology Appendices (Section [13.3](#)).

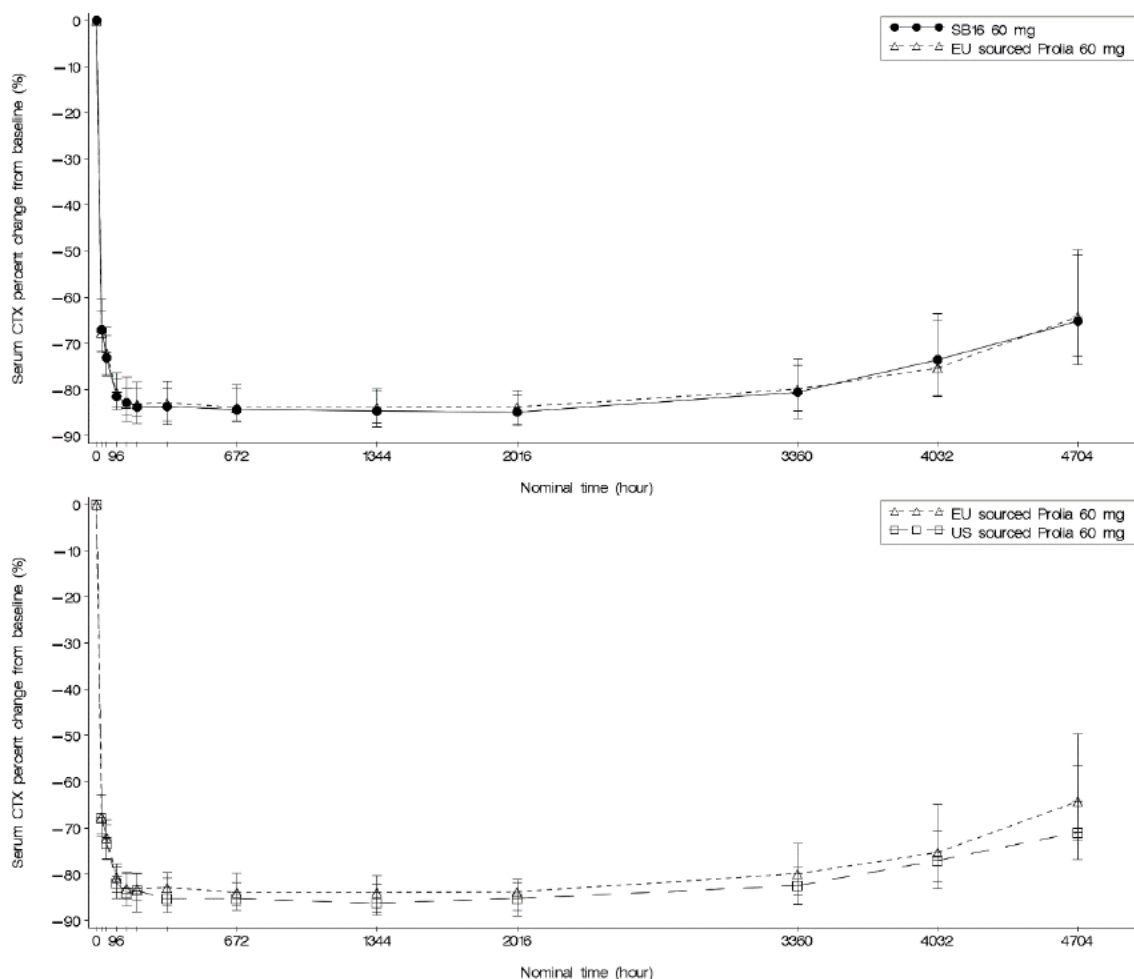
### PD Similarity Assessment

The Applicant collected and analyzed PD data in the clinical studies, for which the results have been presented for completeness. These data were only evaluated to ensure the findings did not conflict with any of the results from the primary endpoint results from other assessments considered as part of decision-making as it pertains to the assessment of biosimilarity.

For the PD parameter in Study SB16-1001, the arithmetic median percent change from baseline in serum CTX concentrations versus nominal time curves on linear scale is presented for pairwise comparisons of all study treatment groups in Figure 2. The PD profiles for s-CTX are similar between SB16 and EU-Prolia, SB16 and US-Prolia, and EU-Prolia and US-Prolia.

**Figure 2: Median Percent Change from Baseline for Serum Concentration of s-CTX versus Time**





Source: Section 5.3.3.1 CSR Study SB16-1001, Figure 5, Figure 6 and Figure 7.

### 5.3.2. STUDY SB16-3001

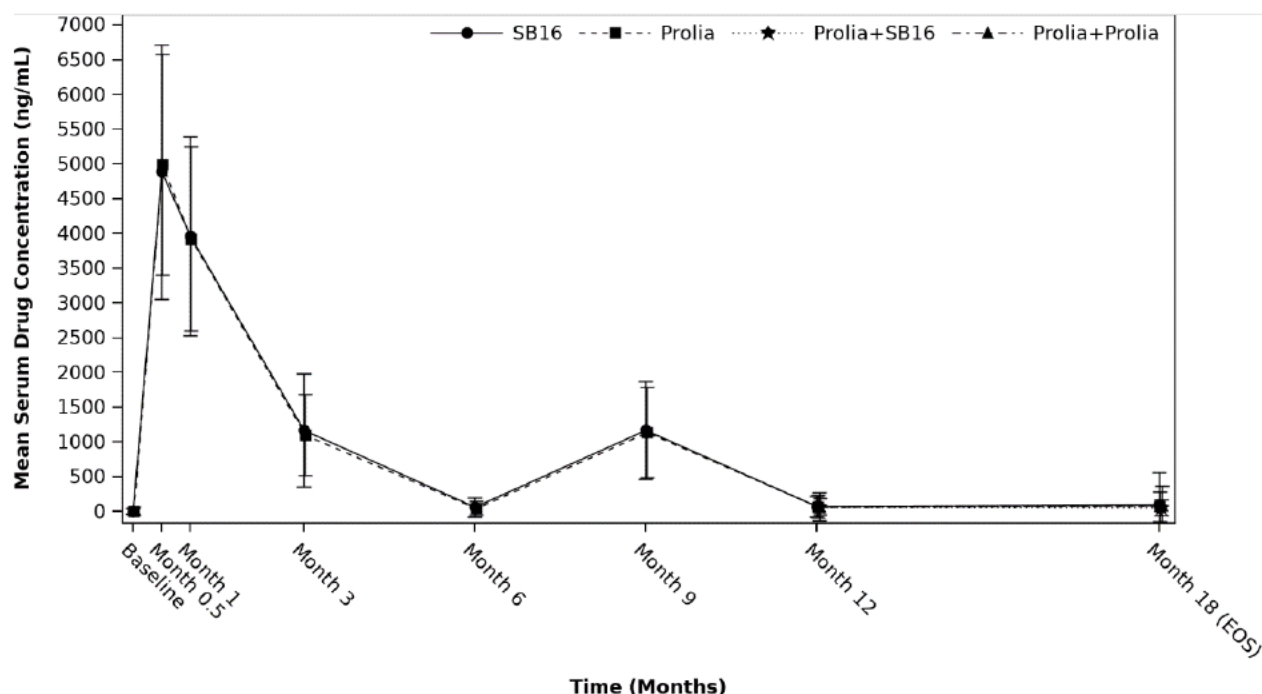
Study SB16-3001 is a clinical Phase III, randomized, double-blind, parallel group, multicenter, equivalence study to evaluate the efficacy, safety, PK, PD, and immunogenicity of SB16 compared to EU-Prolia in PMO. Patients were randomized in a 1:1 ratio to receive either SB16 or EU-Prolia subcutaneously at Months 0 and 6. Study visits occurred at Months 0, 0.5, 1, 3, 6, 9, and 12. BMD assessments were done at Months 6 and 12. Blood samples for safety, PK, PD, and immunogenicity were collected at Months 0, 0.5, 1, 3, 6, 9, and 12.

At Month 12, patients who received EU-Prolia in the main period were randomized again in a 1:1 ratio to either continue on EU-Prolia (EU-Prolia+ EU-Prolia) or were transitioned to SB16 (EU-Prolia+SB16). Patients who received SB16 in the Main period continued to receive SB16, but they also followed the randomization procedure to maintain blinding. Patients were followed up to Month 18. (Refer to Sections [6.2](#) for more detailed information on the design of the study).

## PK Assessment

A total of 456 patients were included in the PK analysis dataset (225 patients from the SB16 and 231 patients from the EU-Prolia treatment groups). The mean study drug concentration-time profiles are similar between SB16 and EU-Prolia ([Figure 3](#)).

**Figure 3: Mean Serum Concentrations Profiles by Treatment in Overall Study Period (Study SB16-3001)**



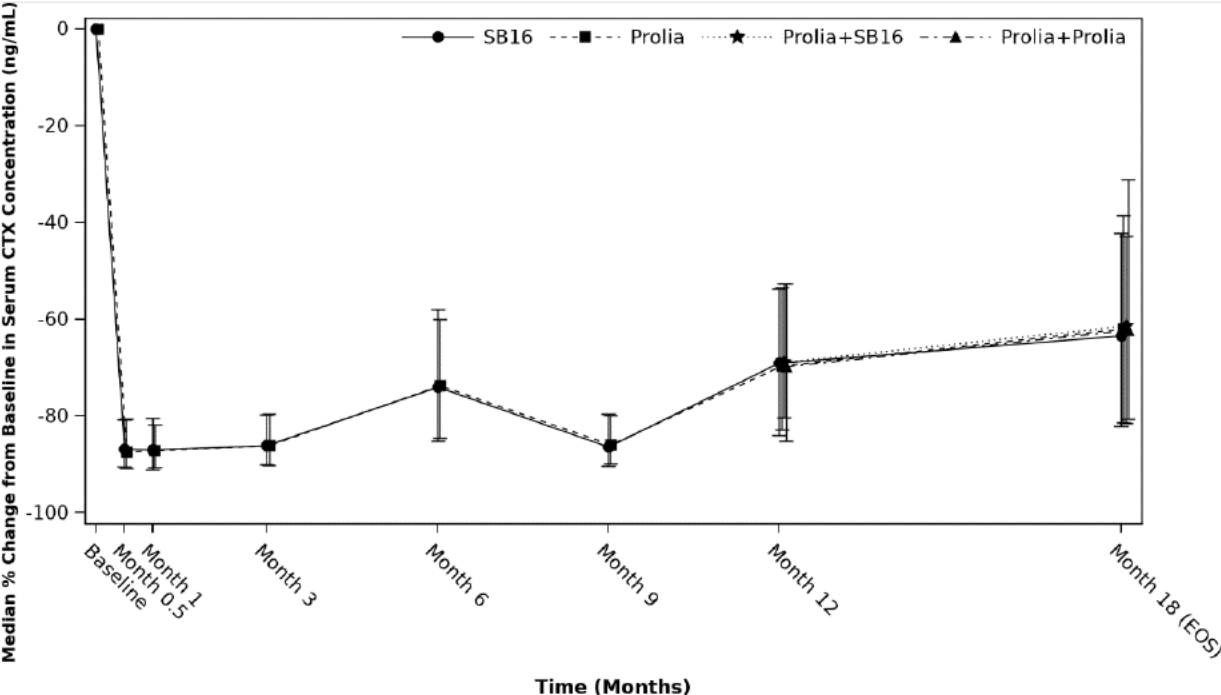
Source: Section 5.3.5.1 CSR Study SB16-3001, Figure 11-9

## PD Assessment

Serum CTX and procollagen type I N-terminal propeptide (P1NP) concentrations were analyzed by treatment group and visit. Blood samples for PD were collected at Months 0, 0.5, 1, 3, 6, 9, 12 and at Month 18 (EOS)/ET.

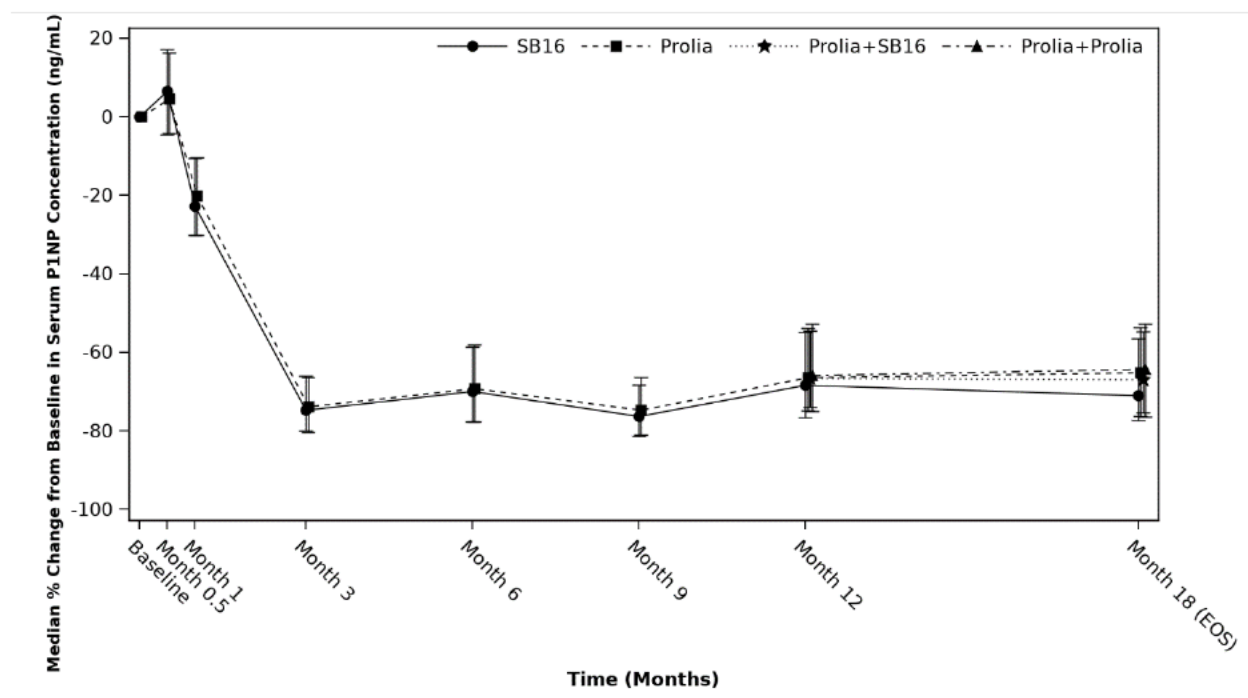
Median percent changes from baseline in s-CTX and P1NP over the complete study period are shown in [Figure 4](#) and [Figure 5](#), respectively. The PD profiles for both markers are similar between SB16 and EU-Prolia treatment groups. The AUEC<sub>0-M6</sub> in percent change from baseline in serum CTX was comparable between the SB16 and EU-Prolia treatment groups and the median percent change from baseline in serum CTX and P1NP concentrations were comparable between the SB16 and EU-Prolia treatment groups up to Month 12. Post-transition median percent change from baseline in serum CTX and P1NP concentrations were also comparable across the SB16+SB16, EU-Prolia+SB16, and EU-Prolia+EU-Prolia treatment groups up to Month 18.

**Figure 4: Median Percent Change from Baseline in Serum C-telopeptide of type I collagen (CTX) Concentration Profiles in Overall Study Period (Study SB16-3001)**



Source: Section 5.3.5.1 CSR Study SB16-3001, Figure 11-7

**Figure 5: Median Percent Change from Baseline in Serum Procollagen Type I N-terminal Propeptide (P1NP) Concentration Profiles in Overall Study Period ( Study SB16-3001)**



Source: Section 5.3.5.1 CSR Study SB16-3001, Figure 11-8

## 5.4. Clinical Immunogenicity Studies

### 5.4.1. STUDIES SB16-1001 and SB16-3001

#### 5.4.1.1. Design features of the clinical immunogenicity assessment

Refer to Sections 5.3.1 and 6.2 for more detailed information on the design of the study.

#### 5.4.1.2. Immunogenicity endpoints

Immunogenicity assessment was proposed as the secondary study endpoints in the following studies:

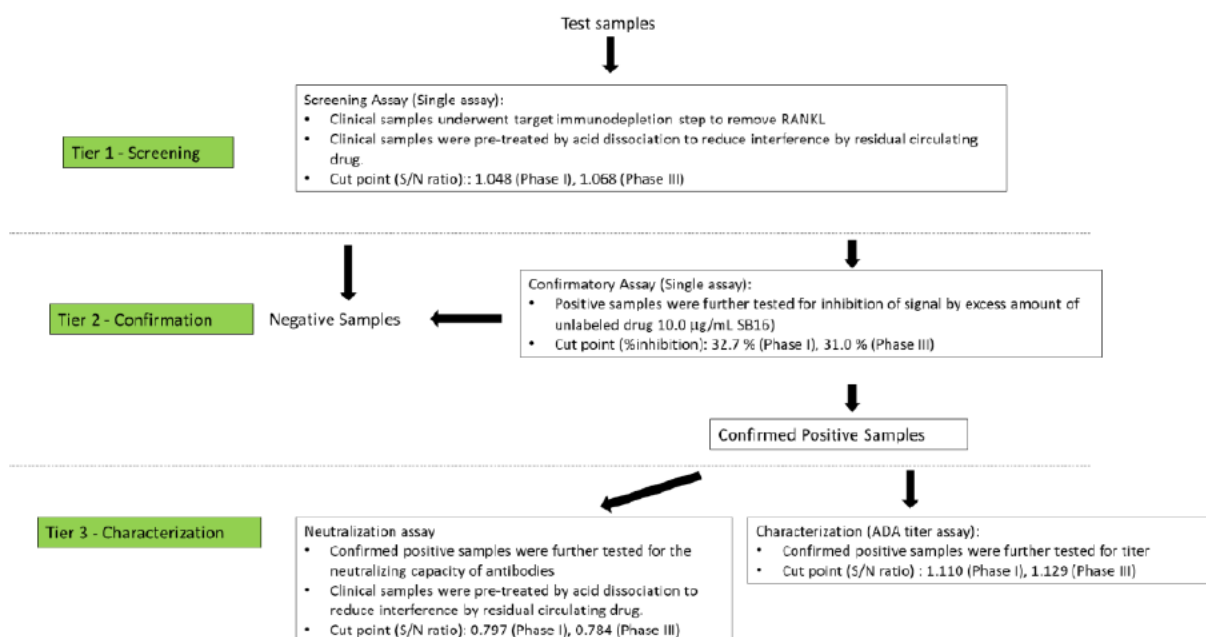
- Study SB16-1001: Incidences of anti-drug antibodies (ADAs) and neutralizing antibodies (NABs)
- Study SB16-3001: Incidence of ADAs and NAB up to month 18.

**Immunogenicity assay's capability of detecting the ADA and NAb in the presence of proposed product, U.S.-licensed reference product, and non-U.S.-licensed comparator product (as applicable) in the study samples**

Anti-drug antibodies (ADA) against denosumab/SB16 in human serum were detected using a ECL method. Samples collected from study SB16-1001 and SB16-3001 were analyzed with a multi-tiered approach ([Figure 6](#)).

At screening assay (Tier 1) was used to detect the potential ADA-positive samples; then samples that were ADA-Positive were further tested under the existence of excess amount of unlabeled drug in the confirmatory assay (Tier 2); the confirmed positive samples were tested whether ADAs have a neutralizing capacity (Tier 3) and the titration of ADA (Tier 3).

**Figure 6 Tiered Approach in the SB16 Anti-drug Antibody, Neutralizing Antibody and Titer Assays**



Source: section 2.7.1 Summary of biopharmaceutic studies and associated analytical methods, Figure 9.

Additionally, the median maximum serum concentration of study drugs in Studies SB16-1001 and SB16-3001 (<6000 ng/mL) is significantly lower than the drug tolerance of the ADAs/NAbs assay (>9000 ng/mL), indicating no interference with the ADAs/NAbs assay in the presence of study drugs in the serum.

Refer to OPQA3's review for an assessment of bioanalytical method validation and performance of the ADAs/NAbs assays.

#### 5.4.1.3. Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA/NAb formation

In Study SB16-1001, ADA samples were collected at pre-dose, Day 15, Day 29, Day 85, Day 141 and Day 197 [EOS/ET]. In Study SB16-3001, ADA samples were collected at pre-dose, Month 0, 0.5, 1, 3, 6, 9, and 12 and at Month 18 (EOS)/ET.

The immunogenicity assessment schedules in Studies SB16-1001 and SB16-3001 are deemed appropriate. These schedules include ADA sampling at baseline (pre-dose) and at multiple post-dose timepoints, extending beyond 5 half-lives of denosumab. This comprehensive sampling strategy allows for a thorough evaluation of the immunogenic response over time.

Furthermore, the study design incorporates concurrent measurement of drug concentrations at the same timepoints as immunogenicity sample collection. This parallel assessment of drug levels and ADA formation enhances the ability to interpret the immunogenicity data in the context of drug exposure.

The inclusion of baseline samples, multiple post-dose timepoints, and corresponding drug concentration measurements provides a robust framework for evaluating the immunogenicity profile of the study drug.

#### 5.4.1.4. Incidence of ADA and NAb (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study)

The incidence of ADA and Nab in Studies SB16-1001 and SB16-3001 are shown in [Table 8](#), [Table 9](#) and [Table 10](#), respectively.

The incidence of ADAs and NAb was low and comparable between treatment groups for each study. There was no NAb detected in all treatment groups in both studies. Pre-treatment of EU-Prolia and transitioning to SB16 did not influence the incidence of ADAs and NAb in SB16 group after the transition ([Table 10](#)).

**Table 8: Immunogenicity results for binding ADA and NAb in Study SB16-1001.**

|           | N  | Anti-Drug Antibody |                   | NAb         |
|-----------|----|--------------------|-------------------|-------------|
|           |    | Baseline           | Treatment-Induced |             |
| SB16      | 56 | 0/56 (0.0%)        | 2/56 (3.6%)       | 0/56 (0.0%) |
| US-Prolia | 56 | 0/56 (0.0%)        | 4/56 (7.1%)       | 0/56 (0.0%) |

|           |    |             |             |             |
|-----------|----|-------------|-------------|-------------|
| EU-Prolia | 56 | 0/56 (0.0%) | 0/55 (0.0%) | 0/56 (0.0%) |
|-----------|----|-------------|-------------|-------------|

Source: Section 5.3.3.1 CSR Study SB16-1001, Table 12-3

**Table 9: Immunogenicity results for binding ADA and NAb in Study SB16-3001 (Month 0- Month 12)**

|           | N   | Anti-Drug Antibody |                   | NAb          |
|-----------|-----|--------------------|-------------------|--------------|
|           |     | Baseline           | Treatment-Induced |              |
| SB16      | 206 | 0/225 (0.0%)       | 1/224 (0.4%)      | 0/224 (0.0%) |
| EU-Prolia | 201 | 0/231 (0.0%)       | 2/226 (0.9%)      | 0/226 (0.0%) |

Source: Section 5.3.5.1 CSR, Study SB16-3001, Table 12-10, Table 12-11

**Table 10: Immunogenicity results for binding ADA and NAb in Study SB16-3001 Transition Period (Month 12 to Month 18)**

|                     | N   | Anti-Drug Antibody | NAb          |
|---------------------|-----|--------------------|--------------|
| SB16/SB16           | 206 | 1/206 (0.5%)*      | 0/206 (0.0%) |
| EU-Prolia/EU-Prolia | 99  | 1/99 (1%)*         | 0/99 (0.0%)  |
| EU-Prolia/SB16      | 99  | 1/99 (1%)          | 0/99 (0%)    |

Source: Section 5.3.5.1 CSR Study SB16-3001, Table 14.3-5.4

\* 1 ADA positive subject in SB16/SB16 arm and 1 ADA positive subject in EU-Prolia/EU-Prolia arm are concluded as "inconclusive". ADA results were determined as 'Inconclusive' for a patient with at least one positive ADA up to Month 12 and without positive result with higher titer level observed after IP administration at Month 12 up to Month 18, compared to the maximum positive ADA up to Month 12.

#### **5.4.1.5. Impact of ADA and NAb on the PK, PD, safety, and clinical outcomes of the proposed product**

##### **Impact of ADA and NAb on PD**

In study SB16-1001, the Analysis of Variance (ANOVA) of the primary PK parameters (AUCinf, Cmax, AUClast) was performed across the three treatment groups by post-dose ADA subgroup to evaluate the impact of immunogenicity on PK more precisely ([Table 11](#)).

**Table 11: Analysis of Variance (ANOVA) for the Primary Pharmacokinetic Parameters by Post-dose Anti-drug Antibody (Study SB16-1001)**

| ADA Status             | PK Parameter                     | Treatment | N  | n  | Geo-LSMeans | Ratio of SB16/Prolia |              | Ratio of EU Prolia /US Prolia |              |
|------------------------|----------------------------------|-----------|----|----|-------------|----------------------|--------------|-------------------------------|--------------|
|                        |                                  |           |    |    |             | Estimate             | 90% CI       | Estimate                      | 90% CI       |
| Post-dose ADA Positive | AUC <sub>inf</sub><br>(h·µg/mL)  | SB16      | 2  | 2  | 5904.7      | -                    | -            | -                             | -            |
|                        |                                  | EU Prolia | 0  | 0  | N/C         | N/C                  | N/C          | -                             | -            |
|                        |                                  | US Prolia | 4  | 4  | 6292.3      | 0.94                 | [0.47, 1.86] | N/C                           | N/C          |
|                        | C <sub>max</sub><br>(µg/mL)      | SB16      | 2  | 2  | 5.554       | -                    | -            | -                             | -            |
|                        |                                  | EU Prolia | 0  | 0  | N/C         | N/C                  | N/C          | -                             | -            |
|                        |                                  | US Prolia | 4  | 4  | 5.376       | 1.03                 | [0.52, 2.04] | N/C                           | N/C          |
|                        | AUC <sub>last</sub><br>(h·µg/mL) | SB16      | 2  | 2  | 5769.8      | -                    | -            | -                             | -            |
|                        |                                  | EU Prolia | 0  | 0  | N/C         | N/C                  | N/C          | -                             | -            |
|                        |                                  | US Prolia | 4  | 4  | 6178.4      | 0.93                 | [0.46, 1.89] | N/C                           | N/C          |
| Post-dose ADA Negative | AUC <sub>inf</sub><br>(h·µg/mL)  | SB16      | 53 | 53 | 6422.7      | -                    | -            | -                             | -            |
|                        |                                  | EU Prolia | 54 | 52 | 6340.5      | 1.01                 | [0.93, 1.11] | -                             | -            |
|                        |                                  | US Prolia | 52 | 51 | 6500.2      | 0.99                 | [0.91, 1.08] | 0.98                          | [0.89, 1.07] |
|                        | C <sub>max</sub><br>(µg/mL)      | SB16      | 53 | 53 | 5.655       | -                    | -            | -                             | -            |
|                        |                                  | EU Prolia | 54 | 54 | 5.541       | 1.02                 | [0.95, 1.10] | -                             | -            |
|                        |                                  | US Prolia | 52 | 52 | 5.299       | 1.07                 | [0.99, 1.15] | 1.05                          | [0.97, 1.13] |
|                        | AUC <sub>last</sub><br>(h·µg/mL) | SB16      | 53 | 53 | 6313.1      | -                    | -            | -                             | -            |
|                        |                                  | EU Prolia | 54 | 54 | 6156.2      | 1.03                 | [0.94, 1.12] | -                             | -            |
|                        |                                  | US Prolia | 52 | 52 | 6265.4      | 1.01                 | [0.92, 1.10] | 0.98                          | [0.89, 1.08] |

Source: Section 5.3.3.1 CSR Study SB16-1001, Table 14.2-2.2

Three subjects (1 subject in the US Prolia and 2 subjects in the EU Prolia treatment groups) were excluded from the PK analysis for AUC<sub>inf</sub> due to incomplete PK profile. One subject in the EU Prolia treatment group was excluded from the PK analysis for all parameters due to incomplete PK profile.

Due to the limited number of subjects determined as post-dose ADA positive per treatment group (2 subjects in the SB16, 4 subjects in the US Prolia, and none in EU Prolia treatment groups) and available for analysis, a meaningful comparative assessment of the immunogenicity impact on the PK parameter is not feasible ([Table 11](#)). Based on the face values, the mean AUC and C<sub>max</sub> values appear to be comparable between subjects with positive and negative ADAs in SB16 and US-Prolia treatment arms.

In addition, given no subject developed NAb to denosumab, the impact of NABs on the PK profiles of SB16, US Prolia, and EU Prolia cannot be discussed for this study.

In [Study SB16-3001](#), only 3 (0.66%) patients (1 in the SB16 treatment group and 2 in the Prolia Overall treatment group) were determined as ADA positive and all three patients were included in the PK data set. PK analysis by overall ADA status were not performed.

### Impact of ADA and NAb on Efficacy

The impact of ADAs on efficacy was evaluated by comparing change from baseline in LS BMD at Month 12 per treatment group and ADA status (i.e., subjects with at least one ADA-positive sample up to Week 52 and ADA-negative subjects) in the Main Period of Study SB16-3001. While the small proportion of subjects in either treatment group that were positive for ADAs is reassuring, it precludes a meaningful comparative assessment of the impact of immunogenicity on efficacy. However, the available data do not suggest that ADAs result in decreased efficacy in either the SB16 or EU-Prolia group (see [Table 12](#)).

**Table 12: Analysis impact of ADA status on percent change from baseline in lumbar spine BMD at Month 12, FAS, Main Period of Study SB16-3001**

| Parameter                                                              | SB16         |              | EU-Prolia    |              |
|------------------------------------------------------------------------|--------------|--------------|--------------|--------------|
|                                                                        | ADA-positive | ADA-negative | ADA-positive | ADA-negative |
| LS mean percent change from baseline to Month 12 lumbar spine BMD (SE) | 11.61 (0)    | 5.6 (0.25)   | 6.26 (0)     | 5.29 (0.26)  |
| N                                                                      | 1            | 223          | 2            | 224          |

ADA=anti-drug antibody; BMD=bone mineral density; SE=standard error; LS mean=least squares mean  
Source: Module 2.7.3 Summary of Clinical Efficacy, Table 9, pages 31 and 32.

### Impact of ADA and NAb on Safety

As discussed in Section [6.3.4.3](#), the clinical reviewer searched the safety dataset for AEs related to anaphylaxis and hypersensitivity.

In [Study SB16-1001](#), there were no events of anaphylaxis in any treatment group. Adverse events related to hypersensitivity were observed in 2/56 (3.6%) subjects in the EU-Prolia group who reported non-serious erythema (moderate) and non-serious rash (mild) (n=1, each), neither of whom were ADA positive. The ADA-positive subjects in this trial did not report adverse events that would likely be related to immunogenicity. Thus, the results from Study SB16-1001 do not indicate that immunogenicity had an effect on the safety of SB16, EU-Prolia, or US-Prolia.

In Study SB16-3001, there were no events of anaphylaxis in any treatment group. In the Main Period, 6/225 (2.7%) versus 12/231 (5.2%) subjects in the SB16 and EU-Prolia groups reported adverse events related to hypersensitivity, while in the Transition Period 2/206 (1%) subjects in the SB16+SB16 group, compared to none in either the EU-Prolia+EU-Prolia or the EU-Prolia+SB16 group, reported adverse events related to hypersensitivity. No subject in any group or period who reported adverse events related to hypersensitivity ever tested positive for post-treatment ADAs. The ADA-positive subjects in this trial did not report adverse events that would likely be related to immunogenicity.

Thus, the results from Study SB16-3001 do not indicate that immunogenicity had an effect on the safety of SB16 or EU-Prolia, including in subjects who underwent the transition from EU-Prolia to SB16. Following transition from EU-Prolia to SB16, there did not appear to be an increase in the incidence of ADAs and there were no ADA associated hypersensitivity reactions in the EU-Prolia+SB16 group.

In conclusion, the approach to demonstrate the impact of ADAs and NAb on the PK, safety, and clinical outcomes appears reasonable. There was no evidence of meaningful influence of ADAs or NAb on the PK, safety, or clinical outcomes between the studied products.

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## 6. Statistical and Clinical Evaluation and Recommendations

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### 6.1. Statistical and Clinical Executive Summary and Recommendation

The Applicant conducted a single comparative clinical study comparing the efficacy and safety of SB16 and EU-Prolia in post-menopausal women with osteoporosis (Study SB16-3001). An adequate scientific bridge was established in the comparative analytical study and the PK similarity study in healthy male subjects (Study SB16-1001) to justify the relevance of clinical data generated using EU-Prolia in the Study SB16-3001 to the assessment of biosimilarity (refer to Section 1.5). The demographic and disease characteristics of the population was overall similar between the two treatment groups. The primary efficacy endpoint was the percentage change in lumbar spine (LS) BMD assessed by DXA at Week 52 compared to baseline. At the end of the Main Period (i.e., Week 52), the difference in the mean percentage change from baseline in LS-BMD between the SB16 and EU-Prolia groups was 0.33, the 90% confidence interval of which were within the margin of +/-1.45% (see Section 6.2.6 and Table 176.2.6). Therefore, the products were shown to be similar with respect to efficacy.

There was no meaningful difference between SB16 and EU-Prolia with respect to the nature or frequency of treatment emergent adverse events (see Section [6.3.2.4](#) and [Table 24](#)). Both SB16 and EU-Prolia were associated with development of hypocalcemia, with the nadir in serum calcium observed within the first two to four weeks after drug administration. There were no meaningful differences between the group in the incidence of hypocalcemia or of other laboratory abnormalities.

The single transition from EU-Prolia to SB16 showed maintenance of efficacy (see [Table 20](#)), and no increase in the nature or frequency of adverse events, or evidence of immunogenic response. Hence, there is no evidence that administration of SB16 following EU-Prolia is associated with meaningful differences in efficacy and safety as compared to remaining on EU-Prolia.

#### **6.1.1. Statistical and Clinical Residual Uncertainties Assessment**

There are no residual uncertainties based on the clinical analyses.

### **6.2. Review of Comparative Clinical Studies with Statistical Endpoints**

**Study SB16-3001:** A Randomized, Double-blind, Multicenter Clinical Study to Compare the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of SB16 and EU-Prolia in Postmenopausal Women with Osteoporosis

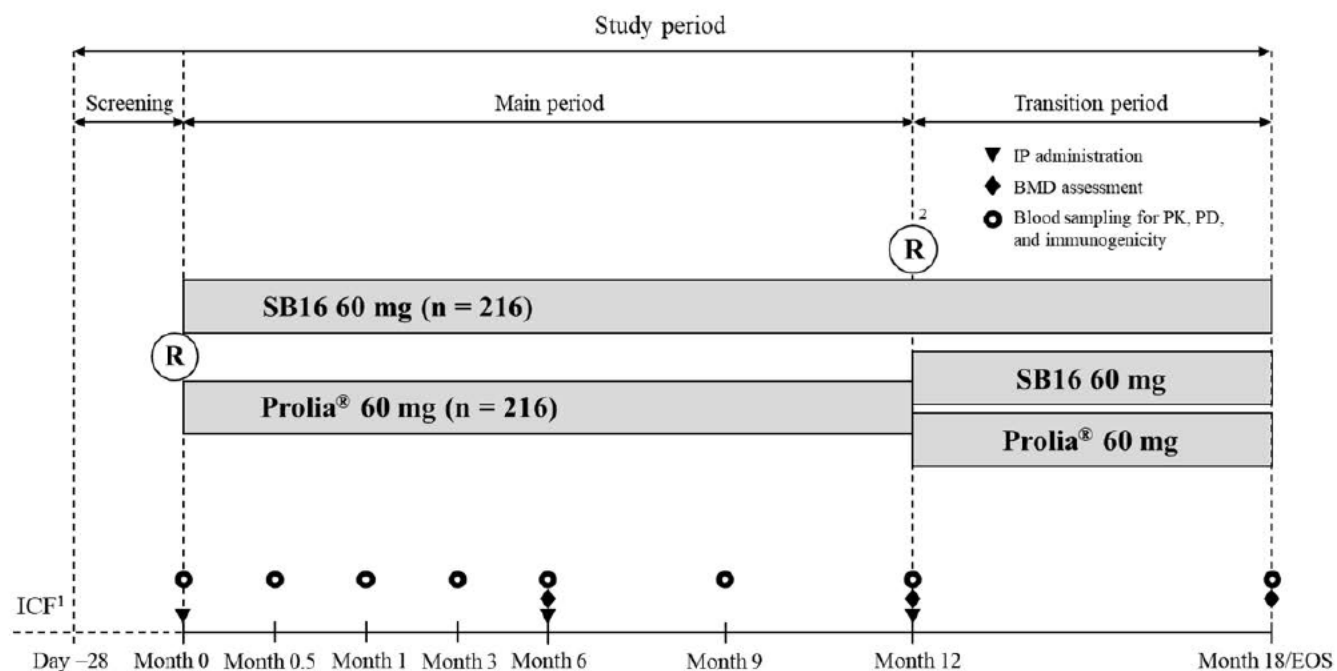
#### **6.2.1. Data and Analysis Quality**

There are no concerns regarding data quality and integrity.

#### **6.2.2. Study Design and Endpoints**

Study SB16-3001 was an international, multicenter, randomized, double-blind comparative clinical study consisting of two treatment periods. For the first treatment period (i.e., “Main Period”) a total of 457 female subjects with post-menopausal osteoporosis (PMO) were randomized in a 1:1 ratio to receive two doses of either 60 mg SB16 or 60 mg EU-Prolia subcutaneously (SC) on Day 1 and at Month 6.

At Month 12, the Transition Period commenced. All subjects in the SB16 group continued treatment with a third dose of 60 mg SC SB16. Subjects who had received EU-Prolia in the Main Period were randomized again in a 1:1 ratio to either continue on 60 mg SC EU-Prolia (EU-Prolia+EU-Prolia) or transitioned to 60 mg SC SB16 (EU-Prolia+SB16). Subjects were followed for an additional 6 months. The study design is shown in [Figure 7](#).

**Figure 7: Study SB16-3001 design**

BMD = bone mineral density; EOS = end of study; ICF = informed consent form; IP = investigational product; n = number of subjects; PD = pharmacodynamic; PK = pharmacokinetic; ® = Randomisation

1. Informed consent was to have been obtained prior to any study related procedures.
2. At Month 12, subjects who had received Prolia were randomised in a 1:1 ratio to either continue to receive Prolia or transitioned to SB16. Subjects who received SB16 continue to receive SB16 up to Month 18, but they also followed the randomisation procedure to maintain blinding.

Source: Module 5.3.5.1, Clinical Study Report SB16-3001, Part I, Figure 9-1, page 28

To qualify for enrollment, subjects had to be post-menopausal, aged 55 to 80 years, and have osteoporosis according to bone mineral density (BMD) criteria on dual-energy x-ray absorptiometry (DXA) scan (absolute T-score at the total hip or lumbar spine of  $\geq -4$  and  $\leq -2.5$ ). Subjects also had to be naïve to therapeutic monoclonal antibody or fusion receptor protein (including denosumab, denosumab biosimilar, or romosozumab). Refer to Section [13.4.2](#) for the list of key eligibility criteria.

SB16 or EU-Prolia were administered by blinded study staff, and SC injection was only administered in the abdomen. The dose used in the trial is the same as the dose of US-Prolia indicated for treatment of post-menopausal osteoporosis (i.e., 60 mg SC every 6 months). All subjects also received at least 1000 mg daily of elemental calcium and at least 800 IU daily of vitamin D, with adjustments made as necessary based on results of calcium and 25-hydroxy (OH) vitamin D levels during treatment.

The primary efficacy endpoint was the percentage change in lumbar spine (LS) BMD assessed by DXA at week 52 compared to baseline, performed in the Full Analysis Set (FAS; defined as all subjects who were randomized and had at least one post baseline

assessment) using an analysis of covariance (ANCOVA) with baseline LS BMD as a covariate and treatment group as a factor. If one or more DXA devices were certified in an investigational site, it was strongly recommended that a subject was to be scanned on the same DXA machine for all study procedures. All DXA scans were submitted to a central imaging vendor for analysis.

The secondary endpoints were intended to provide supportive evidence relating to the primary endpoint, and no formal adjustments for multiplicity were performed.

The secondary efficacy endpoints included percent change from lumbar spine BMD at Months 6 and 18, analyzed similarly to the primary endpoint; and the percent change from baseline in total hip and femoral neck BMD, summarized by treatment group and visit.

The PD endpoint analyzed using an analysis of variance (ANOVA) model was the area under the effect time curve (AUEC) after first dose (AUEC<sub>0-M6</sub>) of percentage change from baseline in serum carboxy-terminal crosslinked telopeptides of type I collagen (CTX). Refer to Section [5.3.2](#).

The study entailed 9 visits to the study clinic (1 Screening visit, 7 visits during the Main Period, and an End of Study visit at the end of the Transition Period). Assessments included periodic testing of vital signs, ECG at screening, and laboratory tests for safety. DXA scan was performed at screening and again at treatment Months 6, 12 and 18. Immunogenicity assessment consisted of anti-drug antibody (ADA) testing. The complete schedule of assessments is shown in [Figure 8](#), in the Appendices.

### **6.2.3. Statistical Methodologies**

The sponsor's primary analysis set, the Full Analysis Set (FAS), consisted of all subjects who were randomized and had at least one post baseline assessment. Subjects were analyzed according to the treatment assigned at randomization. However, subjects who did not have any lumbar spine BMD assessment results after randomization and did not receive any treatment during the study period were excluded from this analysis set.

## Reviewer's Preferred Analysis Population

FDA's preferred analysis population includes all randomized and treated subjects. Note that the primary endpoint, percent change from baseline in lumbar spine (LS) bone mineral density (BMD), requires a corresponding baseline measure in order for the percent change from baseline to be calculated. All randomized and treated subjects had baseline lumbar spine BMD measures in this study.

## Primary Efficacy Analysis

The statistical hypotheses tested to assess similarity between SB16 and EU-Prolia using the primary endpoint, percent change from baseline in LS-BMD at Week 52, was as follows:

$$\begin{array}{c} H0: |SB16 - Prolia| \geq \Delta \\ \text{versus} \\ H1: |SB16 - Prolia| < \Delta \end{array}$$

Similarity was considered confirmed if the two-sided 90% confidence interval (CI) for the difference  $|SB16 - Prolia|$ , in the primary efficacy endpoint is contained within the margins of (-1.45%, 1.45%). The margin was based on a meta-analysis of three historical studies and agreed upon by the FDA. The margin was selected to preserve at least 70% of the treatment effect of the reference product.

The Applicant's prespecified primary analysis was an Analysis of Covariance (ANCOVA) model with missing values imputed using a multiple imputation under a missing at random (MAR) assumption. The ANCOVA model included treatment as a factor, and the baseline LS BMD value as the covariate. The imputation model was a regression model with the following covariates: treatment group, baseline lumbar spine BMD, and percent change from baseline in lumbar spine BMD at Month 6 and Month 12.

## Sensitivity Analysis

A tipping point sensitivity analysis was also conducted (shown in Section 6.2.6 below) which varied assumptions for missing data. The tipping point is defined as the point at which the confidence intervals are no longer contained within the predefined biosimilarity margins (defined above).

### 6.2.4. Subject Disposition

The majority of subjects in both treatment groups completed the Main and Transition Period (see [Table 13](#) and [Table 14](#) respectively). One of the subjects (ID (b) (6)) in the EU-Prolia arm of [Table 13](#), listed as discontinuing from the Main Period prematurely due to a 'protocol deviation' did not actually belong to the full analysis set, as this subject never received a dose of study drug. Additionally, the Applicant listed one subject as discontinuing from the Main Period prematurely for a reason of "other", however, it appears that this subject (ID (b) (6)) was discontinued from the trial as a result of adverse events of erythema, rash, and eyelid swelling (see discussion in [Section 6.3.3](#)).

**Table 13: Subject disposition, Study SB16-3001, Main Period**

| Status                                                          | SB16 (N=225)<br>N (%) | EU-Prolia (N=232)<br>N (%) |
|-----------------------------------------------------------------|-----------------------|----------------------------|
| Randomized                                                      | 225                   | 232                        |
| Completed Main Period                                           | 212 (94.2)            | 205 (88.4)                 |
| <b>Full Analysis Set<sup>a</sup></b>                            | <b>225 (100)</b>      | <b>231 (99.6)</b>          |
| Discontinued prematurely                                        | 13 (5.6)              | 27 (11.6)                  |
| Adverse event                                                   | 2 (0.9)               | 6 (2.6) <sup>b</sup>       |
| Death                                                           | 0                     | 0                          |
| Physician decision                                              | 1 (0.4)               | 0                          |
| Subject decision                                                | 10 (4.4)              | 19 (8.2)                   |
| Protocol deviation                                              | 0                     | 2 (0.9)                    |
| Other                                                           | 0                     | 0                          |
| Completed Main Period but did not transfer to Transition Period | 6 (2.7)               | 4 (1.7)                    |
| Adverse event                                                   | 2 (0.9)               | 3 (1.3)                    |
| Lack of efficacy or disease progression                         | 4 (1.8)               | 1 (0.4)                    |

Source: Data compiled from Study SB16-3001 ADSL dataset and the Module 5.3.5.1, Clinical Study Report for Study SB16-3001, Part I, Table 10-1, pages 60 and 61.

<sup>a</sup> Full Analysis Set consists of subjects who were randomized into the trial and received at least one dose of study drug.

<sup>b</sup> The Applicant noted that 5/232 (2.2%) subjects in the EU-Prolia arm discontinued the Main Period prematurely due to adverse events, and 1 (0.4%) subject in the EU-Prolia arm discontinued the Main Period prematurely due to 'other'. However, on review it appears that this subject (ID (b) (6)) was discontinued from the trial as a result of adverse events of erythema, rash, and eyelid swelling (see discussion in [Section 6.3.3](#)). Thus, this reviewer included this subject in this table as a subject who discontinued prematurely due to an adverse event.

**Table 14: Subject disposition, Study SB16-3001, Transition Period**

| <b>Status</b>                  | <b>SB16+SB16<br/>N (%)</b> | <b>EU-Prolia+EU-<br/>Prolia<br/>N (%)</b> | <b>EU-Prolia+SB16<br/>N (%)</b> |
|--------------------------------|----------------------------|-------------------------------------------|---------------------------------|
| Re-randomized                  | 206                        | 101                                       | 100                             |
| Completed<br>Transition Period | 206 (100)                  | 99 (98)                                   | 99 (99)                         |
| Discontinued<br>prematurely    | 0                          | 2 (2)                                     | 1 (1)                           |
| Subject decision               | 0                          | 2 (2)                                     | 1 (1)                           |

Source: Data compiled from Study SB16-3001 ADSL dataset and the Module 5.3.5.1, Clinical Study Report for Study SB16-3001, Part I, Table 10-1, pages 60 and 61

### 6.2.5. Demographic and Baseline Characteristics

Demographic characteristics were well-balanced between the two treatment groups, with the exception of a slight excess of subjects with body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> in the SB16 group (48%) compared to the EU-Prolia group (43.1%) (see [Table 15](#)). Baseline disease characteristics were also similar, with the exception of a slight excess of subjects in the SB16 group with a history of bisphosphonate use (18.7%) and prior fracture (32.9%) compared to the EU-Prolia group (14.2% and 29.4%, respectively), while the EU-Prolia group had a slightly higher proportion of subjects with baseline 25-OH vitamin D < the lower limit of normal (LLN) compared to the SB16 group: 37.9% vs. 30.7%, respectively (see [Table 16](#)). It is unlikely that these differences in baseline and demographic characteristics are significant or will have an impact on the trial findings.

**Table 15: Demographic Characteristics, Study SB16-3001**

| Demographic variable             |                        | SB16<br>(N=225) | EU-Prolia<br>(N=232) |
|----------------------------------|------------------------|-----------------|----------------------|
| Mean (SD) age, years             |                        | 66.5 (5.9)      | 66.3 (6)             |
| Age, n (%)                       |                        |                 |                      |
|                                  | <65 years              | 89 (39.6)       | 95 (40.9)            |
|                                  | ≥65 years              | 136 (60.4)      | 137 (59.1)           |
| Race, n (%)                      |                        |                 |                      |
|                                  | White                  | 207 (92)        | 208 (89.7)           |
|                                  | Asian                  | 18 (8)          | 23 (9.9)             |
|                                  | Other                  | 0               | 1 (0.4)              |
| Mean (SD) weight, kg             |                        | 64 (9.9)        | 62.5 (9.4)           |
| Mean (SD) BMI, kg/m <sup>2</sup> |                        | 25.2 (3.8)      | 24.9 (3.5)           |
| BMI, n (%)                       |                        |                 |                      |
|                                  | <25 kg/m <sup>2</sup>  | 117 (52)        | 132 (56.9)           |
|                                  | ≥ 25 kg/m <sup>2</sup> | 108 (48)        | 100 (43.1)           |
| Country, n (%)                   |                        |                 |                      |
|                                  | Czech Republic         | 59 (26.2)       | 59 (25.4)            |
|                                  | Denmark                | 5 (2.2)         | 6 (2.6)              |
|                                  | Republic of Korea      | 18 (8)          | 23 (9.9)             |
|                                  | Lithuania              | 13 (5.8)        | 12 (5.2)             |
|                                  | Poland                 | 130 (57.8)      | 132 (56.9)           |

Source: Data compiled from Study SB16-3001 ADSL dataset and the Module 5.3.5.1, Clinical Study Report for Study SB16-3001, Part I, Table 11-2, page 64.

**Table 16: Baseline Disease Characteristics, Study SB16-3001**

| Characteristic                       |           | SB16<br>(N=225) | EU-Prolia<br>(N=232) |
|--------------------------------------|-----------|-----------------|----------------------|
| Prior bisphosphonate use, n (%)      |           |                 |                      |
|                                      | yes       | 42 (18.7)       | 33 (14.2)            |
| History of fracture (any), n (%)     |           |                 |                      |
|                                      | yes       | 74 (32.9)       | 68 (29.3)            |
| Baseline LS BMD (g/cm <sup>2</sup> ) |           |                 |                      |
|                                      | Mean (SD) | 0.77 (0.07)     | 0.77 (0.07)          |
|                                      | Min, Max  | 0.60, 1.01      | 0.52, 1              |
| Baseline LS T-score                  |           |                 |                      |
|                                      | Mean (SD) | -3.0 (0.5)      | -3.1 (0.5)           |
|                                      | Min, max  | -4.5, -1.3      | -5, -1.5             |
| Serum 25-OH vitamin D <LLN           |           |                 |                      |
|                                      | N (%)     | 69 (30.7)       | 88 (37.9)            |

Source: Data compiled from Study SB16-3001 ADSL dataset and the Module 5.3.5.1, Clinical Study Report for Study SB16-3001, Part I, Table 11-3, pages 65 to 67. Abbreviations: LS = lumbar spine; BMD = bone mineral density; LLN = lower limit of normal.

### 6.2.6. Analysis of Primary Clinical Endpoint(s)

The sponsor's prespecified primary analysis results are displayed below ([Table 17](#)). There were 39 (8.5%) subjects with missing month 12 assessments; 26 (11.3%) on the EU-Prolia arm and 13 (5.8%) on the SB16 arm. Missing data were multiply imputed using monotone regression based on missing at random assumption.

**Table 17: Percent Change in LS BMD at Month 12 - Primary Analysis Results**

|                                                         | SB16<br>N=225     | EU-Prolia<br>N=231 |
|---------------------------------------------------------|-------------------|--------------------|
| Percent change at Month 12, mean (SD)                   | 5.65 (3.778)      | 5.29 (3.589)       |
| Missing, n(%)                                           | 13 (6)            | 26 (11)            |
| Percent change at Month 12, adj. <sup>1</sup> mean (SE) | 5.63 (0.250)      | 5.30 (0.254)       |
| Difference from reference, adj. mean (90% CI)           | 0.33 (-0.25,0.91) |                    |

Source: CSR and reviewer's analysis.

CI = confidence interval, SD = standard deviation, SE = standard error. <sup>1</sup>Adjusted means are from a model adjusting for treatment group and baseline BMD. Missing values were imputed within treatment group with 25 multiple imputations assuming missing at random. Rubin's method was used to combine analysis results from 25 imputed datasets.

Since missing at random assumption may not be plausible, FDA reviewer performed analyses using two one-sided tests with missing data imputed under the corresponding null hypothesis. Specifically, missing data in both treatment groups were first multiply imputed based on observed data of the reference product group. The imputed values in the test product group were subsequently subtracted by the margin 1.45% for testing non-inferiority and added by the margin for testing non-superiority, respectively. The imputed datasets were then each analyzed using the same ANCOVA model as the primary analysis. The analyses results (100 imputations) were combined using Rubin's method. Results from the two one-sided tests supported the similarity in LS BMD at month 12 between the two treatment groups. The 90% confidence limits were all within the similarity margin.

**Table 18: Percent Change in LS BMD at Month 12 – Two One-sided Tests**

| Statistical test        |                                                         | SB16<br>N=225      | Prolia<br>N=231 |
|-------------------------|---------------------------------------------------------|--------------------|-----------------|
| Testing non-inferiority | Percent change at Month 12, adj. <sup>1</sup> mean (SE) | 5.54 (0.253)       | 5.29 (0.257)    |
|                         | Difference from reference, adj. mean (90% CI)           | 0.24 (-0.34, 0.83) |                 |
| Test non-superiority    | Percent change at Month 12, adj. <sup>1</sup> mean (SE) | 5.70 (0.252)       | 5.29 (0.256)    |
|                         | Difference from reference, adj. mean (90% CI)           | 0.41 (-0.17, 1.00) |                 |

Source: reviewer. SE: standard error; CI: confidence interval. <sup>1</sup>Adjusted means are from a model adjusting for treatment group and baseline BMD.

Missing values were imputed with multiple imputation under the non-inferiority null assumption when testing non-inferiority and under the non-superiority null assumption when testing non-superiority. Rubin's method was used to combine analysis results from 100 imputed datasets.

### 6.2.7. Potential Effects of Missing Data

The analysis results for the primary endpoint are consistent regardless of the method used to handle missing data.

The sponsor performed a two-way tipping point analysis to investigate the robustness of the similarity conclusion of the primary endpoint analysis to varying missing data assumptions. The analyses were conducted by repeating the primary analysis with

imputed values from the primary analysis added a sequence of constant values for both groups to see when the similarity conclusion would be overturned. The tipping point analyses results shown in [Table 19](#) supported the robustness of the similarity conclusion. The similarity conclusion could be overturned only when the mean difference in the missing values is large to an unlikely extent. For example, for 90% confidence intervals, the analysis conclusion would be overturned when the imputed values in reference product group were further decreased by 6% and the imputed values in the test product group further decreased by no more than 2%.

**Table 19: Tipping Point Analysis**

| SB16     | Prolia          |                 |                 |                  |                  |                  |                  |
|----------|-----------------|-----------------|-----------------|------------------|------------------|------------------|------------------|
|          | Delta=-6        | Delta=-4        | Delta=-2        | Delta=0          | Delta=2          | Delta=4          | Delta=6          |
| Delta=-6 |                 |                 |                 |                  |                  |                  |                  |
| LSM (SE) | 0.66<br>(0.388) | 0.43<br>(0.377) | 0.21<br>(0.370) | -0.02<br>(0.367) | -0.24<br>(0.370) | -0.47<br>(0.377) | -0.69<br>(0.389) |
| 90% CI   | [0.02, 1.30]    | [-0.19, 1.05]   | [-0.40, 0.82]   | [-0.62, 0.59]    | [-0.85, 0.37]    | [-1.09, 0.15]    | [-1.33, -0.05]   |
| Delta=-4 |                 |                 |                 |                  |                  |                  |                  |
| LSM (SE) | 0.77<br>(0.382) | 0.55<br>(0.370) | 0.32<br>(0.363) | 0.10<br>(0.361)  | -0.13<br>(0.363) | -0.35<br>(0.371) | -0.58<br>(0.383) |
| 90% CI   | [0.15, 1.40]    | [-0.06, 1.16]   | [-0.27, 0.92]   | [-0.49, 0.69]    | [-0.72, 0.47]    | [-0.96, 0.26]    | [-1.21, 0.05]    |
| Delta=-2 |                 |                 |                 |                  |                  |                  |                  |
| LSM (SE) | 0.89<br>(0.378) | 0.67<br>(0.366) | 0.44<br>(0.359) | 0.22<br>(0.356)  | -0.01<br>(0.359) | -0.23<br>(0.366) | -0.46<br>(0.379) |
| 90% CI   | [0.27, 1.51]*   | [0.06, 1.27]    | [-0.15, 1.03]   | [-0.37, 0.80]    | [-0.60, 0.58]    | [-0.84, 0.37]    | [-1.08, 0.16]    |
| Delta=0  |                 |                 |                 |                  |                  |                  |                  |
| LSM (SE) | 1.01<br>(0.376) | 0.78<br>(0.364) | 0.56<br>(0.357) | 0.33<br>(0.354)  | 0.11<br>(0.357)  | -0.12<br>(0.365) | -0.34<br>(0.377) |
| 90% CI   | [0.39, 1.62]*   | [0.18, 1.38]    | [-0.03, 1.14]   | [-0.25, 0.91]    | [-0.48, 0.69]    | [-0.72, 0.48]    | [-0.96, 0.28]    |
| Delta=2  |                 |                 |                 |                  |                  |                  |                  |
| LSM (SE) | 1.12<br>(0.377) | 0.90<br>(0.365) | 0.67<br>(0.358) | 0.45<br>(0.355)  | 0.22<br>(0.358)  | -0.00<br>(0.366) | -0.23<br>(0.378) |
| 90% CI   | [0.50, 1.74]*   | [0.30, 1.50]*   | [0.08, 1.26]    | [-0.14, 1.03]    | [-0.37, 0.81]    | [-0.61, 0.60]    | [-0.85, 0.39]    |
| Delta=4  |                 |                 |                 |                  |                  |                  |                  |
| LSM (SE) | 1.24<br>(0.380) | 1.01<br>(0.368) | 0.79<br>(0.361) | 0.56<br>(0.359)  | 0.34<br>(0.362)  | 0.11<br>(0.369)  | -0.11<br>(0.381) |
| 90% CI   | [0.61, 1.86]*   | [0.41, 1.62]*   | [0.19, 1.38]    | [-0.03, 1.15]    | [-0.26, 0.93]    | [-0.50, 0.72]    | [-0.74, 0.51]    |
| Delta=6  |                 |                 |                 |                  |                  |                  |                  |
| LSM (SE) | 1.35<br>(0.386) | 1.13<br>(0.375) | 0.90<br>(0.367) | 0.68<br>(0.365)  | 0.45<br>(0.368)  | 0.23<br>(0.375)  | 0.00<br>(0.387)  |
| 90% CI   | [0.72, 1.99]*   | [0.51, 1.74]*   | [0.30, 1.51]*   | [0.08, 1.28]     | [-0.15, 1.06]    | [-0.39, 0.84]    | [-0.63, 0.64]    |

Source- sponsor's code and dataset; analysis results verified by FDA statistical reviewer; SE: standard error;

CI: confidence interval; \*: similarity conclusion overturned.

### 6.2.8. Analysis of Secondary Clinical Endpoint(s)

The secondary efficacy endpoints were intended to provide supportive evidence relating to the primary endpoint, and no formal adjustments for multiplicity were performed.

The secondary efficacy endpoints included percent change from LS BMD at Months 6 and 18 (see [Table 20](#)), analyzed similarly to the primary endpoint; and the percent change from baseline in total hip (see [Table 21](#)) and femoral neck BMD (see [Table 22](#)), summarized by treatment group and visit.

In general, the change from baseline in mean LS BMD between the SB16+SB16 and EU-Prolia+EU-Prolia groups and EU-Prolia+SB16 and EU-Prolia+EU-Prolia groups at Month 18 are comparable. Similarly, the change from baseline in total hip and femoral neck BMD were comparable between the SB16 and EU-Prolia groups at Month 12, and between the SB16+SB16, EU-Prolia+EU-Prolia, and EU-Prolia+SB16 groups at Month 18.

These results indicate a maintenance of efficacy after the single transition from EU-Prolia to SB16.

**Table 20: Analysis of percent change from baseline in LS BMD at Month 18, FAS, Study SB16-3001**

| <b>SB16+SB16 compared to EU-Prolia+EU-Prolia</b>      | <b>SB16+SB16<br/>N=206</b>      | <b>EU-Prolia+EU-Prolia<br/>N=101</b> |
|-------------------------------------------------------|---------------------------------|--------------------------------------|
| LS mean (SE) percent change from baseline at Month 18 | 6.77 (0.286)                    | 6.8 (0.411)                          |
| LS mean difference (90% CI)                           | -0.03 (-0.85, 0.79)             |                                      |
| <b>EU-Prolia+SB16 compared to EU-Prolia+EU-Prolia</b> | <b>EU-Prolia+SB16<br/>N=100</b> | <b>EU-Prolia+EU-Prolia<br/>N=101</b> |
| LS mean (SE) percent change from baseline at Month 18 | 6.28 (0.412)                    | 6.8 (0.411)                          |
| LS mean difference (90% CI)                           | --0.52 (-1.48, 0.43)            |                                      |

N = total number of subjects in the full analysis set in each treatment group (also the number of subjects with available assessments results at each time point); CI = confidence interval; LS mean = least squares mean; SE = standard error

Source: Module 5.3.5.1, Clinical Study Report SB16-3001, Part I, Table 11-7, page 75

**Table 21: Analysis of percent change from baseline in total hip BMD at Months 6, 12, and 18, FAS, Study SB16-3001**

| <b>Analysis, Main Period</b>                          | <b>SB16<br/>N=225</b>      | <b>EU-Prolia<br/>N=231</b>           |                                 |
|-------------------------------------------------------|----------------------------|--------------------------------------|---------------------------------|
| Mean (SD) percent change from baseline at Month 12    | 3.5 (2.8)<br>n=212         | 3.2 (2.7)<br>n=205                   |                                 |
| <b>Analysis, Transition Period</b>                    | <b>SB16+SB16<br/>N=206</b> | <b>EU-Prolia+EU-Prolia<br/>N=101</b> | <b>EU-Prolia+SB16<br/>N=100</b> |
| LS mean (SE) percent change from baseline at Month 18 | 4.4 (3.2)<br>n=204         | 4 (3.1)<br>n=99                      | 3.5 (2.9)<br>n=99               |

N = total number of subjects in the full analysis set in each treatment group; n = the number of subjects with available assessments results at each time point; CI = confidence interval; SD = standard deviation

Source: Module 5.3.5.1, Clinical Study Report SB16-3001, Part III, Table 14.2-4.1, pages 508 to 509

**Table 22: Analysis of percent change from baseline in femoral neck BMD at Months 6, 12, and 18, FAS, Study SB16-3001**

| <b>Analysis, Main Period</b>                          | <b>SB16<br/>N=225</b>      | <b>EU-Prolia<br/>N=231</b>           |                                 |
|-------------------------------------------------------|----------------------------|--------------------------------------|---------------------------------|
| Mean (SD) percent change from baseline at Month 12    | 2.8 (4.2)<br>n=212         | 2.3 (3.4)<br>n=205                   |                                 |
| <b>Analysis, Transition Period</b>                    | <b>SB16+SB16<br/>N=206</b> | <b>EU-Prolia+EU-Prolia<br/>N=101</b> | <b>EU-Prolia+SB16<br/>N=100</b> |
| LS mean (SE) percent change from baseline at Month 18 | 3.4 (4)<br>n=204           | 2.8 (3.5)<br>n=99                    | 3.1 (3.5)<br>n=99               |

N = total number of subjects in the full analysis set in each treatment group; n = the number of subjects with available assessments results at each time point; CI = confidence interval; SD = standard deviation  
Source: Module 5.3.5.1, Clinical Study Report SB16-3001, Part III, Table 14.2-5.1, pages 512 to 513

### 6.2.9. Other Clinical Endpoints

None.

### 6.2.10. Additional Analysis

None.

## 6.3. Review of Safety Data

### 6.3.1. Methods

#### 6.3.1.1. Clinical Studies Used to Evaluate Safety

The evaluation of safety is based primarily on the comparative clinical study (study SB16-3001), which evaluated safety and efficacy of SB16 and EU-Prolia use in post-menopausal women with osteoporosis. However, safety data from the PK similarity study (Study SB16-1001), which enrolled healthy adult males, will also be examined for known risks of study drugs (e.g., hypersensitivity reactions and hypocalcemia) and to further evaluate any new safety signals that become apparent during review of the data from Study SB16-3001.

### **6.3.1.2. Categorization of Adverse Events**

In both study SB16-3001 and study SB16-1001, an adverse event was defined as any untoward medical occurrence in a subject after providing written informed consent for participation of the study. A treatment emergent adverse event (TEAE) was defined as any adverse event with an onset date on or after date of the initiation of study drug, or that was present prior to administration of study drug but increased in severity afterwards. Abnormal laboratory values or test results constituted adverse events only if they fulfilled at least one of the following criteria:

- induced clinical signs or symptoms.
- were clinically significant.
- required therapy.

Serious adverse events (SAEs) and adverse events (AEs) were categorized by severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

### **6.3.1.3. Safety Analyses**

Safety data were not combined because the study populations and design of the two studies differed.

Study SB16-3001 consisted of two treatment periods, the first comparing SB16 to EU-Prolia and the second period designed to evaluate the safety of a transition from EU-Prolia to SB16, compared to continuing on EU-Prolia. Safety data from the two treatment periods are presented separately.

## **6.3.2. Major Safety Results**

### **6.3.2.1. Relevant Characteristics of the Population Evaluated for Safety**

Study SB16-1001 enrolled healthy adult male volunteers, who do not reflect the population for whom denosumab is indicated. Nonetheless, the population was considered appropriate and sensitive given the primary objectives of the study.

Study SB16-3001 enrolled post-menopausal women with osteoporosis, which is one of the target populations for denosumab. Demographic and baseline disease characteristics of the study population are shown in [Table 15](#) and [Table 16](#), respectively.

### **6.3.2.2. Deaths**

#### **Study SB16-1001**

There was one death (preferred term: completed suicide) in this study in a 33-year-old-male randomized to a single 60 mg dose of SB16. The death was not considered

related to study drug, but rather professional and personal problems that led to suicide 190 days after administration of SB16.

### Study SB16-3001

There were no deaths in this study.

#### 6.3.2.3. Serious Adverse Events

### Study SB16-1001

Three subjects reported a serious adverse event (SAE) during the study, all 3 (5.4%) in the SB16 treatment group: facial bones fracture, depression, and completed suicide. None appear to be related to study drug and no single SAE occurred more than once.

### Study SB16-3001

#### Main Period:

During the Main Period, treatment-emergent SAEs occurred in a comparable proportion between the two treatment groups: 8/225 (3.6%) and 8/231 (3.5%) subjects receiving SB16 and EU-Prolia, respectively. Of these, 2/225 (0.9%) vs 0 subjects receiving SB16 and EU-Prolia, respectively, reported SAEs of fractures: 1/225 (0.4%) subject reported an ankle fracture and 1/225 (0.4%) subject reported a forearm fracture (see [Table 23](#)).

Brief narratives for the two subjects with SAEs of fracture follow:

- **Subject** (b) (6): This was a 71-year-old white female with a history of two prior lower left leg fractures who experienced left ankle fracture on Day 297 of the study, 116 days after the second dose of SB16 administration, following a fall from the stairs. This SAE was reported as a high-energy break (a TEAE of right ankle fracture was reported as well, though it was not serious). At baseline, total hip and femoral neck BMD were 0.996 g/cm<sup>2</sup> and 0.731 g/cm<sup>2</sup>, respectively. Baseline LS T-score was -2.5. The subject was hospitalized and recovered following an open reduction of fracture. She continued in the study through completion. Serum 25-OH vitamin D and calcium levels were normal at baseline and throughout the study. Total hip and femoral neck BMD at Day 181, sixteen weeks prior to the fracture, were 0.959 and 0.717 g/cm<sup>2</sup>, a -0.7% and a -1.9% change, respectively, compared to baseline. Total hip and femoral neck BMD at Day 364, nine weeks after the fracture, were 0.947 and 0.706 g/cm<sup>2</sup>, a -2% and a -3.4% change, respectively, compared to baseline. This SAE of fracture, with decreasing hip and femoral neck BMD with treatment appears to suggest a lack of efficacy of SB16 therapy contributing to this fracture. However, this assessment is also complicated by the fact that this was reported as a high-energy break, which also suggests that assessment of decreased efficacy leading to fracture may be confounded by concomitant trauma.
- **Subject** (b) (6): This was a 68-year-old white female with a history of prior lumbar vertebral fractures of L1 and L5 who experienced *forearm fracture* of the right arm on Day 55 of the study, 54 days after the first dose of SB16 administration, following a fall from a stool. At baseline, total hip and femoral

neck BMD were 0.755 g/cm<sup>2</sup> and 0.647 g/cm<sup>2</sup>, respectively. Baseline LS T-score was -3.1. The subject was hospitalized and recovered following an open reduction and fixation of fracture. She completed Main Period but discontinued prior to treatment in the Transition Period given concern for a lack of efficacy or disease progression. Serum 25-OH vitamin D was low at baseline and remained so at follow up visits. Calcium levels were normal at baseline and throughout the study. Total hip and femoral neck BMD at Day 181, eighteen weeks after the fracture, were 0.731 and 0.601 g/cm<sup>2</sup>, a -3.2% and a -7.1% change, respectively, compared to baseline. The reporting of a forearm fracture following a fall from a stool, in the setting of decreasing hip and femoral neck BMD with treatment and withdrawal from the trial due to a concern of lack of efficacy is possibly indicative of a lack of efficacy of SB16 and the forearm fracture in this subject.

Fractures are discussed further in Section [6.3.4.46.3.4.4](#).

Other SAEs in the SB16 group occurred in a single subject See [Table 23](#) for all SAEs reported during the Main Period of Study SB16-3001.

**Table 23: Serious adverse events, Study SB16-3001, Main Period**

| Preferred Term               | SB16<br>(N=225) | Prolia<br>(N=231) | Total<br>(N=456) |
|------------------------------|-----------------|-------------------|------------------|
| <b>Any SAE (%)</b>           | 8 (3.6)         | 8 (3.5)           | 16 (3.5)         |
| Acute respiratory failure    | 1 (0.4)         | 0                 | 1 (0.2)          |
| Adrenal adenoma              | 1 (0.4)         | 0                 | 1 (0.2)          |
| Ankle fracture               | 1 (0.4)         | 0                 | 1 (0.2)          |
| Breast cancer                | 0               | 1 (0.4)           | 1 (0.2)          |
| Cataract                     | 0               | 1 (0.4)           | 1 (0.2)          |
| COVID-19                     | 1 (0.4)         | 0                 | 1 (0.2)          |
| Forearm fracture             | 1 (0.4)         | 0                 | 1 (0.2)          |
| Hematuria                    | 0               | 1 (0.4)           | 1 (0.2)          |
| Intervertebral disc disorder | 0               | 1 (0.4)           | 1 (0.2)          |
| Intestinal infarction        | 1 (0.4)         | 0                 | 1 (0.2)          |
| Intracranial aneurysm        | 1 (0.4)         | 0                 | 1 (0.2)          |
| Lung adenocarcinoma          | 0               | 1 (0.4)           | 1 (0.2)          |
| Nephrolithiasis              | 0               | 1 (0.4)           | 1 (0.2)          |
| Osteoarthritis               | 1 (0.4)         | 0                 | 1 (0.2)          |
| Pneumonia                    | 1 (0.4)         | 0                 | 1 (0.2)          |
| Retinal detachment           | 0               | 1 (0.4)           | 1 (0.2)          |
| Spinal osteoarthritis        | 1 (0.4)         | 0                 | 1 (0.2)          |
| Transient ischemic attack    | 0               | 1 (0.4)           | 1 (0.2)          |
| Urethral caruncle            | 0               | 1 (0.4)           | 1 (0.2)          |

Source: clinical reviewer generated report

None of the SAEs in either treatment group were considered related to study drug. Review of the narratives yields the same conclusion.

Transition Period:

During the Transition Period, 4 subjects in the SB16+SB16 group, 1 subject in the EU-Prolia+EU-Prolia group, and 2 subjects in the EU-Prolia+SB16 group experienced treatment-emergent serious adverse events. Of these 3 treatment groups, 2 subjects from the SB16+SB16 were the only subjects to report SAEs of fracture: femoral neck fracture and forearm fracture.

Brief narratives for the two subjects with SAEs of fracture follow:

- **Subject** (b) (6): This was a 78-year-old white female diagnosed with *femoral neck fracture* of the left leg on Day 424 of the study, 56 days after the third dose of SB16 administration, following a fall. She was hospitalized and underwent hip arthroplasty. She completed and stayed in the trial and completed the Transition Period. At baseline, total hip and femoral neck BMD were 0.651 g/cm<sup>2</sup> and 0.614 g/cm<sup>2</sup>, respectively. Baseline LS T-score was -3.4. Serum 25-OH vitamin D (only followed in the Main Period) was low at baseline, but normal throughout the Main Period. Calcium levels were normal at baseline and throughout the study. Total hip and femoral neck BMD at Day 359, 8 weeks prior to the fracture, were 0.659 and 0.628 g/cm<sup>2</sup>, a 1.2% and a 2.3% change, respectively, compared to baseline. Total hip and femoral neck BMD following the fracture were not reported. As this subject suffered a fall in the setting of improving hip and femoral neck BMD, it is unlikely that a lack of efficacy of SB16 contributed to this fracture. However, a lack of follow up BMD data after the fracture does preclude a definitive conclusion regarding a lack of association with decreased efficacy.
- **Subject** (b) (6): This was a 70-year-old diagnosed with *forearm fracture* of the left arm on Day 500 of the study, 141 days after the third dose of SB16 administration, following a fall. She was hospitalized and treated with cast fixation initially, but on follow up surgery involving repositioning and osteosynthesis with a splint was performed. She completed and stayed in the trial and completed the Transition Period. At baseline, total hip and femoral neck BMD were 0.665 g/cm<sup>2</sup> and 0.677 g/cm<sup>2</sup>, respectively. Baseline LS T-score was -3.1. Serum 25-OH vitamin D (only followed in the Main Period) and calcium levels were normal at baseline and throughout the study. Total hip and femoral neck BMD at Day 359, twenty weeks prior to the fracture, were 0.708 and 0.688 g/cm<sup>2</sup>, a 6.5% and a 1.6% change, respectively, compared to baseline. Total hip and femoral neck BMD at Day 548, six weeks after the fracture, were 0.742 and 0.707 g/cm<sup>2</sup>, an 11.6% and a 4.4% change, respectively, compared to baseline. As this subject suffered a fall in the setting of improving hip and femoral neck BMD, it is unlikely that a lack of efficacy of SB16 contributed to this fracture.

Other SAEs reported in the SB16+SB16 group include subdural hemorrhage and pulmonary embolism, each reported once. SAEs reported in the EU-Prolia+EU-Prolia

group include general physical health deterioration (following a diagnosis of sepsis), interverbal discitis, and septic shock, all reported by 1 subject.

SAEs reported in the EU-Prolia+SB16 group include atrial fibrillation and osteoarthritis, each reported once.

None of the SAEs in the Transition Period appear to be related to study drug, and there was no clinically meaningful difference in the incidence of serious adverse events in the three treatment groups.

#### 6.3.2.4. Common Treatment Emergent Adverse Events

The review team also conducted an analysis of AEs occurring in Study SB16-3001 using FDA Medical Dictionary for Regulatory Activities Queries (FMQ) or grouped queries (GQ). FMQs were developed by FDA to improve the capture of synonymous AE terms and to improve overall safety signal detection. To further improve safety signal detection, the clinical review team also created GQs which consisted of adverse events that were not already part of an FMQ but were synonymous. Subjects who reported more than 1 individual PT grouped in a single FMQ or GQ are only counted once in the number of subjects reporting that combined term.

#### Study SB16-3001

##### Main Period

Treatment emergent adverse events (TEAEs), listed by combined FMQs or GQs, occurring at  $\geq 3\%$  frequency in either treatment group are listed in [Table 24](#) and GQs and arranged by descending risk difference (see [Table 39](#) in Section [13.4.3](#) for a listing of the individual preferred terms [PTs] included in the most commonly reported combined FMQs).

Overall, a comparable proportion of subjects in each treatment arm (159/225 [70.7%] and 164/231 [71%] subject in the SB16 and EU-Prolia arms, respectively) reported at least one TEAE. In general, the most common TEAEs were similar between the two treatment groups and were consistent with the known safety profile of denosumab or were not uncommon in this patient population.

**Table 24: Most common treatment emergent adverse events (i.e., reported by  $\geq 3\%$  of subjects in either treatment group), Study SB16-3001, Main Period**

| Preferred Term                    | SB16<br>(N=225) | EU-Prolia<br>(N=231) | Risk<br>Difference<br>(%) (95% CI) | Total<br>(N=456) |
|-----------------------------------|-----------------|----------------------|------------------------------------|------------------|
| <b>Any TEAE (%)</b>               | 159 (70.7)      | 164 (71.0)           | -0.3 (-8.7, 8)                     | 323 (70.8)       |
| Headache <sup>†</sup>             | 18 (8.0)        | 10 (4.3)             | 3.7 (-0.7, 8.1)                    | 28 (6.1)         |
| Fracture <sup>†</sup>             | 8 (3.6)         | 1 (0.4)              | 3.1 (0.6, 5.7)*                    | 9 (2.0)          |
| Arthralgia <sup>†</sup>           | 16 (7.1)        | 10 (4.3)             | 2.8 (-1.5, 7)                      | 26 (5.7)         |
| Vitamin D deficiency <sup>†</sup> | 11 (4.9)        | 5 (2.2)              | 2.7 (-0.7, 6.1)                    | 16 (3.5)         |
| Dyslipidemia <sup>†</sup>         | 13 (5.8)        | 8 (3.5)              | 2.3 (-1.5, 6.2)                    | 21 (4.6)         |
| Hypertension <sup>†</sup>         | 13 (5.8)        | 8 (3.5)              | 2.3 (-1.5, 6.2)                    | 21 (4.6)         |
| Diarrhea <sup>†</sup>             | 8 (3.6)         | 3 (1.3)              | 2.3 (-0.6, 5.1)                    | 11 (2.4)         |

| Preferred Term                           | SB16<br>(N=225) | EU-Prolia<br>(N=231) | Risk<br>Difference<br>(%) (95% CI) | Total<br>(N=456) |
|------------------------------------------|-----------------|----------------------|------------------------------------|------------------|
| Arthritis <sup>†</sup>                   | 13 (5.8)        | 9 (3.9)              | 1.9 (-2.1, 5.8)                    | 22 (4.8)         |
| Urinary tract infection <sup>†</sup>     | 16 (7.1)        | 13 (5.6)             | 1.5 (-3, 6)                        | 29 (6.4)         |
| Respiratory tract infection <sup>†</sup> | 15 (6.7)        | 16 (6.9)             | -0.3 (-4.9, 4.4)                   | 31 (6.8)         |
| Hemorrhage <sup>†</sup>                  | 7 (3.1)         | 9 (3.9)              | -0.8 (-4.2, 2.6)                   | 16 (3.5)         |
| Alopecia                                 | 6 (2.7)         | 8 (3.5)              | -0.8 (-4, 2.4)                     | 14 (3.1)         |
| COVID-19 <sup>†</sup>                    | 17 (7.6)        | 20 (8.7)             | -1.1 (-6.1, 3.9)                   | 37 (8.1)         |
| Constipation                             | 4 (1.8)         | 7 (3.0)              | -1.3 (-4.1, 1.6)                   | 11 (2.4)         |
| Back pain <sup>†</sup>                   | 22 (9.8)        | 26 (11.3)            | -1.5 (-7.1, 4.2)                   | 48 (10.5)        |
| Nasopharyngitis <sup>†</sup>             | 14 (6.2)        | 18 (7.8)             | -1.6 (-6.3, 3.1)                   | 32 (7.0)         |
| Abdominal pain <sup>†</sup>              | 7 (3.1)         | 11 (4.8)             | -1.7 (-5.2, 1.9)                   | 18 (3.9)         |
| Hypocalcemia <sup>†</sup>                | 22 (9.8)        | 28 (12.1)            | -2.3 (-8.1, 3.4)                   | 50 (11.0)        |
| Hypersensitivity <sup>†</sup>            | 6 (2.7)         | 12 (5.2)             | -2.5 (-6.1, 1)                     | 16 (3.5)         |
| Post vaccination syndrome                | 1 (0.4)         | 8 (3.5)              | -3 (-5.5, -0.5)*                   | 9 (2.0)          |

Source: MAED analysis using JMP clinical and grouped terms derived from FMQ analysis, clinical reviewer generated report

\* 95% confidence interval excludes zero

<sup>†</sup> Represent preferred terms that were combined FMQs or GQs. Grouping of several related terms in FMQs/GQs rendered incidence that is different from the Applicant's analysis. Refer to [Table 39](#) in Section [13.4.3](#) for a listing of the individual preferred terms included in the most commonly reported combined FMQs or GQs.

The TEAEs by combined FMQ or GQ that were reported by  $\geq 3\%$  of either treatment group that were reported in a significantly higher proportion (risk difference  $\geq 1\%$ ) of subjects in the SB16 group compared to the EU-Prolia group are briefly discussed below, with the exception of fractures, which are discussed in Section [6.3.4.4](#).

- **Headache:**  
A greater incidence of headaches was observed in the SB16 arm compared to the EU-Prolia arm (8% versus 4.3%). Out of the 20 events that occurred in the SB16 arm none were SAEs, all were of mild (65%) or moderate (35%) severity. The onset of event was 1 to 357 days, though the majority of events (17 of 20 cases of headache) occurred more than 4 weeks after receiving a dose of SB16. All but 1 (5%) were reported as recovered or resolving. In 1 (5%) case, SB16 was permanently discontinued, in all other events the dose of study drug was not changed. In 16 (80%) events, the subject required concomitant medication and in 1 (5%) event the subjects required CT scan. No subjects required hospitalization.
- **Urinary tract infection:**  
A greater proportion of subjects in the SB16 group than the EU-Prolia group reported a TEAE related to urinary tract infection (7.1% versus 5.6%). None of the cases in the SB16 arm were serious, out of the 20 relevant TEAEs reported, 13 (65%) were of mild severity, while the rest were of moderate severity. Onset was reported between 1 and 364 days after initiation of SB16 therapy and all cases were reported as resolved with changing or stopping SB16. All but 1 (5%) case required concomitant medication and no subject required hospitalization.

- **Arthralgia:**  
TEAEs in the arthralgia FMQ were reported in 7.1% versus 4.3% subjects in the SB16 group compared to the EU-Prolia group, respectively. Out of the 17 events that occurred in the SB16 arm none were serious, and all were of mild (94.1%) or moderate (5.9%) severity. The onset of the event was 1 to 330 days. A total of 8 (47.1%) were listed as recovered/resolved and 9 (52.9%) were not recovered. In all cases the dose of SB16 was neither changed nor discontinued. In 7 (47.1%) cases the subject required concomitant medication, and orthopedic consultation, physical therapy, imaging of the hip, or surgical procedure were each required in 1 (5.9%) case each. No subjects required hospitalization.
- **Arthritis:**  
A greater incidence of arthritis was observed in the SB16 group compared to the EU-Prolia group (5.8% versus 3.9%). Of the 14 events reported in the SB16 group, 2 (14.3%) were serious, 1 (7.1%) of which was severe. All non-serious TEAEs of arthritis in the SB16 group were of either mild (50%) or moderate (42.9%) severity, did not result in hospitalization, in 8 (57.1%) cases the subject required concomitant medications, physiotherapy was required in 2 (14.3%) cases, and MRI, x-ray, ultrasound, and kinesiotherapy were each required in 1 (7.1%) case. Of non-serious TEAEs of arthritis, 3 (21.4%) versus 9 (64.3%) cases of arthritis were reported as recovered/resolved versus not recovered.

Both SAEs in the SB16 group required concomitant medication, and 1 (7.1%) required surgical procedure (PT: spinal osteoarthritis) while the other required rehabilitation (PT: osteoarthritis). Both SAE cases resulted in hospitalization (3 to 5 days in duration) and both recovered without changing or discontinuing the dose of SB16. Overall, differences in the rates of reporting of the PT of osteoarthritis (4.4% versus 3.9%) and spinal osteoarthritis (0.4% versus 0) between the SB16 and EU-Prolia arms were low, and in the review team concluded that causality of these SAEs is unlikely to be attributed to SB16 exposure.

- **Dyslipidemia:**  
SB16 was associated with a greater incidence of dyslipidemia than EU-Prolia (5.8% versus 3.5%). Of the 13 cases reported in the SB16 arm, none were serious, all were of mild severity, and the onset of the event was 14 to 331 days. A total of 8 (61.5%) cases were not recovered, while the remainder were reported as recovered/resolved. In 8 (61.5%) cases concomitant medication was required and in 2 (15.4%) cases, a low-fat diet was prescribed. No changes or discontinuation of SB16 or hospitalization were required.
- **Hypertension:**  
More subjects in the SB16 arm reported hypertension (5.8%) than did subjects in the EU-Prolia arm (3.5%). There were a total of 14 cases reported in subjects treated with SB16, of which none were serious and all were of either mild (64.3%) or moderate (35.7%) severity. Onset of the events of hypertension were

from Day 30 to Day 324. Five (35.7%) cases were reported as not recovered, the remainder were reported as either recovering or resolved. A total of 12 (85.7%) cases required concomitant medication and the dose of SB16 was not changed or discontinued in any case. No case required hospitalization.

- **Vitamin D deficiency:**  
TEAEs in the vitamin D deficiency FMQ were reported in 4.9% versus 2.2% in the SB16 and EU-Prolia treatment groups, respectively. There were 11 cases of vitamin D deficiency reported in subjects treated with SB16, none of which were SAEs, and 81.8% were of mild severity, the rest were of moderate severity. Onset of the TEAEs were reported between 176 and 365 days. A total of 7 (63.4%) cases were listed as recovered or resolving, 3 (27.3%) as not recovered, and 1 (9.1%) as unknown. All subjects reporting vitamin D deficiency received calcium and/or vitamin D, and SB16 dosing was not changed or discontinued. No subject required hospitalization.
- **Diarrhea:**  
A greater proportion of subjects in the SB16 group than the EU-Prolia group reported a TEAE related to diarrhea (3.6% versus 1.3%). A total of 8 cases of diarrhea were reported by subjects in the SB16 group, none of which were serious, 6 (75%) cases were of mild severity and the rest were of moderate severity. Diarrhea-related cases were reported with an onset of 23 to 346 days after starting SB16 and only 1 (12.5%) case was not recovered, the rest were recovered or resolving. Only 1 (12.5%) case resulted in SB16 dosing being temporarily delayed (the subject received the second planned dose 22 days later than planned), the others required no changes in SB16 dosing. For the subject for whom dosing of SB16 was delayed, it is also noted that an antibiotic the subjects was taking as a concomitant medication was discontinued as well and the event of diarrhea did resolve, making causality of SB16 to diarrhea in this case unlikely. For 5 (62.5%) other cases, the subjects required concomitant medications. No subject required hospitalization.

In all TEAEs discussed above, the differences between incidences of the TEAEs was small and likely due to chance, rather than due to meaningful differences between the products. The majority of cases in subjects treated with SB16 were not serious or severe, or required changes to SB16 dosing or other significant intervention. Hence, these differences do not represent a clinically meaningful safety difference between the two products, and are not considered an unacceptable risk.

Transition Period

TEAEs, listed by combined FMQs or GQs, occurring at  $\geq 3\%$  frequency in any treatment group are listed in [Table 25](#) (see [Table 40](#) in Section [13.4.3](#) for a listing of the individual PTs included in the most commonly reported combined FMQs and GQs).

The TEAE profile during the Transition Period was also largely consistent with the known safety profile of denosumab.

**Table 25: Most common (reported by  $\geq 3\%$  of subjects in either treatment group) treatment emergent adverse events, Study SB16-3001, Transition Period**

| Preferred term                    | EU-Prolia+SB16<br>(N=100) | SB16+SB16<br>(N=206) | EU-Prolia+EU-Prolia<br>(N=101) | Risk Difference<br>Prolia+SB16 -<br>SB16+SB16<br>(%) (95% CI) | Risk<br>Difference<br>Prolia+SB16 –<br>EU-Prolia+EU-<br>Prolia<br>(%) (95% CI) | Total<br>(N=407) |
|-----------------------------------|---------------------------|----------------------|--------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------------|------------------|
| Any AE (%)                        | 29 (29.0)                 | 73 (35.4)            | 35 (34.7)                      | -6.4 (-17.4, 4.6)                                             | -5.7 (-18.5, 7.2)                                                              | 137 (33.7)       |
| Vitamin D Deficiency <sup>†</sup> | 7 (7.0)                   | 6 (2.9)              | 2 (2.0)                        | 4.1 (-1.4, 9.6)                                               | 5 (-0.7, 10.7)                                                                 | 15 (3.7)         |
| Hemorrhage <sup>†</sup>           | 3 (3.0)                   | 0                    | 0                              | 3 (-0.3, 6.3)                                                 | 3 (-0.3, 6.3)                                                                  | 3 (0.7)          |
| Headache <sup>†</sup>             | 3 (3.0)                   | 5 (2.4)              | 2 (2.0)                        | 0.6 (-3.4, 4.5)                                               | 1 (-3.3, 5.3)                                                                  | 10 (2.5)         |
| Arthralgia                        | 1 (1.0)                   | 7 (3.4)              | 2 (2.0)                        | -2.4 (-5.5, 0.8)                                              | -1 (-4.3, 2.4)                                                                 | 10 (2.5)         |
| Dyslipidemia <sup>†</sup>         | 1 (1.0)                   | 9 (4.4)              | 2 (2.0)                        | -3.4 (-6.8, 0)                                                | -1 (-4.3, 2.4)                                                                 | 12 (2.9)         |
| Back Pain <sup>†</sup>            | 1 (1.0)                   | 3 (1.5)              | 3 (3.0)                        | -0.5 (-3, 2.1)                                                | -2 (-5.8, 1.9)                                                                 | 7 (1.7)          |
| Nasopharyngitis <sup>†</sup>      | 1 (1.0)                   | 3 (1.5)              | 5 (5.0)                        | -0.5 (-3, 2.1)                                                | -4 (-8.6, 0.7)                                                                 | 9 (2.2)          |

Source: MAED analysis using JMP clinical and grouped terms derived from FMQ analysis, clinical reviewer generated report

\* 95% confidence interval excludes zero

<sup>†</sup> These preferred terms represent preferred terms that were combined FMQs or GQs. Grouping of several related terms in FMQs/GQs rendered incidence that is different from the Applicant's analysis. Refer to [Table 40](#) in Section [13.4.3](#) for a listing of the individual PTs included in the most commonly reported combined FMQs and GQs.

The most commonly reported TEAE by FMQ analysis in the group that transition from treatment with EU-Prolia to SB16 was vitamin D deficiency (7%).

The TEAEs reported by  $\geq 3\%$  of any treatment group that were reported in a significantly higher proportion (risk difference  $\geq 1\%$ ) of subjects in subjects who transitioned from EU-Prolia to SB16 compared to either of the other two treatment arms are briefly discussed below. In all TEAEs discussed below, the differences between incidences of the TEAEs among the three groups was small and likely due to chance, rather than due to meaningful differences between the products, the majority of cases in

subjects treated with EU-Prolia+SB16 were not serious or severe, or required changes to SB16 dosing or other significant intervention.

- **Vitamin D deficiency:**  
Subjects who transitioned from EU-Prolia to SB16 reported a higher incidence of FMQs related to vitamin D deficiency (7%) versus subjects treated only with SB16 (2.9%) or EU-Prolia (2%). Subjects in the transition group reported a total of 7 cases of vitamin D deficiency, none of these cases were SAEs, all were of mild (57.4%) or moderate (42.9%) severity and were reported with an onset of just before (day 361) to just after (day 366) transition. All cases were reported as recovering or resolving without action taken with study drug and all cases received calcium and/or vitamin D. No case resulted in hospitalization.
- **Hemorrhage:**  
TEAEs related to the FMQ related to hemorrhage were reported by 3% of subjects in the transition group, compared to none in the other 2 groups. These TEAEs related to 2 (66.7%) cases of contusion, both of which were mild and 1 (33.3%) case of hematuria which was of moderate severity. Additionally, the two cases of contusion both occurred in subjects who were 71 years old, and contusion is common in the elderly. No cases were SAEs and onset was reported between 452 and 547 days of enrollment in the trial, or about 87 to 182 days after transition. Only the case of hematuria was listed as not resolved, the others were resolved/resolving. "Resting" was listed as action taken with 1 case of contusion, no case required hospitalization or alteration in study drug therapy.
- **Headache:**  
Subjects who transitioned from EU-Prolia to SB16 reported a higher incidence of FMQs related to headache (3%) versus subjects treated with only SB16 (2.4%) or EU-Prolia (2%). Subjects in the transition group reported 3 cases of headache, all of which were mild and non-serious. Onset of headache in the transition group ranged from 479 to 500 days after enrollment (about 114 to 135 days after transition), 2 (66.7%) cases were reported as recovered, while the outcome of the third case is unknown. Dosing of study drug was not changed or discontinued in any case of headache and no subjects required hospitalization.

In conclusion, a greater incidence of vitamin D deficiency, hemorrhage, and headache following transition from US-Prolia to SB16 neither represents a clinically meaningful safety difference between the two products nor is an unacceptable risk of transition.

### **6.3.3. Dropouts and/or Discontinuations due to Adverse Events**

#### **Study SB16-3001**

##### **Main Period:**

A slightly higher proportion of subjects in the EU-Prolia arm (9/231 [3.9%]) discontinued therapy early due to a TEAE compared to the SB16 (4/225 [1.8%]). These subjects

either discontinued treatment during the Main Period or completed the Main Period but did not continue into the Transition Period due to TEAEs.

One of the subjects (ID (b) (6)), not listed by the Applicant as discontinuing due to a TEAE, but rather due to “other” likely discontinued treatment with EU-Prolia due to a TEAE and this subject is thus included in the 9 subjects listed above. This subject reported mild, non-serious erythema, rash, and eyelid swelling on Day 4 after the first administration of study drug, all of which resolved by Day 11. She remained on study for 179 days, then it was reported she was “not willing to take the second dose of IP due to fear of appearing AEs which occurred after the first dose”. Thus, this subject likely had a hypersensitivity-like reaction (anti-drug antibodies were negative) to study drug which led to her discontinuing continued therapy.

See [Table 26](#) for all TEAEs leading to treatment discontinuation in the Main Period of Study SB16-3001.

**Table 26: Treatment emergent adverse events leading to treatment discontinuation, Study SB16-3001, Main Period**

| Preferred Term                    | SB16<br>(N=225) | Prolia<br>(N=231) | Total<br>(N=456) |
|-----------------------------------|-----------------|-------------------|------------------|
| <b>Any AE (%)</b>                 | 4 (1.8)         | 9 (3.9)           | 13 (2.9)         |
| Alopecia                          | 1 (0.4)         | 1 (0.4)           | 2 (0.4)          |
| Acute phase reaction              | 1 (0.4)         | 0                 | 1 (0.2)          |
| Arachnoid cyst                    | 1 (0.4)         | 0                 | 1 (0.2)          |
| Breast cancer                     | 0               | 1 (0.4)           | 1 (0.2)          |
| COVID-19                          | 0               | 1 (0.4)           | 1 (0.2)          |
| Dental caries                     | 0               | 1 (0.4)           | 1 (0.2)          |
| Diverticulitis                    | 0               | 1 (0.4)           | 1 (0.2)          |
| Erythema                          | 0               | 1 (0.4)           | 1 (0.2)          |
| Hemorrhoids                       | 0               | 1 (0.4)           | 1 (0.2)          |
| Headache                          | 1 (0.4)         | 0                 | 1 (0.2)          |
| Lung adenocarcinoma               | 0               | 1 (0.4)           | 1 (0.2)          |
| Noninfective gingivitis           | 0               | 1 (0.4)           | 1 (0.2)          |
| Presyncope                        | 0               | 1 (0.4)           | 1 (0.2)          |
| Rash                              | 0               | 1 (0.4)           | 1 (0.2)          |
| Swelling of the eyelid            | 0               | 1 (0.4)           | 1 (0.2)          |
| Tooth fracture                    | 1 (0.4)         | 0                 | 1 (0.2)          |
| Upper respiratory tract infection | 0               | 1 (0.4)           | 1 (0.2)          |

Source: clinical reviewer generated report

#### **Transition Period:**

No TEAEs leading to discontinuation of study drug were reported during this period.

### 6.3.4. Additional Safety Evaluations

The Applicant included TEAEs of hypocalcemia, hypersensitivity, osteonecrosis of the jaw, atypical femoral fractures, and skin infections as adverse events of special interest (AESI), all of which are included as labeled warnings on the US-Prolia prescribing information. Each of these AESIs will be discussed in detail below, in addition to discussion of injection site reactions, fractures (which includes the discussion on atypical femoral fractures), and laboratory findings (which includes the discussion of hypocalcemia).

#### 6.3.4.1. Laboratory Findings

##### Study SB16-1001

Safety laboratory testing occurred at screening and post-injection days 2, 3, 7, 15, 29, 43, 57, 85, 141, and 197 and consisted of hematology, chemistry (including calcium), and urinalysis. There were no meaningful differences in treatment groups in median change in chemistry, hematology, or urinalysis parameters over time, and shift analysis revealed no concerns or notable differences among the three treatment groups.

All subjects were required to take supplemental calcium and vitamin D beginning at screening and lasting throughout the duration of the trial. The incidence of hypocalcemia within two weeks after study drug injection, which coincides with the anticipated calcium nadir following denosumab injection, was comparable across the three treatment groups (see [Table 27](#)).

No subjects reported TEAEs related to hypocalcemia.

**Table 27: Number (%) of subjects experiencing shift in serum calcium from normal at baseline to less than the lower limit of normal (< LLN) during the 14-day period after study drug injection, Study SB16-1001**

| Parameter                                                              | SB16<br>(N = 56) | EU-Prolia<br>(N = 56) | US-Prolia<br>(N = 56) |
|------------------------------------------------------------------------|------------------|-----------------------|-----------------------|
| Serum calcium transition from normal at baseline to < LLN during study | 15 (27%)         | 16 (29%)              | 14 (25%)              |

Source: clinical reviewer analysis

##### Study SB16-3001

##### Main Period

During the Main Period, safety laboratory testing (including hematology, serum chemistry, 25-hydroxy (OH) vitamin D, and urinalysis) was performed at baseline, and at 0.5, 1, 6, 9, and 12 months after treatment initiation. There were no clinically meaningful differences between treatment groups in median change in chemistry, hematology, vitamin D, or urinalysis parameters over time during the Main Period.

During the 12-month duration of the Main Period, subjects received study drug (i.e., either SB16 or EU-Prolia) injection at study day 0 and study day 182 (month 6). Denosumab can cause hypocalcemia and disturbances in bone-related mineral levels (i.e., reduced phosphorus and magnesium) and was associated with a higher incidence of anemia in the US-Prolia post-menopausal osteoporosis indication registration trial. The US-Prolia package insert advises that calcium, phosphorus, and magnesium be monitored within 14 days of injection. However, in Study SB16-3001, the Applicant did not assess magnesium levels. Therefore, this review includes a shift analysis of calcium, phosphorus, and hemoglobin laboratory parameters.

### *Hypocalcemia*

Relative to the period of interest, (i.e., 14 days after injection, as the nadir for serum calcium occurs within the first 2 weeks following study drug injection), serum calcium was measured at baseline and 2 weeks after the first injection. The first serum calcium measured after the second injection was at month 9 of the trial (3 months after the second injection and thus unlikely to capture the period of calcium nadir after the second injection). The risk of hypocalcemia is greater in patients with severe renal impairment (i.e., glomerular filtration rate < 30 mL/min), and this study excluded patients with an estimated glomerular filtration rate (eGFR) < 45 mL/min.

The Applicant provided results for both serum and albumin-corrected serum calcium. Since approximately 40% of total body calcium is protein bound, serum calcium may be artificially low in the setting of hypoalbuminemia. In those situations, a correction formula to account for the low albumin is used to estimate actual serum calcium levels. Ionized calcium is the preferred measurement but is not readily available in all laboratories.<sup>3</sup>

Only 1 subject (ID (b) (6)) developed hypoalbuminemia during the trial (value at month 6 was 31 g/L [normal range 32 to 55 g/L], all previous albumin levels were normal, and the subject withdrew consent after month 6, prior to further levels of albumin being drawn) and had normal serum calcium and albumin-corrected serum calcium at all visits. Since there are reported inaccuracies with various correction formulas and the role for such formulas when albumin levels are normal is unclear, this review examines only serum calcium measurements, not the corrected calcium values.

The median change from baseline in serum calcium was comparable in both treatment groups at all measurements following the initial and the second study drug administration (see [Table 28](#)).

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<sup>3</sup> Lian IA, Åsberg A. Should total calcium be adjusted for albumin? A retrospective observational study of laboratory data from central Norway. *BMJ Open*. 2018 Apr 7;8(4):e017703

**Table 28: Median (min, max) change from baseline in serum calcium (mmol/L) following first study drug administration, Study SB16-3001, Main Period**

| Parameter                                | SB16                         | EU-Prolia                    |
|------------------------------------------|------------------------------|------------------------------|
| <b>Change from baseline at month 0.5</b> |                              |                              |
| Median (min, max)                        | -0.08 (-0.56, 0.25)<br>N=220 | -0.07 (-0.36, 0.22)<br>N=219 |
| <b>Change from baseline at month 1</b>   |                              |                              |
| Median (min, max)                        | -0.08 (-0.42, 0.16)<br>N=221 | -0.06 (-0.39, 0.36)<br>N=222 |
| <b>Change from baseline at month 3</b>   |                              |                              |
| Median (min, max)                        | -0.04 (-0.24, 0.65)<br>N=220 | -0.04 (-0.22, 0.26)<br>N=220 |
| <b>Change from baseline at month 6</b>   |                              |                              |
| Median (min, max)                        | -0.01 (-0.2, 0.39)<br>N=220  | -0.01 (-0.23, 0.35)<br>N=216 |
| <b>Change from baseline at month 9</b>   |                              |                              |
| Median (min, max)                        | -0.05 (-0.35, 0.41)<br>N=214 | -0.03 (-0.27, 0.23)<br>N=208 |
| <b>Change from baseline at month 12</b>  |                              |                              |
| Median (min, max)                        | -0.02 (-0.23, 0.35)<br>N=212 | -0.01 (-0.24, 0.37)<br>N=205 |

Source: clinical reviewer analysis

The incidence of serum calcium below the lower limit of normal (8.58 mg/dL) during treatment was similar between the two treatment groups. Most of the shifts occurred following the first dose of study drug. After the second dose of study drug at month 6, the incidence of hypocalcemia was rare.

**Table 29: N (%) of subjects with a shift in serum calcium to below the lower limit of normal (< LLN) after the first and second study drug administration during Study SB16-3001, Main Period**

| Parameter                                                          | SB16      | EU-Prolia |
|--------------------------------------------------------------------|-----------|-----------|
| <b>Number of subjects with normal or elevated baseline calcium</b> | 224       | 230       |
| <b>Hypocalcemia at any time during Main Period</b>                 | 19 (8.5%) | 21 (9.1%) |
| <b>Following first study drug injection</b>                        |           |           |
| First 2-week period post-injection                                 | 9 (4%)    | 11 (4.8%) |
| Month 1, 3, or 6 post-injection                                    | 9 (4%)    | 10 (4.3%) |

| Following second study drug administration              |          |          |
|---------------------------------------------------------|----------|----------|
| Month 3 or 6 post-injection<br>(Month 9 or 12 of study) | 2 (0.9%) | 4 (1.7%) |

Source: clinical reviewer analysis

Among the patients with laboratory evidence of serum hypocalcemia, the degree of hypocalcemia was mild in all cases, with no subject in either group reporting a calcium value < 2 mmol/L (8 mg/dL) during the Main Period, and most were asymptomatic (one subject [ID (b) (6)] in the SB16 group reported a TEAE of paresthesia about 10 days after onset of hypocalcemia, and calcium/vitamin D supplementation was listed as the action taken for both).

Hypocalcemia was also considered an AESI. As shown in [Table 24](#), while hypocalcemia was the most frequently reported TEAE during the Main Period, the proportion of subjects reporting TEAEs of hypocalcemia was slightly lower in the SB16 group (9.8%) compared to the US-Prolia group (12.1%). In both groups, the TEAEs of hypocalcemia were all non-serious and all were of mild or moderate severity. In subjects randomized to SB16, the majority (22/24; 91.7%) of reported hypocalcemia TEAEs in this period occurred after the first dose of SB16 (range of 1 to 86 days after the first dose), while in the remaining 2 subjects the TEAE of hypocalcemia occurred on study Day 274, approximately 90 days after the second dose of SB16. A similar finding was noted in subjects randomized to EU-Prolia (27/30 [90%] TEAEs of hypocalcemia were reported 1 to 92 days after the first dose of study drug, while the remaining 3 subjects the TEAE of hypocalcemia occurred on study Days 267 to 273, or approximately 83 to 89 days after the second dose of study drug).

#### *Hypophosphatemia and anemia*

The incidence of transitions from normal or high at baseline to below the normal range for serum hemoglobin and phosphorus were similar between treatment groups (see [Table 30](#)).

**Table 30: N (%) of subjects with a shift in hemoglobin or phosphorus to below the lower limit of normal (< LLN) during Study SB16-3001, Main Period**

| Parameter                                                    | SB16               | EU-Prolia          |
|--------------------------------------------------------------|--------------------|--------------------|
| Hemoglobin<br>(N with normal or elevated values at baseline) | 19 (8.7%)<br>N=218 | 20 (9%)<br>N=222   |
| Phosphorus<br>(N with normal or elevated values at baseline) | 12 (5.4%)<br>N=223 | 10 (4.4%)<br>N=229 |

Source: clinical reviewer analysis

#### Transition Period

The Transition Period commenced at the Month 12 visit when subjects received the third and final dose of study drug. Subjects who received EU-Prolia during the Main Period were re-randomized 1:1 to receive either EU-Prolia or SB16 for their final dose.

Laboratory evaluation of hematology, serum chemistry, 25-hydroxy (OH) vitamin D, and urinalysis occurred prior to administration of denosumab at the Month 12 visit and at the end of study visit (Month 18, or early termination). There were no meaningful differences between treatment groups in median change in chemistry, hematology, vitamin D, or urinalysis parameters over time during the Transition Period.

#### *Hypocalcemia*

There was no meaningful difference in median change from the Transition Period baseline (Month 12) in serum calcium to the End of Study visit (Month 78) between the three groups (see [Table 31](#)).

**Table 31: Median (min, max) change in calcium (mmol/L) from Transition Period baseline (Month 12) to End of Study (Month 78), Study SB16-3001**

| Parameter                                          | EU-Prolia+SB16            | SB16+SB16                   | EU-Prolia+EU-Prolia         |
|----------------------------------------------------|---------------------------|-----------------------------|-----------------------------|
| Median (min, max) change from Month 12 to Month 78 | 0.03 (-0.23, 0.3)<br>N=98 | 0.04 (-0.21, 0.39)<br>N=206 | 0.01 (-0.42, 0.43)<br>N=100 |

Source: clinical reviewer analysis

The incidence of serum calcium below the lower limit of normal during the Transition Period was low: only 1 (0.5%) subject in the SB16+SB16 group, and no subjects in the EU-Prolia+SB16 or EU-Prolia+EU-Prolia groups had hypocalcemia during the transition period (see [Table 32](#)). No subject had serum calcium < 2 mmol/L (8 mg/dL).

**Table 32: N (%) of subjects with a shift in serum calcium from normal or elevated at Transition Period baseline (i.e., Month 12) to below the lower limit of normal (< LLN) during Study SB16-3001, Transition Period**

| Parameter                                                            | EU-Prolia+SB16 | SB16+SB16 | EU-Prolia+EU-Prolia |
|----------------------------------------------------------------------|----------------|-----------|---------------------|
| Number of subjects with normal or elevated serum calcium at Month 12 | 100            | 205       | 101                 |
| Calcium < LLN                                                        | 0              | 1 (0.5%)  | 0                   |
| Calcium < 2 mmol/L                                                   | 0              | 0         | 0                   |

Source: clinical reviewer analysis

Hypocalcemia was also considered an AESI. Hypocalcemia was not a frequently reported TEAE during the Transition Period. During this period, 0, 3 (1.5%), and 1 (1%) subject reported a TEAE of hypocalcemia in the EU-Prolia+SB16, SB16+SB16 (the TEAEs were reported approximately 0 to 180 days after the dose of study drug), and EU-Prolia+EU-Prolia groups (the TEAE was reported on the day of dosing), respectively. In all cases, the TEAEs of hypocalcemia were non-serious and of mild severity.

*Hypophosphatemia and anemia*

There was no notable difference in the incidence of anemia or hypophosphatemia among the three treatment groups (see [Table 33](#)).

**Table 33: N (%) subjects with hemoglobin or phosphorus below the lower limit of normal (< LLN) during Study SB16-3001, Transition Period**

| Parameter                             | EU-Prolia+SB16<br>N=100 | SB16+SB16<br>N=206 | EU-Prolia+EU-Prolia<br>N=101 |
|---------------------------------------|-------------------------|--------------------|------------------------------|
| <b>Hemoglobin</b>                     |                         |                    |                              |
| Start of Transition Period (Month 12) | 7 (7%)                  | 14 (6.8%)          | 6 (5.9%)                     |
| End-of-Study (Month 18)               | 5 (5%)                  | 15 (7.3%)          | 6 (5.9%)                     |
| <b>Phosphorus</b>                     |                         |                    |                              |
| Start of Transition Period (Month 12) | 1 (1%)                  | 3 (1.5%)           | 0                            |
| End-of-Study (Month 18)               | 1 (1%)                  | 1 (0.5%)           | 0                            |

Source: clinical reviewer analysis

### 6.3.4.2. Injection Site Reactions (ISRs)

#### Study SB16-1001

Local tolerance at the injection site was evaluated by the Investigator or designee at the time of injection, and 12 hours, and 1, 2, 4, 6, and 8 days after injection. In particular, local reactions were evaluated in terms of redness, bruising, swelling, itching, and pain, with subjects asked to report sensations at the injection site to evaluate itching and pain. The severity of these parameters was evaluated using the following severity scale: None = 0; Mild = 1; Moderate = 2; Severe = 3 (as per [Figure 9](#) Figure 9 in Section [13.4.4](#)).

The score was the sum of these points and any injection site reaction (ISR) with a score  $\geq 2$  was documented as a TEAE. Once an ISR is documented as a TEAE, the severity of the TEAE was assessed as mild (defined as usually transient events that do not interfere with the subject's daily activities), moderate (defined as events with a low level of inconvenience or concern to the subject that may interfere with daily activities), or severe (defined as events that interrupt the subject's usual daily activities).

In Study SB16-1001, median ISR scores at every timepoint was zero in all treatment groups (see Table 34). The only treatment group with any subjects receiving a score of 2 was the SB16 group (a total of 3 [5.4%] subjects). At all time points, in all subjects with a total ISR score of 2, bruising (score 2) was the only parameter with a score above 0. No subjects in any group reported an ISR with a score of  $\geq 3$ .

**Table 34: Injection site reaction total score, Study SB16-1001**

| Parameter               | SB16<br>N=56         |                                                              | EU-Prolia<br>N=56    |                                                              | US-Prolia<br>N=56    |                                                              |
|-------------------------|----------------------|--------------------------------------------------------------|----------------------|--------------------------------------------------------------|----------------------|--------------------------------------------------------------|
|                         | Median<br>(min, max) | Number<br>(%) of<br>subjects<br>with total<br>score $\geq 2$ | Median<br>(min, max) | Number<br>(%) of<br>subjects<br>with total<br>score $\geq 2$ | Median<br>(min, max) | Number<br>(%) of<br>subjects<br>with total<br>score $\geq 2$ |
| Baseline                | 0 (0, 1)             | 0                                                            | 0 (0, 1)             | 0                                                            | 0 (0, 1)             | 0                                                            |
| 12 hours post-injection | 0 (0, 1)             | 0                                                            | 0 (0, 0)             | 0                                                            | 0 (0, 1)             | 0                                                            |
| 1 day post-injection    | 0 (0, 1)             | 0                                                            | 0 (0, 0)             | 0                                                            | 0 (0, 1)             | 0                                                            |
| 2 days post-injection   | 0 (0, 2)             | 1 (1.8%)                                                     | 0 (0, 0)             | 0                                                            | 0 (0, 1)             | 0                                                            |
| 4 days post-injection   | 0 (0, 2)             | 2 (3.6%)                                                     | 0 (0, 0)             | 0                                                            | 0 (0, 1)             | 0                                                            |
| 6 days post-injection   | 0 (0, 2)             | 3 (5.4%)                                                     | 0 (0, 0)             | 0                                                            | 0 (0, 0)             | 0                                                            |
| 8 days post-injection   | 0 (0, 2)             | 1 (1.8%)                                                     | 0 (0, 0)             | 0                                                            | 0 (0, 0)             | 0                                                            |

Source: clinical reviewer analysis

In the US-Prolia group, 1/56 (1.8%) subject also reported a TEAE related to ISRs (PT of injection site pruritis) at 1 day post-injection, though the subject only had an ISR score of 1 related to itching at the time.

Thus, injection site reactions were reported as TEAEs in a total of 3 (5.4%) subjects in the SB16 group (PTs: injection site hematoma, injection site reaction, and injection site hemorrhage) and 1 (1.8%) subject in the US-Prolia group (PT: injection site pruritis). In all cases, the TEAE was of mild severity, was non-serious, and did not lead to discontinuation from the study.

In conclusion, there were no meaningful differences in ISRs among the three groups.

### **Study SB16-3001**

The Investigator assessed for TEAEs related to ISRs on the day of each study drug administration: Months 0 and 6 (Main Period) and Month 12 (Transition Period).

#### Main Period:

The proportion of subjects reporting an ISR TEAE was similar between the two treatment groups: 3/225 (1.3%) vs. 1/231 (0.4%) subjects in the SB16 and EU-Prolia groups, respectively. Individual PTs related to ISRs in the SB16 group were injection site erythema, injection site swelling, and injection site pain, while the single TEAE related to ISRs in the EU-Prolia group had a PT of injection site erythema. In all cases,

the TEAE was mild, non-serious, and did not lead to study or study drug discontinuation.

Transition Period:

No TEAEs related to ISRs were reported in any group during the Transition Period.

### 6.3.4.3. Hypersensitivity Reactions

Overall, there were no meaningful differences in hypersensitivity reactions between the treatment arms in either study. No subjects reporting a TEAE related to hypersensitivity in either trial were noted to be positive for anti-drug antibodies. These findings support the conclusion that SB16 has no clinically meaningful differences from US-Prolia and US-Xgeva.

#### Study SB16-1001

The clinical reviewer searched the safety dataset for AEs related to anaphylaxis and hypersensitivity. There were no events of anaphylaxis in any treatment group. Events related to hypersensitivity were only reported in the EU-Prolia group: 2/56 (3.6%) subjects in this group reported TEAEs related to hypersensitivity, with PTs of erythema (moderate) and rash (mild) (n=1, each). Neither event was serious or severe.

#### Study SB16-3001

Main Period

The clinical reviewer searched the safety dataset for AEs related to anaphylaxis and hypersensitivity. SB16 was not associated with a greater risk of hypersensitivity reactions compared to EU Prolia (see [Table 35](#)).

**Table 35: Number (%) of subjects with TEAEs of hypersensitivity, Study SB16-3001, Main Period**

| Preferred Term               | SB16 (N=225) | EU-Prolia (N=231) |
|------------------------------|--------------|-------------------|
| Any TEAE of hypersensitivity | 6 (2.7)      | 12 (5.2)          |
| Dermatitis allergic          | 1 (0.4)      | 3 (1.3)           |
| Erythema                     | 0            | 2 (0.9)           |
| Acute phase reaction         | 1 (0.4)      | 1 (0.4)           |
| Pruritus                     | 1 (0.4)      | 1 (0.4)           |
| Rash                         | 0            | 2 (0.9)           |
| Angioedema                   | 0            | 1 (0.4)           |
| Asthma                       | 1 (0.4)      | 0                 |
| Dermatitis atopic            | 0            | 1 (0.4)           |
| Eosinophil count increased   | 1 (0.4)      | 0                 |
| Exfoliative rash             | 0            | 1 (0.4)           |
| Hand dermatitis              | 1 (0.4)      | 0                 |
| Swelling of eyelid           | 0            | 1 (0.4)           |

| Preferred Term    | SB16 (N=225) | EU-Prolia (N=231) |
|-------------------|--------------|-------------------|
| Urticaria chronic | 0            | 1 (0.4)           |

Source: clinical reviewer analysis

All TEAEs related to hypersensitivity were non-serious, and of mild or moderate severity. As discussed in Section [6.3.3](#), above, 1/231 (0.4%) subject in the EU-Prolia group likely discontinued treatment due to hypersensitivity-like TEAEs, (mild, non-serious erythema, rash, and eyelid swelling on Day 4 after the first administration of study drug).

Similarly, 1/225 (0.4%) subject in the SB16 group, discontinued the trial on Day 1 due to TEAEs of acute phase reaction and headache after receiving study drug. The acute phase reaction was described as “an innate defense mechanism evoked in response to inflammation-related to study drug”, that the investigator did not think would classify as an AESI of hypersensitivity. The TEAEs of acute phase reaction and headache were of moderate and mild severity, respectively, neither were serious, and both recovered without further actions. Given the description noted for the TEAE of acute phase reaction, this subject likely did discontinue treatment due to a hypersensitivity-like TEAE.

#### Transition Period:

Few TEAEs related to hypersensitivity were reported during the Transition Period and were only in the SB16+SB16 group: 2/206 (1%) subjects reported PTs of erythema nodosum (mild) and asthma (moderate) (n=1, each). Neither TEAE was serious or severe, and the dose of SB16 was not changed or discontinued.

### **6.3.4.4. Fractures**

#### **Study SB16-3001**

Lateral thoraco-lumbar spine x-rays were only performed at screening, in order to determine any potential exclusions due to vertebral fractures, according to Genant classification and determined by central imaging center. Potential subjects were excluded if they were found at screening to have one severe or more than two moderate vertebral fractures on spinal X-ray.

#### Main Period:

During the Main Period, a higher proportion of subjects reported non-vertebral fractures in the SB16 group (8/225 [3.6%] subjects) compared to the EU-Prolia group (1/231 [0.4%] subjects) (see [Table 36](#)). Of these, 2 events were serious (ankle fracture and forearm fracture), both in the SB16 group (see Section [6.3.2.3](#) for narratives). With the exception of the SAE of ankle fracture, which was severe, all other TEAEs of non-vertebral fractures were of mild or moderate severity.

**Table 36: Number (%) of subjects experiencing TEAEs of non-vertebral fracture, Study SB16-3001, Main Period**

| Non-vertebral fracture        | SB16 (N=225) | EU-Prolia (N=231) |
|-------------------------------|--------------|-------------------|
| Any                           | 8 (3.6)      | 1 (0.4)           |
| Ankle fracture <sup>a</sup>   | 2 (0.9)      | 0                 |
| Radius fracture               | 1 (0.4)      | 1 (0.4)           |
| Rib fracture                  | 2 (0.9)      | 0                 |
| Foot fracture                 | 1 (0.4)      | 0                 |
| Forearm fracture <sup>a</sup> | 1 (0.4)      | 0                 |
| Patella fracture              | 1 (0.4)      | 0                 |

Source: clinical reviewer analysis

<sup>a</sup> one event of ankle fracture and the event of forearm fracture were serious adverse events.

Vertebral fractures were present in 104/225 (46.2%) and 116/231 (50.2%) subjects at baseline in the SB16 and EU-Prolia groups, respectively. No subjects were noted to have TEAEs related to vertebral fractures during the Main Period of the study.

Atypical femoral fractures were included as an AESI. There were no femur fractures noted in either group during the Main Period of the trial.

As discussed in Section [6.3.2.3](#), the SAE of forearm fracture was a result of a fall from a stool and it is notable that while this subject completed the Main Period, the subject discontinued from the study prior to initiation of study drug administration in the Transition Period due to “lack of efficacy or disease progression”. This raises a concern that, despite treatment with SB16, the treatment was ineffective, and a fragility fracture still occurred in a subject with post-menopausal osteoporosis. The other SAE of fracture (left ankle fracture) occurred in a subject whose hip and femoral neck BMD were decreasing despite treatment, which may also raise a concern that SB16 treatment was ineffective. Though, as noted in the narrative described in Section [6.3.2.3](#), the fracture also occurred as the result of a high energy break following a fall from the stairs, confounding assessment of causality related to lack of efficacy. However, while limited information is available regarding the other non-vertebral fracture TEAEs, the proportion of subjects reporting a fracture that may be consistent with a fragility fracture (i.e., a fracture from low energy trauma, most often occurring at the hip, vertebra, or distal forearm) was comparable between the two groups: 2 (0.9%) subjects in SB16 (PTs of radius fracture and forearm fracture) vs. 1 (0.4%) subject in EU-Prolia (PT of radius fracture).

Additionally, while a narrative is not provided for the second subject reporting a TEAE of ankle fracture (non-serious) in the SB16 group, the reported term for this TEAE notes that it occurred as a result of being hit by a car. As such, while there was limited information provided relating to the cause of fractures experienced by the other subjects in the SB16 group, for this subject reporting ankle fracture, based on the information provided, it was likely secondary to significant trauma. Finally, all other subjects in both treatment groups with non-vertebral fractures completed both the Main and Treatment Periods.

While in the Main Period there was overall a higher proportion of subjects reported with non-vertebral fractures in the SB16 group (3.6%) compared to the EU-Prolia group (0.4%), it is unlikely there are meaningful differences between the products leading to a higher risk of fractures in the SB16 group compared to the EU-Prolia group. As discussed above, available information indicates that for one case of fracture reported in the SB16 group, the fracture may be due to a lack of efficacy, while in another case in the SB16 group, the description of the fracture as a high energy break confounds assessment of whether the fracture may be due to a lack of efficacy versus trauma. However, of the other cases of fractures reported, there is either not enough information to conclude a causal association between SB16 and fracture, or there are reports of significant trauma. Only a few cases consistent with the typical descriptions of fragility fractures may indicate a concern for a lack of efficacy, and the proportion of subjects reporting such fractures were comparable between the two groups.

#### Transition Period:

During the Transition Period, no subject in the EU-Prolia+SB16 group reported a non-vertebral fracture, while a comparable proportion of subjects in the SB16+SB16 and EU-Prolia+EU-Prolia group had TEAEs of non-vertebral fractures: 4/206 (1.9%) and 2/101 (2%) subjects, respectively (see [Table 37](#)). One subject in the SB16+SB16 reported two non-vertebral fractures (patella fracture and forearm fracture), all other subjects reported only 1 non-vertebral fracture each. The only serious non-vertebral fractures (forearm fracture and femoral neck fracture) were reported in the SB16+SB16 group (see Section [6.3.2.3](#) for narratives). With the exception of the serious TEAE of femoral neck fracture, which was severe, all other TEAEs of non-vertebral fractures were of mild or moderate severity.

**Table 37: Number (%) of subjects experiencing TEAEs of non-vertebral fracture, Study SB16-3001, Transition Period**

| Non-vertebral fracture       | EU-Prolia+SB16<br>(N=100) | SB16+SB16<br>(N=206) | EU-Prolia+EU-Prolia<br>(N=101) |
|------------------------------|---------------------------|----------------------|--------------------------------|
| Any                          | 0                         | 4 (1.9)              | 2 (2)                          |
| Patella fracture             | 0                         | 1 (0.5)              | 0                              |
| Forearm fracture             | 0                         | 1 (0.5)              | 0                              |
| Rib fracture                 | 0                         | 1 (0.5)              | 0                              |
| Skull fracture base          | 0                         | 1 (0.5)              | 0                              |
| Femoral neck fracture        | 0                         | 1 (0.5)              | 0                              |
| Ankle fracture               | 0                         | 0                    | 1 (1)                          |
| Traumatic fracture<br>(foot) | 0                         | 0                    | 1 (1)                          |

Source: clinical reviewer analysis

Of the subjects treated during the Transition period, 57/100 (57%) subjects in the EU-Prolia+SB16 group, 92/206 (44.7%) subjects in the SB16+SB16 group, and 49/101 (57.2%) subjects in the EU-Prolia+EU-Prolia group had vertebral fractures at study enrollment (prior to the Main Period).

During the Transition Period, only one subject, from the EU-Prolia+EU-Prolia group (1/101 [1%] subject), reported a TEAE of a vertebral fracture (PT spinal compression fracture). This TEAE was non-serious and of moderate severity. This subject did not have vertebral fracture on screening lateral thoraco-lumbar spine x-ray.

Atypical femoral fractures were included as an AESI. There was only 1 femur fracture noted in the Transition Period, in the SB16+SB16 group (0.5%). It is unclear that this femur fracture would be considered an atypical femoral fracture as it occurred because of a fall. Refer to Section [6.3.2.3](#) for a summary of the narrative.

#### **6.3.4.5. Skin Infections**

##### **Study SB16-3001**

Overall, there were no meaningful differences in TEAEs related to skin infections between the treatment arms. These findings support the conclusion that SB16 has no clinically meaningful differences from US-Prolia and US-Xgeva.

##### Main Period

During this period, 2 (0.9%) subjects in the SB16 arm reported TEAEs of skin infection (both with herpes zoster) while in the EU-Prolia group, 3 (1.3%) subjects reported TEAEs of skin infection (2 subjects reported herpes zoster and 1 subject reported

erysipelas). None of these events were serious and all events in the SB16 arm were of mild severity, while all those in the EU-Prolia arm were of moderate severity.

#### Transition Period

During this period, no subjects in the EU-Prolia+SB16 or SB16+SB16 arms reported relevant TEAEs. In the EU-Prolia+EU-Prolia arm, 1 (1%) subject reported a TEAE related to skin infection: a moderate, non-serious TEAE of herpes zoster.

#### **6.3.4.6. Osteonecrosis of the jaw**

No subjects in any arm or any period of Study SB16-3001 had a TEAE of osteonecrosis of the jaw.

### **6.4. Clinical Conclusions on Immunogenicity**

The assessment of immunogenicity occurred in Studies SB16-1001 and SB16-3001. There was no meaningful difference between the treatment arms in either trial with respect to development of anti-drug antibodies (ADA) or neutralizing antibodies (NABs). Further, the presence of ADAs or NABs had no impact on the safety in either trial or on the clinical outcome of Study SB16-3001. Refer to Section [5.4](#) for complete details and conclusions from the clinical pharmacology review team.

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### **6.5. Risk in Terms of Safety or Diminished Efficacy of Switching Between Products and the Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)**

The Applicant's development program established that SB16, US-Prolia, and US-Xgeva share identical primary structures and comparable secondary and tertiary structures. Functional assays showed similarity among SB16, US-Prolia, and US-Xgeva with respect to pharmacologic activity. There were no meaningful differences in pharmacokinetics between SB16 and US-Prolia, between SB16 and EU-Prolia, and between US-Prolia and EU-Prolia in the PK similarity study.

The comparative clinical study showed no meaningful difference in PK, efficacy, safety, or immunogenicity between SB16 and EU-Prolia in the treatment of post-menopausal women with osteoporosis. Presence of ADAs had no impact on PK, efficacy, or safety. Although some numerical differences were observed between SB16 and EU-Prolia in terms of incidences of certain adverse events, the absolute differences were not large and not considered clinically meaningful. Importantly, the adverse event profile of both products was comparable.

A transition from EU-Prolia to SB16 was well tolerated with no meaningful impact on PK, efficacy, or safety. At six months post-transition (i.e., Month 18), the LS mean percentage change from baseline in lumbar spine BMD was comparable in the two treatment groups. There was no meaningful increase in ADA titers or incidence of NAb after transitioning from EU-Prolia to SB16.

The Applicant provided sufficient justification that SB16 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient. The scientific justification considered the following issues that are described in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product.

#### Mechanism of Action

Across all approved indications for US-Prolia and US-Xgeva, the clinical efficacy is based on denosumab binding to RANKL and prohibiting its binding to the RANK receptor. Functional assays established that SB16 exhibits the same pharmacologic activity as US-Prolia and US-Xgeva and has identical primary structure to US-Prolia and US-Xgeva. Furthermore, there was no clinically meaningful difference in the effect of SB16 and US-Prolia on the bone turnover marker CTX and lumbar spine bone mineral density, which further supports a shared mechanism of action.

The Applicant provided adequate justification to support that SB16 has the same, known, and potential mechanisms of action, as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

#### Pharmacokinetics

The applicant provided adequate justification that SB16 is expected to have a similar PK profile as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

#### Immunogenicity

In the SB16 development program, immunogenicity was evaluated in populations considered sensitive for detecting clinically meaningful differences: female subjects with post-menopausal osteoporosis (PMO) and healthy subjects. Immunogenicity was found to be similar when comparing SB16 and US-Prolia in the PK Similarity Study, SB16-1001 in healthy subjects, and between SB16 and EU-Prolia in the comparative clinical study, Study SB16-3001. The Applicant provided adequate justification that SB16 is expected to have a similar immunogenicity as US-Prolia and US-Xgeva for each indication for which US-Prolia and US-Xgeva are licensed.

#### Toxicity

Comparative safety was assessed in the comparative clinical study SB16-3001, which was conducted in female subjects with PMO. Supportive safety information was also available from the PK similarity study, Study SB16-1001. The Applicant provided adequate justification that SB16 is expected to have a similar safety profile as US-Prolia and US-Xgeva for each indication being sought for licensure.

The Applicant also provided sufficient scientific justification that the risk in terms of safety or diminished efficacy of alternating or switching between use of SB16 and US-Prolia or US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alternation or switch. The Applicant referenced the comparative analytical data provided in their application that evaluated and compared critical quality attributes of SB16 and US-Prolia and US-Xgeva and the results from the comparative clinical study (SB16-3001) to support their justification. The Applicant also described that the results from the single transition included in Study SB16-3001 provided supportive evidence of a low immunogenic risk and no safety concerns with switching between SB16 and US-Prolia or US-Xgeva.

FDA considers the risk of a clinically impactful immunogenic response when alternating or switching between SB16 and US-Prolia or US-Xgeva to be low. Thus, a switching study that compares immunogenicity and PK and/or PD to assess whether there could be diminished efficacy or safety issues associated with alternating or switching between use of SB16 and US-Prolia or US-Xgeva was considered unnecessary to support a demonstration of interchangeability for SB16.

#### Conclusion

In summary, the data and information provided by the Applicant are sufficient to demonstrate that SB16 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient and that the risk, in terms of safety or diminished efficacy of alternating or switching between use of SB16 and US-Prolia, or SB16 and US-Xgeva, is not greater than the risk of using US-Prolia or US-Xgeva without alternation or switch.

#### Authors:

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Sabiha Khan, MD, Scientific Reviewer, OTBB  
Michelle Luo, MD, PhD, Scientific Reviewer, OTBB  
Christy Osgood, MD, Supervisory Associate Director, DO1

## 6.6. Extrapolation

### 6.6.1. Division of General Endocrinology and Office of Oncology Drugs

The Applicant submitted data and information in support of a demonstration that SB16 is highly similar to US-Prolia and US-Xgeva notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between SB16 and US-Prolia, or SB16 and US-Xgeva, in terms of safety, purity, and potency. In addition, the totality of evidence submitted in the application sufficiently demonstrates that SB16 can be expected to produce the same clinical result as US-Prolia and US-Xgeva in any given patient and that, the risk in terms of safety or diminished efficacy of alternating or switching between use of SB16 and US-Prolia or SB16 and US-Xgeva is not greater than the risk of using US-Prolia or US-Xgeva without such alteration or switch.

The Applicant is seeking licensure of SB16 for the following indication(s) for which US-Prolia and US-Xgeva have been previously licensed and for which SB16 has not been directly studied:

- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for prostate cancer
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer
- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of SB16 as an interchangeable biosimilar for each such indication for which licensure is sought and for which US-Prolia and US-Xgeva have been previously approved.

Therefore, the totality of the evidence provided by the Applicant supports licensure of SB16 as a biosimilar to and interchangeable with US-Prolia and US-Xgeva for each of the following indication(s) for which the Applicant is seeking licensure of SB16:

- Treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to

remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for prostate cancer.
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

## Conclusions

The Division of General Endocrinology and the Office of Oncology Drugs 1 conclude that the Applicant has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity and toxicity profile) for extrapolation of the data and information submitted in the application to support licensure of SB16 for all indications for which US-Prolia and US-Xgeva are licensed.

### Authors:

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Michelle Luo, MD, PhD, Scientific Review, OTBB

Christy Osgood, MD, Supervisory Associate Director, DO1

## 7. Labeling Recommendations

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### 7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, denosumab-**dssb**, was found to be conditionally accepted by the Agency.

#### Author:

Nicholas Heiniger, MD

Clinical Reviewer, DGE

### 7.2. Proprietary Name

The proposed proprietary names for SB16 are conditionally approved as "Ospomyv" (denosumab-dssb in a 60 mg/mL PFS) and "Xbryk" (denosumab-dssb in a 120 mg/1.7

mL vial). These names have been reviewed by DMEPA, who concluded the names were acceptable.

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### 7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

In the Applicant's original submission of the BLA on February 11, 2024, Section (b) (4) (Preparation and Administration) of the Applicant's proposed 60 mg/mL SB16 Prescribing information (PI) included instructions for healthcare professionals on preparation and administration of the prefilled syringe which were not consistent with the corresponding text in the in the Prolia PI section 2.4 (Preparation and Administration). On April 03, 2024, the Office of Surveillance and Epidemiology (OSE) sent an Information Request to the Applicant requesting that the Applicant update the Preparation and Administration section of the 60 mg/mL SB16 PI to be consistent with that of Prolia, except for information that is specific to their proposed product and necessary to inform safe and effective use. On April 05, 2024, the Applicant submitted an updated PI with the requested updates.

FDA requested a safety labeling change (SLC) on November 07, 2023, for the reference product Prolia (BLA 125320) following completion of a newly identified safety signal (NISS) assessment of the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD) treated with denosumab.<sup>4</sup> In the NISS assessment, FDA concluded that denosumab has been shown to substantially increase the risk of severe and potentially fatal hypocalcemia compared to oral bisphosphonates in dialysis dependent and advanced CKD patients, and that current labeling is insufficient to convey this risk. The SLC called for addition of a boxed warning, and several changes to Section 2, 5, and 8 of the Prolia label to address this risk. On January 19, 2024, the Prolia BLA 125320/S-216, which updated the Prolia PI to reflect these changes, was approved.

Therefore, on April 26, 2024, the Division sent a request to the Applicant to resubmit Prescribing Information for 60 mg/mL SB16 that is consistent with the current labeling for Prolia. On May 17, 2024, the Applicant provided an updated proposed PI for 60 mg/mL SB16 that included these changes.

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<sup>4</sup> NISS Integrated Safety Assessment ID 1004972 of BLA 125320 finalized in DARRTS on October 20, 2023.

Following DMEPA's conclusion that the proprietary names were conditionally acceptable, FDA sent a request to the Applicant to resubmit the PI for both 60 mg/mL and 120 mg/1.7 mL SB16 with these proprietary names (i.e., Ospomyv and Xbryk, rather than the placeholders SB16, SB16 60 mg/mL PFS, or SB16 120 mg/1.7 mL vial). Additionally, specifically for Xbryk, FDA requested the Applicant include standard language for parental products and to update Section 6.3 Immunogenicity to provide background and context to the information provided in this section. On November 13, 2024, the Applicant provided updated proposed PI for 60 mg/mL and 120 mg/1.7 mL SB16 that included these changes. This submission also included unbranded biological product labeling for both SB16 60 mg/mL PFS and SB16 120 mg/1.7 mL vial.

On February 5, 2025, FDA sent additional labeling comments to the applicant. One comment recommended the addition of "[Xbryk/Denosumab-dssb] should be administered by a healthcare provider" in Section 2.1 of the [Xbryk/Denosumab-dssb] Prescribing Information, to provide specific direction for the administration of this product (see 21 CFR 201.57(c)(3)(iv)).<sup>5</sup>

At the time of original BLA submission, the active ingredient statement in Section 5 of the PI for both the 60 mg/mL and 120 mg/1.7 mL branded products stated "(b) (4)

." With subsequent labeling edits, FDA requested that the Applicant amend these statements to state only, "Patients receiving [Ospomyv/Xbryk/Denosumab-dssb] should not receive other denosumab products concomitantly" for the branded and unbranded products and recommended that the Applicant change denosumab-xxxx to denosumab-dssb throughout all labels, following conditional approval of this non-proprietary name.

**Authors:**

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LaiMing Lee  
Associate Director for Labeling

Shivangi Vachhani, MD  
Cross Disciplinary Team Leader, DGE

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<sup>5</sup> Separately, a prior approval supplement request letter was sent to Amgen identifying that a statement should be added in Section 2.1 of the Xgeva (denosumab) Prescribing Information and carton and container labeling that the product should be administered by a healthcare provider. See DARRTS for BLA 125320.

## **8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure**

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The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section [13.1](#) and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

### **Authors:**

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Shivangi Vachhani, MD  
Clinical Team Leader

## **9. Advisory Committee Meeting and Other External Consultations**

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No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

### **Author:**

Nicholas Heiniger, MD  
Clinical Reviewer, DGE

## **10. Pediatrics**

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Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product

is not considered to have a “new active ingredient” for purposes of PREA.

At the time of this review, other denosumab products, Jubbonti and Wyost, have been approved as interchangeable biosimilars and have qualified for FIE. FDA has previously determined that FIE for the Jubbonti and Wyost products will expire on October 29, 2025. Therefore, because SB16 will be approved first as a biosimilar (and not as interchangeable), this biologic will be considered to have a new active ingredient for purpose of PREA.

At a meeting with the Pediatric Review Committee (PeRC) on April 18, 2023, the PeRC agreed to the Applicant’s plan to request a full waiver in all pediatric age groups because the Applicant proposes to extrapolate pediatric information available in the US-Prolia and US-Xgeva prescribing information to those proposed biosimilar, SB16.<sup>6</sup>

The general plan of the agreed initial Pediatric Study Plan (iPSP) is outlined below (initial agreement letter sent to the sponsor on April 21, 2023):

There is a lack of pediatric information for the following indications in the reference product labeling, and PREA requirements were waived for, or inapplicable to, US-Prolia and US-Xgeva:

- US-Prolia
  - Treatment of post-menopausal women with osteoporosis at high risk for fracture.
  - Treatment to increase bone mass in men with osteoporosis at high risk for fracture.
  - Treatment of glucocorticoid-induced osteoporosis in pediatric patients < 5 years of age at high risk for fracture
  - Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.
  - Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
- US-Xgeva:
  - Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.
  - Treatment of adults with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
  - Treatment of pediatric patients who are not skeletally mature (usually those < 12 years old) with giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity
  - Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

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<sup>6</sup> Refer to the meeting minutes of the April 18, 2023, PeRC meeting filed to IND 141802 on May 05, 2023.

Deferral of the following US-Prolia indication until pediatric data from the reference product (Amgen: Prolia) clinical trial become publicly available:

- Treatment of pediatric patients aged 5 to 17 years with glucocorticoid induced osteoporosis at high risk for fracture.

Extrapolation based on establishment of biosimilarity for the following US-Xgeva indication:

- Treatment of skeletally mature adolescents (aged 12 to 16 years) with giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity.

In this BLA, the Applicant submitted a pediatric assessment for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where resection is likely to result in severe morbidity. Refer to section 6.6 for review of the assessment.

US-Prolia has a post-market requirement (PMR) to conduct a study to evaluate the safety and efficacy of denosumab in pediatric patients aged 5-17 years old with glucocorticoid-induced osteoporosis (final report submission date: May 2024). Because SB16 is approved as biosimilar, a PREA PMR is required for the assessment of SB16 for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age and can be deferred until the pediatric data from US-Prolia becomes available. PeRC discussed this application on February 11, 2025, and concurred with the Division's recommendations.

**Authors:**

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Shivangi Vachhani, MD  
Clinical Team Leader

## **11. REMS and Postmarketing Requirements and Commitments**

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### **11.1. Recommendations for Risk Evaluation and Mitigation Strategies**

Prolia was initially approved with a REMS consisting of a Medication Guide (MG), communication plan (CP), and timetable for submission of assessments. The Prolia REMS goal was to mitigate the risks of hypocalcemia, osteonecrosis of the jaw (ONJ), atypical femur fracture (AFF), serious infections, and adverse dermatological reactions by informing healthcare providers (HCPs) and patients on these risks and to inform HCPs that they should counsel patients on these risks. On November 7, 2023, a Safety Labeling Change (SLC) was issued to update Prolia's labeling regarding the risk of severe hypocalcemia in patients with advanced chronic kidney disease. Following the SLC, a modification to the Prolia REMS was approved on March 5, 2024, to align the risk messaging in the REMS with the updated prescribing information (PI). The Prolia REMS goal was updated to mitigate the risk of severe hypocalcemia in patients with

advanced chronic kidney disease (CKD), including dialysis-dependent patients. The REMS modification also removed the risks of ONJ, AFF, serious infections, and dermatologic reactions from the REMS and removed the MG as an element of the REMS.

On February 11, 2024, the Applicant submitted a BLA with a proposed REMS for Ospomyv that initially consisted of a MG, CP, and timetable for submission of assessments. The proposed REMS goal was to mitigate the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fracture, serious infections, and dermatologic reactions, similar to the US Prolia REMS at the time of the BLA submission.

Due to the REMS modifications approved for the Prolia REMS on March 5, 2024, the Agency informed the Applicant on March 14, 2024, to update their REMS proposal for Ospomyv to align with the approved changes to the Prolia REMS. The Applicant submitted REMS amendments on April 11, 2024, December 6, 2024, January 13, 2025, and January 23, 2025 in response to the Agency's comments.

The Division of Risk Management (DRM) reviewed the amended REMS and found the Ospomyv REMS, submitted on January 23, 2025, acceptable. The Ospomyv REMS is comparable to the Prolia REMS and is designed to communicate the same key risk messages and achieve the same level of patient safety. The requirements of the Ospomyv REMS will also apply to any unbranded denosumab-dssb distributed by the Applicant.

The Ospomyv REMS goal and objective are:

The goal of the Ospomyv REMS is to mitigate the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD), including dialysis-dependent patients, associated with Ospomyv. The following describes the objective associated with the REMS:

Objective 1: Inform healthcare providers on:

- Risk of severe hypocalcemia in patients with advanced chronic kidney disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m<sup>2</sup>)
- Need to assess for presence of chronic kidney disease-mineral bone disorder (CKD-MBD) before initiating Ospomyv in patients with advanced chronic kidney disease

The REMS elements consist of a Communication plan (CP) and timetable for submission of assessments.

The Communication Plan elements include:

- REMS Letter to Healthcare Providers

- REMS Letter to Professional Societies
- Patient Guide
- REMS website

Timetable for submission of assessments is at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS. The Ospomyv REMS assessment plan was reviewed by the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) and found to be acceptable.

## 11.2. Recommendations for Postmarket Requirements and Commitments

The following post-marketing requirement (PMR) will be requested:

PMR 4799-1: Provide an assessment of Ospomyv (denosumab-dssb) for the treatment of glucocorticoid-induced osteoporosis in pediatric patients 5 to 17 years of age.

Final report submission: June 2026

### Authors:

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Clinical Reviewer, DGE

Brian Caruth, Pharm.D.  
Risk Management Analyst, DRM

## 12. Division Director Comments

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### 12.1. Division Director (OND-Clinical) Comments

I concur with the review team's assessment of the data and information submitted in this BLA. The data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that SB16 is biosimilar to US-Prolia and US-Xgeva. I also concur with the team's recommendation to provisionally determine that SB16 meets the standards for interchangeability under section 351(k)(4) of the PHS Act. We have not identified any deficiencies that would justify a complete response action. Although we have provisionally determined that SB16 meets the requirements for licensure as interchangeable biosimilar product, pursuant to section 351(k)(6) of the Public Health Service Act, we are unable to make such a determination because of unexpired first interchangeable exclusivity for US-licensed Jubbonti and Wyost, as discussed in [Section 1.7](#) above. Accordingly, I also concur with the review team's recommendation to provisionally determine that:

- SB16, 60 mg/mL injection for SC use in a single-dose PFS meets the applicable standards for interchangeability with US-Prolia, 60 mg/mL injection for SC use in a single-dose PFS, and

- SB16, 120 mg/1.7 mL injection for SC use in a single-dose vial meets the applicable standards for interchangeability with US-Xgeva, 120 mg/1.7 mL injection for SC use in a single-dose vial,

These SB16 products have met the statutory interchangeability requirements for the following indications for which US-Prolia and US-Xgeva have previously been approved and for which the applicant is seeking licensure:

U.S.-Prolia:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients denosumab also reduced the incidence of vertebral fractures
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

U.S.-Xgeva:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

When action is taken for this BLA, it will be administratively split to facilitate an approval action for SB16 as a biosimilar product ("Original 1") and a provisional determination that SB16 is an interchangeable biosimilar product ("Original 2"), as described in Section 1.7 above. The Applicant is expected to submit an amendment seeking approval of BLA 761392/Original 2 no more than six months prior to the expiration of exclusivity, or when the Applicant believes that BLA 761392/Original 2 will become eligible for approval.

**Author:**

Theresa Kehoe, M.D

Division Director, Division of General Endocrinology

**13. Appendices****13.1. Financial Disclosure****Covered Clinical Study: SB16-1001**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         |                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant)        |
| Total number of investigators identified: 16                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                         |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                         |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                         |                                                                  |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <input type="text"/></p> <p>Significant payments of other sorts: <input type="text"/></p> <p>Proprietary interest in the product tested held by investigator: <input type="text"/></p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <input type="text"/></p> |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request explanation from Applicant) |

**Covered Clinical Study: SB16-3001**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         |                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant)        |
| Total number of investigators identified: 139                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                         |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                         |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                         |                                                                  |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <input type="text"/></p> <p>Significant payments of other sorts: <input type="text"/></p> <p>Proprietary interest in the product tested held by investigator: <input type="text"/></p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <input type="text"/></p> |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request explanation from Applicant) |

**13.2. Nonclinical Appendices**

This section has been removed because nonclinical study reports were not submitted for review.

### 13.3. Clinical Pharmacology Appendices

#### 13.3.1. Summary of Bioanalytical Method Validation and Performance

##### Pharmacokinetics

For the PK similarity study SB16-1001 and the efficacy and safety study SB16-3001, serum concentrations of SB16, EU-Prolia and US-Prolia were measured using a validated electrochemiluminescence (ECL) assay of Meso Scale Discovery (MSD) platform. This method was fully validated over a range of 5 to 150 ng/mL for study drug in accordance with the Bioanalytical Method Validation Guidance from the agency, and is considered suitable for the assessment of serum concentrations of denosumab.

The method validation entitled *Validation of an MSD-ECL Method for the Quantitation of SB16 and Prolia® (Denosumab)* (Project RPID2) in Human Serum and sample analysis for the study were performed at (b) (4). In this method, a MSD-streptavidin coated plate was blocked and then coated with a biotinylated anti-denosumab antibody (HCA282) (Samsung, Incheon, Republic of Korea). Denosumab present in samples was captured by biotinylated anti-denosumab antibody. A sulfo-tagged non-inhibitory anti-idiotypic antibody (HCA283) (Samsung, Incheon, Republic of Korea), was applied for detection of bound analytes. [Table 38](#) shows the summary of the ECL method validation and performance in quantification of SB16, EU-Prolia and US-Prolia.

**Table 38 Summary of bioanalytical method validation and in-study performance measurement of SB16, EU-Prolia and US-Prolia**

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| Bioanalytical method review summary                  | An Electrochemiluminescence (ECL) platform was utilized to determine the free or partially bound denosumab concentration in Human Serum. A streptavidin coated plate is blocked and then coated with biotinylated anti-denosumab antibody. Denosumab present in samples is captured by biotinylated anti-denosumab antibodies. Sulfo-tagged anti-denosumab antibodies are then used to detect denosumab. In the presence of tripropylamine-containing read buffer, the Sulfo-Tag produces an electrochemiluminescent signal that is triggered when voltage is applied. Only samples that contain denosumab bound to both biotinylated anti-denosumab antibodies and sulfo-tagged anti-denosumab antibodies will generate an ECL signal. |
| Materials used for calibration curve & concentration | Matrix: Pooled normal human serum<br>Tested product: SB16<br>Calibration concentration (in undiluted [neat] serum): 10.0 [anchor], 20.0 [LLOQ], 40.0, 80.0, 200.0, 500.0, 1000.0, and 2000.0 [ULOQ] ng/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Validated assay range                                | 20.0 to 2000.0 ng/mL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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| Material used for QCs & concentration                                                                                                                                                                                                              | Matrix: Pooled normal human serum<br>Tested product: SB16, US/EU Prolia<br>QC concentrations (in undiluted [neat] serum): 20.0 (LLOQ), 60.0 (LQC), 200.0 (MQC), 1500.0 (HQC), and 2000.0 (ULOQ) ng/mL |                                                |                      |
| Minimum required dilutions (MRDs)                                                                                                                                                                                                                  | MRD: 1:10                                                                                                                                                                                             |                                                |                      |
| Source & lot of reagents (LBA)                                                                                                                                                                                                                     | <b>Capture protein</b><br>Biotinylated anti-denosumab antibody, lot RN200600142<br><b>Detection antibody</b><br>Sulfo-tagged anti-denosumab antibody, lot RN200600145                                 |                                                |                      |
| Regression model & weighting                                                                                                                                                                                                                       | 5-PL (parameter logistic), 1/response weighting                                                                                                                                                       |                                                |                      |
| <b>Validation Parameters</b>                                                                                                                                                                                                                       | <b>Method Validation Summary</b>                                                                                                                                                                      |                                                | <b>Acceptability</b> |
| Calibration curve performance during accuracy & precision<br><br>Per BMV,<br>At least 75% and minimum of 6 non-zero calibrators without anchor points and LBA: $\pm 20\%$ bias ( $\pm 25\%$ at lower limit of quantitation (LLOQ)), $\leq 20\%$ CV | No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)                                                                                                                            | 7                                              | Acceptable           |
|                                                                                                                                                                                                                                                    | Cumulative accuracy (%bias) from LLOQ to ULOQ<br>SB16                                                                                                                                                 | -3.07 to 6.84%                                 | Acceptable           |
|                                                                                                                                                                                                                                                    | Cumulative precision (%CV) from LLOQ to ULOQ<br>SB16                                                                                                                                                  | $\leq 4.08\%$                                  | Acceptable           |
| QCs performance during accuracy & precision<br>Per BMV,<br>LBA QCs: $\pm 20\%$ bias ( $\pm 25\%$ at LLOQ), $\leq 20\%$ CV and $\leq 30\%$ total error ( $\leq 40\%$ at LLOQ)                                                                       | Cumulative accuracy (%bias) in 5 QCs<br>SB16<br>EU- Prolia<br>US- Prolia                                                                                                                              | 1.72 to 10.2<br>-1.49 to 5.90<br>0.806 to 9.06 | Acceptable           |
|                                                                                                                                                                                                                                                    | Inter-batch %CV<br>SB16<br>EU- Prolia<br>US- Prolia                                                                                                                                                   | $\leq 9.59$<br>$\leq 12.4$<br>$\leq 11.5$      | Acceptable           |
|                                                                                                                                                                                                                                                    | Percent total error (TE)<br>SB16<br>EU- Prolia<br>US- Prolia                                                                                                                                          | $\leq 18.8$<br>$\leq 15.1$<br>$\leq 19.4$      | Acceptable           |

|                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |            |
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| Selectivity & matrix effect          | <p>The selectivity of SB16, US Prolia and EU Prolia at LLOQ and HQC met target acceptance criteria recovering within <math>\pm 25\%</math> for LLOQ and <math>\pm 20\%</math> for HQC of the nominal concentration.</p> <p>Nine out of ten normal healthy individual donors fortified with SB16 at the LLOQ and ten out of ten normal healthy individual donor fortified with SB16 at the HQC met the acceptance criteria.</p> <p>Nine out of ten normal healthy individual donors fortified with US Prolia at the LLOQ and nine out of ten normal healthy individual donors fortified with US Prolia at the HQC met the acceptance criteria.</p> <p>Eight out of ten normal healthy individual donors fortified with EU Prolia at the LLOQ and ten out of ten normal healthy individual donors fortified with EU Prolia at the HQC met the acceptance criteria.</p> <p><b>Selectivity</b><br/><b>SB16</b><br/>10 individual lots tested</p> <ul style="list-style-type: none"> <li>- LLOQ: 9/10 passed, <math>-2.34</math> to <math>31.0\%</math> bias</li> <li>- HQC: 10/10 passed, <math>-10.4</math> to <math>12.5\%</math> bias</li> </ul> <p><b>US Prolia</b><br/>10 individual lots tested</p> <ul style="list-style-type: none"> <li>- LLOQ: 9/10 passed, <math>-1.73</math> to <math>33.9\%</math> bias</li> <li>- HQC: 9/10 passed, <math>-2.55</math> to <math>31.1\%</math> bias</li> </ul> <p><b>EU Prolia</b><br/>10 individual lots tested</p> <ul style="list-style-type: none"> <li>- LLOQ: 8/10 passed, <math>-7.16</math> to <math>43.5\%</math> bias</li> </ul> <p><b>Matrix Effect</b><br/>10 individual lots tested<br/>10/10 passed, no quantifiable values were observed.</p> | Acceptable |
| Diseased Selectivity & matrix effect | <p>The selectivity of SB16 and EU Prolia at LLOQ and HQC met target acceptance criteria recovering within <math>\pm 25\%</math> for LLOQ and <math>\pm 20\%</math> for HQC of the nominal concentration.</p> <p>Nine out of ten disease state individuals fortified with SB16 at the LLOQ and nine out of ten disease state</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Acceptable |

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|                            | <p>individuals fortified with SB16 at the HQC met the acceptance criteria.</p> <p>Nine out of ten disease state individuals fortified with Prolia at the LLOQ and nine out of ten disease state individuals fortified with Prolia at the HQC met the acceptance criteria.</p> <p><b>Selectivity</b></p> <p><b>SB16</b></p> <p>10 individual lots tested</p> <ul style="list-style-type: none"> <li>- LLOQ: 9/10 passed, 1.10 to 1930% bias</li> <li>- HQC: 9/10 passed, -7.45 to 36.3% bias</li> </ul> <p><b>EU Prolia</b></p> <p>10 individual lots tested</p> <ul style="list-style-type: none"> <li>- LLOQ: 9/10 passed, -2.82 to 1940% bias</li> <li>- HQC: 9/10 passed, 1.77 to 54.8% bias</li> </ul> <p><b>Matrix Effect</b></p> <p>10 individual lots tested</p> <p>9/10 passed</p>                                                                                                                                                                                            |  |
| Interference & specificity | <p>Receptor activator of nuclear factor kappa-B-ligand (RANKL), osteoprotegerin (OPG), anti-denosumab antibody (ADA) interference test was performed by spiking the material in pooled normal human serum matrix with or without denosumab (SB16, US-Prolia, EU-Prolia).</p> <ul style="list-style-type: none"> <li>• Total lot tested: 1 lot of pooled NHS</li> </ul> <p><b>[RANKL interference]</b></p> <p>1) SB16</p> <p><u>No effect from RANKL on the quantitation of SB16 up to 16.2 ng/mL at LLOQ and 46.5 ng/mL at ULOQ level</u></p> <ul style="list-style-type: none"> <li>• Pooled NHS spiked with 0.00, 0.30, 1.00, 4.00, 16.2, 64.7 ng/mL of RANKL at LLOQ level (20.0 ng/mL) of SB16</li> <li>• Pooled NHS spiked with 0.00, 46.5, 64.7 ng/mL of RANKL at ULOQ level (2000 ng/mL) of SB16</li> <li>• Result</li> <li>- Not quantifiable at blank serum with RANKL</li> <li>- Range of observed bias at LLOQ with RANKL up to 16.2 ng/mL: -3.89 to 16.6% bias</li> </ul> |  |

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|  | <ul style="list-style-type: none"> <li>- Observed bias at ULOQ with 46.5 ng/mL RANKL: – 0.57% bias</li> </ul> <p>2) US Prolia</p> <p><u>No effect from RANKL on the quantitation of US Prolia up to 16.2 ng/mL at LLOQ and 64.7 ng/mL at ULOQ level</u></p> <ul style="list-style-type: none"> <li>• Pooled NHS spiked with 0.00, 0.30, 1.00, 4.00, 16.2, 64.7 ng/mL of RANKL at LLOQ level (20.0 ng/mL) of US Prolia</li> <li>• Pooled NHS spiked with 0.00, 64.7 ng/mL of RANKL at ULOQ level (2000 ng/mL) of US Prolia</li> <li>• Result</li> <li>- Not quantifiable at blank serum with RANKL</li> <li>- Range of observed bias at LLOQ with RANKL up to 16.2 ng/mL: 0.610 to 13.8% bias</li> <li>- Observed bias at ULOQ with 64.7 ng/mL RANKL: – 5.04% bias</li> </ul> <p>3) EU Prolia</p> <p><u>No effect from RANKL on the quantitation of EU-Prolia up to 16.2 ng/mL at LLOQ and 64.7 ng/mL at ULOQ level</u></p> <ul style="list-style-type: none"> <li>• Pooled NHS spiked with 0.00, 0.30, 1.00, 4.00, 16.2, 64.7 ng/mL of RANKL at LLOQ level (20.0 ng/mL) of EU Prolia</li> <li>• Pooled NHS spiked with 0.00, 64.7 ng/mL of RANKL at ULOQ level (2000 ng/mL) of EU Prolia</li> <li>• Result</li> <li>- Not quantifiable at blank serum with RANKL</li> <li>- Range of observed bias at LLOQ with RANKL up to 16.2 ng/mL: 16.2 to 19.4% bias</li> <li>- Range of observed bias at ULOQ with 64.7 ng/mL RANKL: 1.72% bias</li> </ul> <p><b>[OPG interference]</b></p> <p>1) SB16</p> <p><u>No effect from OPG on the quantitation of SB16 up to 33.0 ng/mL at LLOQ and ULOQ level</u></p> <ul style="list-style-type: none"> <li>• Pooled NHS spiked with 0.00, 33.0 ng/mL OPG</li> <li>• Test level: Blank, LLOQ (20.0 ng/mL), ULOQ (2000 ng/mL)</li> <li>• Result</li> <li>- Not quantifiable at blank serum with OPG</li> <li>- Range of observed bias at LLOQ with OPG up to 33.0 ng/mL: 4.55% bias</li> </ul> |  |
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|  | <ul style="list-style-type: none"> <li>- Range of observed bias at ULOQ with OPG up to 33.0 ng/mL: 24.7% bias</li> </ul> <p>2) US Prolia</p> <p><u>No effect from OPG on the quantitation of US Prolia up to 33.0 ng/mL at LLOQ and ULOQ level</u></p> <ul style="list-style-type: none"> <li>• Pooled NHS spiked with 0.00, 33.0 ng/mL OPG</li> <li>• Test level: Blank, LLOQ (20.0 ng/mL), ULOQ (2000 ng/mL)</li> <li>• Result</li> </ul> <ul style="list-style-type: none"> <li>- Not quantifiable at blank serum with OPG</li> <li>- Range of observed bias at LLOQ with OPG up to 33.0 ng/mL: -12.0% bias</li> <li>- Range of observed bias at ULOQ with OPG up to 33.0 ng/mL: -0.991% bias</li> </ul> <p>3) EU Prolia</p> <p><u>No effect from OPG on the quantitation of EU Prolia up to 33.0 ng/mL at LLOQ and ULOQ level</u></p> <ul style="list-style-type: none"> <li>• Pooled NHS spiked with 0.00, 33.0 ng/mL OPG</li> <li>• Test level: Blank, LLOQ (20.0 ng/mL), ULOQ (2000 ng/mL)</li> <li>• Result</li> </ul> <ul style="list-style-type: none"> <li>- Not quantifiable at blank serum with OPG</li> <li>- Range of observed bias at LLOQ with OPG up to 33.0 ng/mL: 5.76% bias</li> <li>- Range of observed bias at ULOQ with OPG up to 33.0 ng/mL: 2.61% bias</li> </ul> <p><b>[ADA interference]</b></p> <p>1) SB16:</p> <p><u>No effect from ADA on the quantitation of SB16 up to 10.0 ng/mL at LLOQ and 100.0 ng/mL at ULOQ level</u></p> <ul style="list-style-type: none"> <li>• Pooled NHS spiked with 0.00, 10.0, 100 ng/mL of ADA at LLOQ level (20.0 ng/mL) of SB16</li> <li>• Pooled NHS spiked with 0.00, 5.00, 10.0, 50.0, 100 ng/mL of ADA at ULOQ level (2000 ng/mL) of SB16</li> <li>• Result</li> </ul> <ul style="list-style-type: none"> <li>- Not quantifiable at blank serum with ADA</li> <li>- Range of observed bias at LLOQ with 10.0 ng/mL ADA: -6.18% bias</li> <li>- Range of observed bias at ULOQ with ADA up to 100 ng/mL: -2.45 to 35.1%* bias</li> </ul> <p>2) US Prolia:</p> |  |
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|                  | <p><u>No effect from ADA on the quantitation of US Prolia up to 10.0 ng/mL at LLOQ and 100.0 ng/mL at ULOQ level</u></p> <ul style="list-style-type: none"> <li>• Pooled NHS spiked with 0.00, 10.0, 100 ng/mL of ADA at LLOQ (20.0 ng/mL) and ULOQ (2000 ng/mL) level of US-Prolia</li> <li>• Result <ul style="list-style-type: none"> <li>- Not quantifiable at blank serum with ADA</li> <li>- Range of observed bias at LLOQ with 10.0 ng/mL ADA: 14.5% bias</li> <li>- Range of observed bias at ULOQ with ADA up to 100 ng/mL: 0.437 to 1.07% bias</li> </ul> </li> </ul> <p>3) EU Prolia:</p> <p><u>No effect from ADA on the quantitation of EU-Prolia up to 10.0 ng/mL at LLOQ and 100.0 ng/mL at ULOQ level</u></p> <ul style="list-style-type: none"> <li>• Pooled NHS spiked with 0.00, 10.0, 100 ng/mL of ADA at LLOQ (20.0 ng/mL) and ULOQ (2000 ng/mL) level of EU-Prolia</li> <li>• Result <ul style="list-style-type: none"> <li>- Not quantifiable at blank serum with ADA</li> <li>- Range of observed bias at LLOQ with 10.0 ng/mL ADA: -5.57% bias</li> </ul> </li> </ul> <p>Range of observed bias at ULOQ with ADA up to 100 ng/mL: -5.38 to -0.236% bias</p> |            |
| Hemolysis effect | <ul style="list-style-type: none"> <li>• Hemolyzed matrix containing 5% fully lysed whole blood</li> <li>• Test level: Blank, LLOQ (20.0 ng/mL), and HQC (1500.0 ng/mL)</li> </ul> <p><b>SB16</b></p> <p><u>No effect from hemolysis up to 5% fully lysed whole blood on the quantitation of SB16</u></p> <ul style="list-style-type: none"> <li>- Not quantifiable at blank hemolyzed serum</li> <li>- LLOQ: 5/5 passed, -3.39 to 13.2% bias</li> <li>- HQC: 5/5 passed, -0.98 to 21.8% bias</li> </ul> <p><b>US Prolia</b></p> <p><u>No effect from hemolysis up to 5% fully lysed whole blood on the quantitation of US Prolia</u></p> <ul style="list-style-type: none"> <li>- Not quantifiable at blank hemolyzed serum</li> <li>- LLOQ: 5/5 passed, 14.3 to 24.6% bias</li> <li>- HQC: 5/5 passed, -7.89 to 30.0% bias</li> </ul> <p><b>EU Prolia</b></p> <p><u>No effect from hemolysis up to 5% fully lysed whole blood on the quantitation of EU Prolia</u></p> <ul style="list-style-type: none"> <li>- Not quantifiable at blank hemolyzed serum</li> </ul>                                                                                                                | Acceptable |

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|                                  | <ul style="list-style-type: none"> <li>- LLOQ: 5/5 passed, -24.5 to -3.38% bias</li> <li>HQC: 5/5 passed, -15.2 to -12.1% bias</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |            |
| Lipemic effect                   | <ul style="list-style-type: none"> <li>• Lipemic matrix containing &gt; 300 mg/dL triglycerides</li> <li>• Test level: Blank, LLOQ (20.0 ng/mL), HQC (1500 ng/mL)</li> </ul> <p><b>SB16</b><br/> <u>No effect from lipemia up to &gt; 300 mg/dL on the quantitation of SB16</u></p> <ul style="list-style-type: none"> <li>- Not quantifiable at blank lipemic serum</li> <li>- LLOQ: 4/5 passed, -4.62 to 908% bias</li> <li>- HQC: 4/5 passed, 13.4 to 393% bias</li> </ul> <p><b>US Prolia</b><br/> <u>No effect from lipemia up to &gt; 300 mg/dL on the quantitation of US Prolia</u></p> <ul style="list-style-type: none"> <li>- Not quantifiable at blank lipemic serum</li> <li>- LLOQ: 4/5 passed, 9.84 to 895% bias</li> <li>- HQC: 4/5 passed, 2.08 to 87.5% bias</li> </ul> <p><b>EU Prolia</b><br/> <u>No effect from lipemia up to &gt; 300 mg/dL on the quantitation of EU Prolia</u></p> <ul style="list-style-type: none"> <li>- Not quantifiable at blank lipemic serum</li> <li>- LLOQ: 4/5 passed, -12.6 to 902% bias</li> </ul> <p>HQC: 4/5 passed, -10.8 to 64.1% bias</p> | Acceptable |
| Dilution linearity & hook effect | <p>20,000 ng/mL undiluted, and serially diluted in 4-, 16-, 66.7-, 333.3, and 666.7 fold (5 dilution factors)</p> <p>No apparent hook effect up to 20,000 ng/mL</p> <p>Range of observed bias within quantitation range:</p> <p>1) In normal human serum:</p> <ul style="list-style-type: none"> <li>• SB16: -6.04 to 1.65% bias</li> <li>• US Prolia: -3.49 to 2.48% bias</li> <li>• EU Prolia: 1.07 to 5.73% bias</li> </ul> <p>2) In disease state human serum:</p> <ul style="list-style-type: none"> <li>• SB16: -6.08 to 10.2% bias</li> </ul> <p>EU Prolia: -3.45 to -0.00619% bias</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Acceptable |
| Bench-top/process stability      | <p><b>SB16:</b> Acceptable for 72 hours for NHS, Acceptable for 72 hours for PMO</p> <p><b>US Prolia:</b> Acceptable for 48 hours for NHS</p> <p><b>EU Prolia:</b> Acceptable for 72 hours for NHS, Acceptable for 72 hours for PMO</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Acceptable |

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| Freeze-Thaw stability                                            | <p><b>SB16:</b> Acceptable for up to 8 cycles thawed at RT for NHS, Acceptable for up to 8 cycles thawed at RT for PMO</p> <p><b>US Prolia:</b> Acceptable for up to 8 cycles thawed at RT for NHS</p> <p><b>EU Prolia:</b> Acceptable for up to 8 cycles thawed at RT for NHS, Acceptable for up to 8 cycles thawed at RT for PMO</p>                                                                                                                                                                                                                                                                                                                | Acceptable |
| Long-term storage                                                | <p><b>SB16:</b><br/>Acceptable for up to 731 days at &lt; –25°C for NHS<br/>Acceptable for up to 760 days at &lt; –80°C for NHS<br/>Acceptable for up to 724 days at &lt; –25°C for PMO<br/>Acceptable for up to 760 days at &lt; –80°C for PMO</p> <p><b>US Prolia:</b><br/>Acceptable for up to 731 days at &lt; –25°C for NHS<br/>Acceptable for up to 760 days at &lt; –80°C for NHS</p> <p><b>EU Prolia:</b><br/>Acceptable for up to 731 days at &lt; –25°C for NHS<br/>Acceptable for up to 760 days at &lt; –80°C for NHS<br/>Acceptable for up to 545 days at &lt; –25°C for PMO<br/>Acceptable for up to 760 days at &lt; –80°C for PMO</p> | Acceptable |
| Parallelism                                                      | See results in study Performance report                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |            |
| Carry over                                                       | Not applicable. TECAN EVO workstation was used for this method. However, method-specific carry over test were not performed since disposable tips were used and disposed at each step.                                                                                                                                                                                                                                                                                                                                                                                                                                                                |            |
| <b>Method Performance in Study # SB16-1001 (Report No. RPIE)</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |            |
| Assay passing rate                                               | <p>88.9% (192/216)</p> <ul style="list-style-type: none"> <li>Total runs: 216 (including ISR runs)</li> <li>Accepted runs: 192</li> </ul> <p>Rejected runs: 24</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Acceptable |
| Standard curve performance                                       | <ul style="list-style-type: none"> <li>Cumulative accuracy (%bias) from LLOQ to ULOQ: –1.3 to 7.0%</li> <li>Cumulative precision (%CV) from LLOQ to ULOQ: ≤ 3.6%</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Acceptable |
| QC performance                                                   | <ul style="list-style-type: none"> <li>Cumulative bias (%bias): –1.8 to 4.4%</li> <li>Cumulative precision (%CV): ≤ 9.6%</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Acceptable |

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| Method reproducibility                                            | ISR was performed in 10.2% (320/3,136) of study samples and 100.0% (320/320) of samples met the pre-specified criteria                                                                                                                                                                                                                | Acceptable |
| Study sample analysis/ stability                                  | <b>Sample:</b> <ul style="list-style-type: none"> <li>LTS established for 760 days in NHS at <math>&lt; -80^{\circ}\text{C}</math></li> <li>All samples were analyzed within the established duration with the longest sample storage at 357 days</li> </ul>                                                                          | Acceptable |
| Parallelism in Healthy Individuals                                | Five individuals from the clinical Phase I sample analysis (Project RPIE) were serially diluted to four dilutions within the range of the quantitation. All 5 individuals met the acceptance criteria.<br>Five individuals tested (5-, 10-, 50-, and 100-fold dilution)<br>Result: 5/5 passed, 5.55 to 8.83% precision (Project RPIE) | Acceptable |
| <b>Method Performance in Study # SB16-3001 (Report No. RPIE2)</b> |                                                                                                                                                                                                                                                                                                                                       |            |
| Assay passing rate                                                | 86.7% (143/165) <ul style="list-style-type: none"> <li>Total runs: 165 (including ISR runs)</li> <li>Accepted runs: 143</li> <li>Rejected runs: 22</li> </ul>                                                                                                                                                                         | Acceptable |
| Standard curve performance                                        | <ul style="list-style-type: none"> <li>Cumulative accuracy (%bias) from LLOQ to ULOQ: <math>-2.2</math> to <math>7.1\%</math></li> <li>Cumulative precision (%CV) from LLOQ to ULOQ: <math>\leq 4.0\%</math></li> </ul>                                                                                                               | Acceptable |
| QC performance                                                    | <ul style="list-style-type: none"> <li>Cumulative accuracy (%bias): <math>-4.4</math> to <math>2.6\%</math></li> <li>Cumulative precision (%CV): <math>\leq 8.0\%</math></li> </ul>                                                                                                                                                   | Acceptable |
| Method reproducibility                                            | <ul style="list-style-type: none"> <li>ISR was performed in 7.9% (272/3456) of study samples and 82.5% (224/272) of samples met the pre-specified criteria</li> </ul>                                                                                                                                                                 | Acceptable |
| Study sample analysis/ stability                                  | <b>Sample:</b> <ul style="list-style-type: none"> <li>LTS established for 760 days in PMO at <math>&lt; -80^{\circ}\text{C}</math></li> <li>All samples were analyzed within the established duration with the longest sample storage at 647 days</li> </ul>                                                                          | Acceptable |
| Parallelism in Healthy Individuals                                | Five individuals from the clinical Phase III sample analysis (Project RPIE2) were serially diluted to four dilutions within the range of the quantitation. All 5 individuals met the acceptance criteria.<br>Five individuals tested (5-, 10-, 50-, and 100-fold dilution)                                                            | Acceptable |

|  |                                                             |  |
|--|-------------------------------------------------------------|--|
|  | Result: 5/5 passed, 4.05 to 9.66% precision (Project RPIE2) |  |
|--|-------------------------------------------------------------|--|

*\*Concentration data from impacted samples removed for PK analysis*

Sources: Bioanalytical Report for Method Validation (Project RPID2) ([Link](#)); Bioanalytical Report for Clinical Study SB16-1001 (Project RPIE) ([Link](#)); Other Analytical and Validation Report for Clinical Study SB16-3001 (Project RPIE2) ([Link](#)).

## Pharmacodynamics

Serum carboxy terminal cross-linking telopeptide of type I collagen (s-CTX) and procollagen type 1 N-terminal propeptide (P1NP) in human serum were quantified in Clinical Study SB16-1001 and Clinical Study SB16-3001.

### Bioanalytical methods that were used to assess the PD biomarker(s) and/or the PD effect(s) of the study drug(s)

Levels of s-CTX and P1NP were evaluated using Elecsys kits from Roche Diagnostics on an automated Cobas 8000 system. For s-CTX, the  $\beta$ -CrossLaps assay uses two monoclonal antibodies to recognize specific CTX1 degradation fragments. The P1NP assay follows a similar principle. Both assays employ a sandwich immunoassay technique where the target molecule is captured by a biotinylated monoclonal antibody and then detected by a ruthenium complex-labeled monoclonal antibody. The detection is based on electrochemiluminescence (ECL), where an applied voltage causes the ruthenium complex to emit light. This light is measured by a photomultiplier, and the concentration of the target molecule is determined using a master curve generated by the instrument. These methods allow for the quantitative measurement of these bone turnover markers in patient samples.

These PD assays based on commercially diagnostic kits were refined and fully validated with respect to precision, accuracy, hemolyzed/lipemic serum interference, parallelism, selectivity, dilution linearity, robustness, carry-over, and tested for stability (short-term, long-term, freeze/thaw cycles).

### 13.3.2. Other Clinical Pharmacology Information

Not Applicable.

## 13.4. Clinical Appendices

### Authors:

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Clinical Reviewer, DGE

### 13.4.1. Schedule of Assessments, Study SB16-3001

**Figure 8: Assessment Schedule, Study SB16-3001**

| Assessment                                                               | Study Period           |                         |                           |            |            |            |            |                   |             |                  |
|--------------------------------------------------------------------------|------------------------|-------------------------|---------------------------|------------|------------|------------|------------|-------------------|-------------|------------------|
|                                                                          | Screening <sup>1</sup> | Main Period             |                           |            |            |            |            | Transition Period |             | ET <sup>28</sup> |
|                                                                          |                        | 1                       | 2                         | 3          | 4          | 5          | 6          | 7                 | EOS         |                  |
| Study Visit                                                              |                        |                         |                           |            |            |            |            |                   |             |                  |
| Timepoint                                                                |                        | Month <sup>2</sup><br>0 | Month<br>0.5 <sup>3</sup> | Month<br>1 | Month<br>3 | Month<br>6 | Month<br>9 | Month<br>12       | Month<br>18 |                  |
| Days from Month 0                                                        | -28 to -1              | 0                       | 15                        | 30         | 91         | 182        | 273        | 364               | 546         |                  |
| Visit Window (Day)                                                       | 0                      | 0                       | ± 3                       | ± 3        | ± 7        | ± 7        | ± 7        | ± 7               | ± 7         | ± 7              |
| Informed consent <sup>4</sup>                                            | ✓                      |                         |                           |            |            |            |            |                   |             |                  |
| Demographic information <sup>5</sup>                                     | ✓                      |                         |                           |            |            |            |            |                   |             |                  |
| Medical and surgical history <sup>6</sup>                                | ✓                      |                         |                           |            |            |            |            |                   |             |                  |
| ECG <sup>7</sup>                                                         | ✓                      |                         |                           |            |            |            |            |                   |             |                  |
| Serum FSH, PTH, TSH and virology markers <sup>8</sup>                    | ✓                      |                         |                           |            |            |            |            |                   |             |                  |
| Lateral spine X-ray (lumbar and thoracic) <sup>9</sup>                   | ✓                      |                         |                           |            |            |            |            |                   |             |                  |
| Vital signs <sup>10</sup>                                                | ✓                      | ✓                       | ✓                         | ✓          | ✓          | ✓          | ✓          | ✓                 | ✓           | ✓                |
| Physical examination <sup>11</sup>                                       | ✓                      | ✓                       | ✓                         | ✓          | ✓          | ✓          | ✓          | ✓                 | ✓           | ✓                |
| Height and weight <sup>12</sup>                                          | ✓                      | ✓                       | ✓                         | ✓          | ✓          | ✓          | ✓          | ✓                 | ✓           | ✓                |
| Haematology, biochemistry tests, and urinalysis (dipstick) <sup>13</sup> | ✓                      | ✓                       | ✓                         | ✓          | ✓          | ✓          | ✓          | ✓                 | ✓           | ✓                |
| BMD (lumbar spine, total hip, and femoral neck) <sup>14</sup>            | ✓                      |                         |                           |            |            | ✓          |            | ✓                 | ✓           | ✓                |
| Serum vitamin D <sup>15</sup>                                            | ✓                      |                         |                           |            |            | ✓          |            | ✓                 |             |                  |
| Inclusion/exclusion criteria                                             | ✓                      | ✓                       |                           |            |            |            |            | ✓                 |             |                  |
| Randomisation <sup>16</sup>                                              |                        | ✓                       |                           |            |            |            |            | ✓ <sup>17</sup>   |             |                  |
| PK assessment <sup>18</sup>                                              |                        | ✓                       | ✓                         | ✓          | ✓          | ✓          | ✓          | ✓                 | ✓           | ✓                |
| Immunogenicity assessment <sup>19</sup>                                  |                        | ✓                       | ✓                         | ✓          | ✓          | ✓          | ✓          | ✓                 | ✓           | ✓                |

| Assessment                                                               | Study Period           |                         |                           |            |            |            |            |                   |             |                  |
|--------------------------------------------------------------------------|------------------------|-------------------------|---------------------------|------------|------------|------------|------------|-------------------|-------------|------------------|
|                                                                          | Screening <sup>1</sup> | Main Period             |                           |            |            |            |            | Transition Period |             | ET <sup>28</sup> |
|                                                                          |                        | 1                       | 2                         | 3          | 4          | 5          | 6          | 7                 | EOS         |                  |
| Study Visit                                                              |                        |                         |                           |            |            |            |            |                   |             |                  |
| Timepoint                                                                |                        | Month <sup>2</sup><br>0 | Month<br>0.5 <sup>3</sup> | Month<br>1 | Month<br>3 | Month<br>6 | Month<br>9 | Month<br>12       | Month<br>18 |                  |
| Days from Month 0                                                        | -28 to -1              | 0                       | 15                        | 30         | 91         | 182        | 273        | 364               | 546         |                  |
| Visit Window (Day)                                                       | 0                      | 0                       | ± 3                       | ± 3        | ± 7        | ± 7        | ± 7        | ± 7               | ± 7         | ± 7              |
| PD assessment (bone turnover markers [serum CTX/P1NP]) <sup>20, 21</sup> |                        | ✓ <sup>22</sup>         | ✓                         | ✓          | ✓          | ✓          | ✓          | ✓                 | ✓           | ✓                |
| IP administration <sup>23</sup>                                          |                        | ✓                       |                           |            |            | ✓          |            | ✓                 |             |                  |
| Injection site reaction <sup>24</sup>                                    |                        | ✓                       |                           |            |            | ✓          |            | ✓                 |             |                  |
| Non-IP administration <sup>25</sup>                                      |                        | Continuously            |                           |            |            |            |            |                   |             |                  |
| Previous and concomitant medications <sup>26</sup>                       |                        | Continuously            |                           |            |            |            |            |                   |             |                  |
| Adverse events <sup>27</sup>                                             |                        | Continuously            |                           |            |            |            |            |                   |             |                  |

BMD = bone mineral density; CTX = C-telopeptide of type I collagen; ECG = electrocardiogram; EOS = end of study; ET = early termination; FSH = follicle-stimulating hormone; IP = investigational product; P1NP = procollagen type I N-terminal propeptide; PD = pharmacodynamic; PK = pharmacokinetic; PTH = parathyroid hormone; TSH = thyroid stimulating hormone

- In subjects who were not eligible only due to vitamin D deficiency, serum vitamin D (25-hydroxyvitamin D) was re-tested only once after vitamin D repletion and the re-test result was used for eligibility review. Additional 28 days was allowed to those subjects. Vitamin D repletion method was determined by the Investigator considering subject's serum vitamin D level.
- To avoid repetition of unnecessary procedures, screening procedures previously performed other than vitamin D re-test were not repeated in this case.

2. Visit date was calculated based on Month 0.

3. Month 0.5 was 15 days after Month 0.

4. Informed consent was obtained prior to any study related procedures.

5. Demographic information included the year of birth, race, ethnicity, current smoking status, daily alcohol consumption amount, and parent fractured hip history.

6. Medical and surgical history of 5 years prior to Screening was included. Also, previous fracture history in a lifetime was collected.

7. Standard 12-lead ECGs were recorded at Screening.

8. Blood sample for serum FSH (optional), PTH, TSH and virology markers (hepatitis B and C virology [HBsAg and HCV Ab]) were collected at Screening.

9. Lateral spine X-ray (lumbar and thoracic) was done at Screening.

10. Vital signs included body temperature measurement, blood pressure, and heart rate. Vital signs were assessed at Screening, prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET.

11. Physical examination was done at Screening, prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET. The result for physical examinations was confirmed by the Investigator.

## Biosimilar Multi-disciplinary Evaluation and Review (BMER)

12. Body weight was measured and recorded at Screening and prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET. Whereas height was measured and recorded only at Screening.
13. Samples for haematology, biochemistry tests, and urinalysis (dipstick) were collected at Screening, prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, EOS/ET, and additionally for subject's safety purpose during the study period at the Investigator's discretion.
  - Haematology: Haemoglobin, haematocrit, platelet count, red blood cell count, and white blood cell count (total and differential)
  - Chemistry: Sodium, potassium, chloride, creatinine, blood urea nitrogen, eGFR using MDRD equation, glucose, calcium, albumin corrected serum calcium, phosphorus, total bilirubin, albumin, total cholesterol, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase
  - Urinalysis (dipstick): Protein, blood, leucocytes, nitrite, glucose, ketone, pH, specific gravity, bilirubin, and urobilinogen
14. Lumbar spine, total hip, and femoral neck BMD were measured at Screening, prior to dosing at Months 6 and 12, and EOS/ET.
15. Blood sample for serum vitamin D (25-hydroxyvitamin D) was collected at Screening and prior to dosing at Months 6 and 12.
16. Randomisation proceeded after all screening procedures including eligibility confirmation.
17. At Month 12, subjects who received Prolia were re-randomised in a 1:1 ratio to either continue to receive Prolia or were transitioned to SB16. Subjects who received SB16 continued to receive SB16 up to Month 18, but they also followed the randomisation procedure to maintain blinding.
18. Blood sample for PK assessment was collected prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET.
19. Blood sample for immunogenicity assessment was collected prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET.
20. Blood sample for PD assessment was collected prior to dosing at Months 0, 6, and 12, Months 0.5, 1, 3, and 9, and EOS/ET.
21. Blood sample for CTX and PINP was collected in the morning hours after fasting for at least 8 hours.
22. On the day of baseline PD assessment (Month 0), calcium was not given before the PD blood sampling.
23. SB16 and Prolia were subcutaneously administered 60 mg every 6 months.
24. Monitoring for injection site reactions was done after IP administration at Months 0, 6, and 12.
25. Daily elemental calcium ( $\geq 1$  g) and vitamin D ( $\geq 800$  IU) was given to the subjects from Randomisation to EOS/ET. Instruction for non-IP supplementation was done at Months 0, 0.5, 1, 3, 6, 9, and 12.
26. Previous and concomitant medication within 5 years prior to Screening and concomitant medication thereafter. Also, previous oral bisphosphonate history in a lifetime was collected.
27. AEs were collected from the time of signing the ICF until the EOS/ET. SAEs were collected until 6 months after the last IP dose or EOS/ET, whichever longer. If the subject withdrew before receiving the first dose of IP, AEs and SAEs were collected up until the time the subject withdrew.
28. Subjects who withdrew from the study before EOS were asked to return to the investigational site for the ET procedures performed at 6 months from the last IP dose.

Source: Module 5.3.5.1, Clinical Study Report for Study SB16-3001, Part I, Table 9-2, pages 37-39

### **13.4.2. Eligibility Criteria, Study SB16-3001**

#### **Key Inclusion Criteria**

1. Postmenopausal women (defined as lack of menstrual period for at least 12 months prior to Screening, for which there was no other pathological or physiological cause).
2. Aged 55 to 80 years at Screening.
3. Body weight  $\geq 50$  kg and  $\leq 90$  kg at Screening.
4. Absolute BMD consistent with T-score at the total hip or lumbar spine of  $\geq -4$  and  $\leq -2.5$ , determined by central imaging center at Screening.
5. At least three evaluable vertebrae within L1 to L4, one evaluable femoral neck, and one evaluable hip joint for BMD measurement, determined by central imaging center at Screening.
6. Biologic (defined as any therapeutic monoclonal antibody or fusion receptor protein, including denosumab, denosumab biosimilars, or romosozumab) naïve at Screening.
7. Had to have been enrolled and completed the scheduled Month 12 visit of the Main Period to enroll in the Transition Period.

#### **Key Exclusion Criteria**

1. One severe or more than two moderate vertebral fractures on spinal X-ray according to Genant classification, determined by central imaging center at Screening.
2. History of hip fracture or bilateral hip replacement at Screening.
3. Uncorrected Vitamin D deficiency (defined as serum 25-OH vitamin D level  $< 20$  ng/mL [50 nmol/L]) at Screening.
4. Hyper- or hypocalcemia (defined as albumin-adjusted serum calcium for hypocalcemia  $< 2.1$  mmol/L [8.4 mg/dL] or for hypercalcemia  $> 2.62$  mmol/L [10.5 mg/dL]) at Screening.
5. Inadequate hematological function at Screening:
  - a. White blood cell count  $< 3.5 \times 10^3$  cells/mcL ( $< 3.5 \times 10^9$  cells/L).
  - b. Hemoglobin  $< 9$  g/dL
  - c. Platelet count  $< 100,000/\text{mm}^3$  ( $< 100 \times 10^9/\text{L}$ )
6. Inadequate renal or hepatic function at Screening:
  - a. Estimated glomerular filtration rate (eGFR)  $< 45$  mL/min.
  - b. Serum alanine transaminase and aspartate transaminase  $\geq 2 \times$  upper limit of normal
7. Known allergic reactions, hypersensitivity, or intolerance to denosumab or any ingredient of the investigational product (IP), including latex allergy or hereditary problems of fructose intolerance at Screening.
8. Not able to tolerate long-term, or had malabsorption of, calcium or vitamin D supplementation at Screening.
9. Use of any of the following medications that can affect BMD:
  - a. Oral bisphosphonate at any dose for osteoporosis treatment:

- i. Use for > 3 years cumulatively at Screening.
    - ii. Use for ≤ 3 years cumulatively and < 1 year since the last dose prior to Screening.
  - b. Intravenous bisphosphonate at any dose within 5 years prior to Screening.
  - c. Parathyroid hormone (PTH) or PTH analogues at any dose within 2 years prior to Screening.
  - d. Systemic hormone replacement therapy (oral or transdermal estrogen), selective estrogen receptor modulators (SERMs), tibolone, aromatase inhibitors, or androgens at any dose within 1 year prior to Screening.
    - i. Non-systemic vaginal estrogen treatment was permitted.
  - e. Calcitonin or its derivatives, calcimimetics (such as cinacalcet or etelcalcetide), or calcitriol at any dose within 3 months prior to Screening.
  - f. Systemic glucocorticoids (≥ 5 mg prednisone equivalence per day or cumulative dose ≥ 50 mg) for more than 10 days within 3 months prior to Screening.
  - g. Fluoride or strontium intended for osteoporosis treatment at any dose at any time.
  - h. Any non-biologic IP for osteoporosis treatment with a mechanism of action that was not described in the excluded medications at any dose within 5 years prior to Screening.
  - i. Other bone active drugs at any dose within 3 months prior to Screening.
10. Use of any non-biologic IP not indicated to treat osteoporosis from another study at any dose within 5 half-lives of that IP prior to Randomization, or use of an investigational device at Screening.
11. Non-osteoporosis medical conditions that could affect BMD at Screening.
- a. History of, or current, hyper- or hypoparathyroidism.
  - b. Current uncontrolled hyper- or hypothyroidism.
  - c. History of bone disease such as osteomalacia, osteogenesis imperfecta, osteopetrosis, achondroplasia, or Paget's disease of the bone.
  - d. History of chronic inflammatory disease, obvious sclerosis, osteophytosis, severe scoliosis, or other degenerative changes due to other co-morbidities that could interfere with the interpretation of DXA imaging results.
  - e. History of metabolic or other endocrinologic diseases such as malabsorption syndrome (including celiac disease), Cushing disease, acromegaly, or hyperprolactinemia.
12. History of osteonecrosis of the jaw or auditory canal, or atypical femoral fracture at Screening, or related risk based on the physical and oral examination including at Screening.
13. History of active periodontal disease or invasive dental procedure within 6 months prior to Screening or planned to do invasive dental procedures during the study period.
14. Fracture (except atypical femoral fracture and hip fracture) which had been in active healing within 12 months prior to Screening (at the discretion of the Investigator).

15. History of clinically significant active infection within 2 weeks prior to Randomization, and for cellulitis, erysipelas, or infections that required hospitalization or intravenous antibiotics, within 8 weeks prior to Randomization.
16. Known history for hepatitis B or C or human immunodeficiency virus (HIV) infection, or positive testing for hepatitis B or C at Screening.
17. History of acute or chronic pancreatitis at Screening.
18. History of acute myocardial infarction (MI) or New York Heart Association III or IV congestive heart failure within 1 year prior to Randomization.
19. History of cardiac arrhythmia or long QT syndrome or electrocardiogram (ECG) abnormalities indicating safety risk at Screening.
20. Malignancy not cured within 5 years prior to Randomization.
  - a. Completely excised and cured basal cell carcinoma or cervical carcinoma *in situ* was permitted.
21. History of organ transplantation.
22. History of alcohol or substance abuse within 12 months of Screening.
23. Any clinically significant disease or disorder or laboratory abnormality which, in the opinion of the Investigator, would prevent the subject from completing the study or the interpretation of the study results at Screening and Randomization.

#### 13.4.3. Adverse event tables including individual PTs included in combined terms

**Table 39: Most common (reported by  $\geq 3\%$  of subjects in either treatment arm) treatment emergent adverse events, including *individual PTs* within the combined terms, Study SB16-3001, Main Period**

| Preferred Term        | SB16<br>(N=225) | EU-Prolia<br>(N=231) | Risk<br>Difference<br>(%) (95% CI) | Total<br>(N=456) |
|-----------------------|-----------------|----------------------|------------------------------------|------------------|
| Any TEAE (%)          | 159 (70.7)      | 164 (71.0)           | -0.3 (-8.7, 8)                     | 323 (70.8)       |
| Headache              | 18 (8.0)        | 10 (4.3)             | 3.7 (-0.7, 8.1)                    | 28 (6.1)         |
| Headache              | 16 (7.1)        | 10 (4.3)             | 2.8 (-1.5, 7)                      | 26 (5.7)         |
| Migraine              | 2 (0.9)         | 0                    | 0.9 (-0.3, 2.1)                    | 2 (0.4)          |
| Fracture              | 8 (3.6)         | 1 (0.4)              | 3.1 (0.6, 5.7)*                    | 9 (2.0)          |
| Ankle fracture        | 2 (0.9)         | 0                    | 0.9 (-0.3, 2.1)                    | 2 (0.4)          |
| Rib fracture          | 2 (0.9)         | 0                    | 0.9 (-0.3, 2.1)                    | 2 (0.4)          |
| Radius fracture       | 1 (0.4)         | 1 (0.4)              | 0 (-1.2, 1.2)                      | 2 (0.4)          |
| Foot fracture         | 1 (0.4)         | 0                    | 0.4 (-0.4, 1.3)                    | 1 (0.2)          |
| Forearm fracture      | 1 (0.4)         | 0                    | 0.4 (-0.4, 1.3)                    | 1 (0.2)          |
| Patella fracture      | 1 (0.4)         | 0                    | 0.4 (-0.4, 1.3)                    | 1 (0.2)          |
| Arthralgia            | 16 (7.1)        | 10 (4.3)             | 2.8 (-1.5, 7)                      | 26 (5.7)         |
| Arthralgia            | 16 (7.1)        | 9 (3.9)              | 3.2 (-1, 7.4)                      | 25 (5.5)         |
| Joint swelling        | 0               | 1 (0.4)              | -0.4 (-1.3, 0.4)                   | 1 (0.2)          |
| Vitamin D deficiency  | 11 (4.9)        | 5 (2.2)              | 2.7 (-0.7, 6.1)                    | 16 (3.5)         |
| Vitamin D deficiency  | 6 (2.7)         | 2 (0.9)              | 1.8 (-0.6, 4.2)                    | 8 (1.8)          |
| Vitamin D decreased   | 5 (2.2)         | 3 (1.3)              | 0.9 (-1.5, 3.3)                    | 8 (1.8)          |
| Dyslipidemia          | 13 (5.8)        | 8 (3.5)              | 2.3 (-1.5, 6.2)                    | 21 (4.6)         |
| Hypercholesterolemia  | 9 (4.0)         | 5 (2.2)              | 1.8 (-1.3, 5)                      | 14 (3.1)         |
| Type V hyperlipidemia | 1 (0.4)         | 0                    | 0.4 (-0.4, 1.3)                    | 1 (0.2)          |
| Dyslipidemia          | 2 (0.9)         | 2 (0.9)              | 0 (-1.7, 1.7)                      | 4 (0.9)          |

|                                                |          |           |                  |           |
|------------------------------------------------|----------|-----------|------------------|-----------|
| <i>Hyperlipidemia</i>                          | 1 (0.4)  | 1 (0.4)   | 0 (-1.2, 1.2)    | 2 (0.4)   |
| Hypertension                                   | 13 (5.8) | 8 (3.5)   | 2.3 (-1.5, 6.2)  | 21 (4.6)  |
| <i>Hypertension</i>                            | 10 (4.4) | 5 (2.2)   | 2.3 (-1, 5.6)    | 15 (3.3)  |
| <i>Blood pressure increased</i>                | 3 (1.3)  | 1 (0.4)   | 0.9 (-0.8, 2.6)  | 4 (0.9)   |
| <i>Essential hypertension</i>                  | 1 (0.4)  | 1 (0.4)   | 0 (-1.2, 1.2)    | 2 (0.4)   |
| <i>Accelerated hypertension</i>                | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| Diarrhea                                       | 8 (3.6)  | 3 (1.3)   | 2.3 (-0.6, 5.1)  | 11 (2.4)  |
| <i>Diarrhea</i>                                | 4 (1.8)  | 3 (1.3)   | 0.5 (-1.8, 2.7)  | 7 (1.5)   |
| <i>Colitis</i>                                 | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Enteritis</i>                               | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Food poisoning</i>                          | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Irritable bowel syndrome</i>                | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| Arthritis                                      | 13 (5.8) | 9 (3.9)   | 1.9 (-2.1, 5.8)  | 22 (4.8)  |
| <i>Osteoarthritis</i>                          | 10 (4.4) | 9 (3.9)   | 0.5 (-3.1, 4.2)  | 19 (4.2)  |
| <i>Arthritis</i>                               | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Nodal osteoarthritis</i>                    | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Spinal osteoarthritis</i>                   | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| Urinary tract infection                        | 16 (7.1) | 13 (5.6)  | 1.5 (-3, 6)      | 29 (6.4)  |
| <i>Urinary tract infection</i>                 | 12 (5.3) | 5 (2.2)   | 3.2 (-0.3, 6.7)  | 17 (3.7)  |
| <i>Urethritis</i>                              | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Cystitis</i>                                | 3 (1.3)  | 3 (1.3)   | 0 (-2.1, 2.1)    | 6 (1.3)   |
| <i>Dysuria</i>                                 | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Escherichia urinary tract infection</i>     | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Pyelonephritis</i>                          | 1 (0.4)  | 3 (1.3)   | -0.9 (-2.6, 0.8) | 4 (0.9)   |
| Respiratory tract infection                    | 15 (6.7) | 16 (6.9)  | -0.3 (-4.9, 4.4) | 31 (6.8)  |
| <i>Pneumonia</i>                               | 3 (1.3)  | 1 (0.4)   | 0.9 (-0.8, 2.6)  | 4 (0.9)   |
| <i>Viral upper respiratory tract infection</i> | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Upper respiratory tract infection</i>       | 11 (4.9) | 12 (5.2)  | -0.3 (-4.3, 3.7) | 23 (5.0)  |
| <i>Influenza</i>                               | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Lower respiratory tract infection</i>       | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Respiratory tract infection</i>             | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| Hemorrhage                                     | 7 (3.1)  | 9 (3.9)   | -0.8 (-4.2, 2.6) | 16 (3.5)  |
| <i>Epistaxis</i>                               | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Rectal hemorrhage</i>                       | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Vaginal hemorrhage</i>                      | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Blood urine present</i>                     | 1 (0.4)  | 1 (0.4)   | 0 (-1.2, 1.2)    | 2 (0.4)   |
| <i>Nevus hemorrhage</i>                        | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Hematuria</i>                               | 2 (0.9)  | 4 (1.7)   | -0.8 (-2.9, 1.2) | 6 (1.3)   |
| <i>Contusion</i>                               | 1 (0.4)  | 3 (1.3)   | -0.9 (-2.6, 0.8) | 4 (0.9)   |
| Alopecia                                       | 6 (2.7)  | 8 (3.5)   | -0.8 (-4, 2.4)   | 14 (3.1)  |
| COVID-19                                       | 17 (7.6) | 20 (8.7)  | -1.1 (-6.1, 3.9) | 37 (8.1)  |
| <i>COVID-19</i>                                | 16 (7.1) | 15 (6.5)  | 0.6 (-4, 5.2)    | 31 (6.8)  |
| <i>COVID-19 pneumonia</i>                      | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Asymptomatic COVID-19</i>                   | 1 (0.4)  | 5 (2.2)   | -1.7 (-3.8, 0.3) | 6 (1.3)   |
| Constipation                                   | 4 (1.8)  | 7 (3.0)   | -1.3 (-4.1, 1.6) | 11 (2.4)  |
| Back pain                                      | 22 (9.8) | 26 (11.3) | -1.5 (-7.1, 4.2) | 48 (10.5) |
| <i>Back pain</i>                               | 10 (4.4) | 8 (3.5)   | 1 (-2.6, 4.6)    | 18 (3.9)  |
| <i>Lumbar radiculopathy</i>                    | 3 (1.3)  | 2 (0.9)   | 0.5 (-1.4, 2.4)  | 5 (1.1)   |
| <i>Sciatica</i>                                | 5 (2.2)  | 5 (2.2)   | 0.1 (-2.6, 2.7)  | 10 (2.2)  |
| <i>Intervertebral disc protrusion</i>          | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Spinal pain</i>                             | 3 (1.3)  | 6 (2.6)   | -1.3 (-3.8, 1.3) | 9 (2.0)   |
| <i>Intervertebral disc disorder</i>            | 1 (0.4)  | 4 (1.7)   | -1.3 (-3.2, 0.6) | 5 (1.1)   |
| Nasopharyngitis                                | 14 (6.2) | 18 (7.8)  | -1.6 (-6.3, 3.1) | 32 (7.0)  |
| <i>Pharyngitis</i>                             | 3 (1.3)  | 2 (0.9)   | 0.5 (-1.4, 2.4)  | 5 (1.1)   |

|                                   |          |           |                  |           |
|-----------------------------------|----------|-----------|------------------|-----------|
| <i>Pharyngitis bacterial</i>      | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Rhinitis</i>                   | 1 (0.4)  | 3 (1.3)   | -0.9 (-2.6, 0.8) | 4 (0.9)   |
| <i>Nasopharyngitis</i>            | 10 (4.4) | 14 (6.1)  | -1.6 (-5.7, 2.5) | 24 (5.3)  |
| Abdominal pain                    | 7 (3.1)  | 11 (4.8)  | -1.7 (-5.2, 1.9) | 18 (3.9)  |
| <i>Abdominal distension</i>       | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Abdominal pain</i>             | 2 (0.9)  | 3 (1.3)   | -0.4 (-2.3, 1.5) | 5 (1.1)   |
| <i>Abdominal pain upper</i>       | 3 (1.3)  | 5 (2.2)   | -0.8 (-3.2, 1.6) | 8 (1.8)   |
| <i>Dyspepsia</i>                  | 2 (0.9)  | 4 (1.7)   | -0.8 (-2.9, 1.2) | 6 (1.3)   |
| Hypocalcemia                      | 22 (9.8) | 28 (12.1) | -2.3 (-8.1, 3.4) | 50 (11.0) |
| <i>Blood calcium decreased</i>    | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Hypocalcemia</i>               | 22 (9.8) | 27 (11.7) | -1.9 (-7.6, 3.8) | 49 (10.7) |
| Hypersensitivity                  | 6 (2.7)  | 12 (5.2)  | -2.5 (-6.1, 1)   | 16 (3.5)  |
| <i>Asthma</i>                     | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Eosinophil count increased</i> | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Hand dermatitis</i>            | 1 (0.4)  | 0         | 0.4 (-0.4, 1.3)  | 1 (0.2)   |
| <i>Acute phase reaction</i>       | 1 (0.4)  | 1 (0.4)   | 0 (-1.2, 1.2)    | 2 (0.4)   |
| <i>Pruritus</i>                   | 1 (0.4)  | 1 (0.4)   | 0 (-1.2, 1.2)    | 2 (0.4)   |
| <i>Angioedema</i>                 | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Dermatitis atopic</i>          | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Exfoliative rash</i>           | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Swelling of eyelid</i>         | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Urticaria chronic</i>          | 0        | 1 (0.4)   | -0.4 (-1.3, 0.4) | 1 (0.2)   |
| <i>Dermatitis allergic</i>        | 1 (0.4)  | 3 (1.3)   | -0.9 (-2.6, 0.8) | 4 (0.9)   |
| <i>Erythema</i>                   | 0        | 2 (0.9)   | -0.9 (-2.1, 0.3) | 2 (0.4)   |
| <i>Rash</i>                       | 0        | 2 (0.9)   | -0.9 (-2.1, 0.3) | 2 (0.4)   |
| Post vaccination syndrome         | 1 (0.4)  | 8 (3.5)   | -3 (-5.5, -0.5)* | 9 (2.0)   |

Source: MAED analysis using JMP clinical and grouped terms derived from FMQ analysis, clinical reviewer generated report

\* 95% confidence interval excludes zero

**Table 40: Most common (reported by  $\geq 3\%$  of subjects in either treatment arm) treatment emergent adverse events, including *individual PTs* within the combined terms, Study SB16-3001, Transition Period**

| Preferred term              | EU-Prolia+SB16<br>(N=100) | SB16+SB16<br>(N=206) | EU-<br>Prolia+EU-<br>Prolia<br>(N=101) | Risk Difference<br>Prolia+SB16 -<br>SB16+SB16<br>(%) (95% CI) | Risk Difference<br>Prolia+SB16 -<br>EU-Prolia+EU-<br>Prolia<br>(%) (95% CI) | Total<br>(N=407) |
|-----------------------------|---------------------------|----------------------|----------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------|------------------|
| Any AE (%)                  | 29 (29.0)                 | 73 (35.4)            | 35 (34.7)                              | -6.4 (-17.4, 4.6)                                             | -5.7 (-18.5, 7.2)                                                           | 137 (33.7)       |
| Vitamin D Deficiency        | 7 (7.0)                   | 6 (2.9)              | 2 (2.0)                                | 4.1 (-1.4, 9.6)                                               | 5 (-0.7, 10.7)                                                              | 15 (3.7)         |
| <i>Vitamin D deficiency</i> | 5 (5.0)                   | 5 (2.4)              | 2 (2.0)                                | 2.6 (-2.2, 7.3)                                               | 3 (-2, 8.1)                                                                 | 12 (2.9)         |
| <i>Vitamin D decreased</i>  | 2 (2.0)                   | 1 (0.5)              | 0                                      | 1.5 (-1.4, 4.4)                                               | 2 (-0.7, 4.7)                                                               | 3 (0.7)          |
| Hemorrhage                  | 3 (3.0)                   | 0                    | 0                                      | 3 (-0.3, 6.3)                                                 | 3 (-0.3, 6.3)                                                               | 3 (0.7)          |
| <i>Contusion</i>            | 2 (2.0)                   | 0                    | 0                                      | 2 (-0.7, 4.7)                                                 | 2 (-0.7, 4.7)                                                               | 2 (0.5)          |
| <i>Hematuria</i>            | 1 (1.0)                   | 0                    | 0                                      | 1 (-1, 3)                                                     | 1 (-1, 3)                                                                   | 1 (0.2)          |
| Headache                    | 3 (3.0)                   | 5 (2.4)              | 2 (2.0)                                | 0.6 (-3.4, 4.5)                                               | 1 (-3.3, 5.3)                                                               | 10 (2.5)         |
| <i>Tension headache</i>     | 1 (1.0)                   | 0                    | 0                                      | 1 (-1, 3)                                                     | 1 (-1, 3)                                                                   | 1 (0.2)          |
| <i>Headache</i>             | 2 (2.0)                   | 5 (2.4)              | 2 (2.0)                                | -0.4 (-3.9, 3)                                                | 0 (-3.8, 3.9)                                                               | 9 (2.2)          |
| Arthralgia                  | 1 (1.0)                   | 7 (3.4)              | 2 (2.0)                                | -2.4 (-5.5, 0.8)                                              | -1 (-4.3, 2.4)                                                              | 10 (2.5)         |
| Dyslipidemia                | 1 (1.0)                   | 9 (4.4)              | 2 (2.0)                                | -3.4 (-6.8, 0)                                                | -1 (-4.3, 2.4)                                                              | 12 (2.9)         |
| <i>Hyperlipidemia</i>       | 0                         | 1 (0.5)              | 0                                      | -0.5 (-1.4, 0.5)                                              | 0                                                                           | 1 (0.2)          |

## Biosimilar Multi-disciplinary Evaluation and Review (BMER)

| Preferred term                            | EU-Prolia+SB16<br>(N=100) | SB16+SB16<br>(N=206) | EU-<br>Prolia+EU-<br>Prolia<br>(N=101) | Risk Difference<br>Prolia+SB16 -<br>SB16+SB16<br>(%) (95% CI) | Risk Difference<br>Prolia+SB16 -<br>EU-Prolia+EU-<br>Prolia<br>(%) (95% CI) | Total<br>(N=407) |
|-------------------------------------------|---------------------------|----------------------|----------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------|------------------|
| <i>Hypercholesterolemia</i>               | 1 (1.0)                   | 7 (3.4)              | 1 (1.0)                                | -2.4 (-5.5, 0.8)                                              | 0 (-2.7, 2.8)                                                               | 9 (2.2)          |
| <i>Dyslipidemia</i>                       | 0                         | 1 (0.5)              | 1 (1.0)                                | -0.5, -1.4, 0.5)                                              | -1 (-2.9, 0.9)                                                              | 2 (0.5)          |
| Back Pain                                 | 1 (1.0)                   | 3 (1.5)              | 3 (3.0)                                | -0.5 (-3, 2.1)                                                | -2 (-5.8, 1.9)                                                              | 7 (1.7)          |
| <i>Sciatica</i>                           | 1 (1.0)                   | 1 (0.5)              | 1 (1.0)                                | 0.5 (-1.7, 2.7)                                               | 0 (-2.7, 2.8)                                                               | <i>Sciatica</i>  |
| <i>Lumbar radiculopathy</i>               | 0                         | 1 (0.5)              | 0                                      | -0.5 (-1.4, 0.5)                                              | 0                                                                           | 1 (0.2)          |
| <i>Lumbosacral<br/>radiculopathy</i>      | 0                         | 1 (0.5)              | 0                                      | -0.5 (-1.4, 0.5)                                              | 0                                                                           | 1 (0.2)          |
| <i>Back pain</i>                          | 0                         | 0                    | 1 (1.0)                                | 0                                                             | -1 (-2.9, 0.9)                                                              | 1 (0.2)          |
| <i>Intervertebral disc<br/>protrusion</i> | 0                         | 0                    | 1 (1.0)                                | 0                                                             | -1 (-2.9, 0.9)                                                              | 1 (0.2)          |
| Nasopharyngitis                           | 1 (1.0)                   | 3 (1.5)              | 5 (5.0)                                | -0.5 (-3, 2.1)                                                | -4 (-8.6, 0.7)                                                              | 9 (2.2)          |
| <i>Rhinitis</i>                           | 0                         | 2 (1.0)              | 0                                      | -1 (-2.3, 0.4)                                                | 0                                                                           | 2 (0.5)          |
| <i>Pharyngitis</i>                        | 0                         | 0                    | 1 (1.0)                                | 0                                                             | -1 (-2.9, 0.9)                                                              | 1 (0.2)          |
| <i>Nasopharyngitis</i>                    | 1 (1.0)                   | 1 (0.5)              | 4 (4.0)                                | 0.5 (-1.7, 2.7)                                               | -3 (-7.2, 1.3)                                                              | 6 (1.5)          |

Source: MAED analysis using JMP clinical and grouped terms derived from FMQ analysis, clinical reviewer generated report

\* 95% confidence interval excludes zero

#### 13.4.4. Injection site reaction scoring

**Figure 9: Global irritation score for injection site reactions**

**Redness**

**Grade Description**

0 = NONE: No visible redness

1 = MILD:  $\leq 2$  cm redness

2 = MODERATE:  $> 2$  to  $\leq 5$  cm redness

3 = SEVERE:  $> 5$  cm redness

**Bruising**

**Grade Description**

0 = NONE: No visible bruising

1 = MILD:  $\leq 2$  cm bruising

2 = MODERATE:  $> 2$  to  $\leq 5$  cm bruising

3 = SEVERE:  $> 5$  cm bruising

**Swelling**

**Grade Description**

0 = NONE: No swelling detected

1 = MILD: Palpable 'firmness' only

2 = MODERATE:  $\leq 4$  cm swelling

3 = SEVERE:  $> 4$  cm swelling

**Itching**

**Grade Description**

0 = NONE

1 = MILD

2 = MODERATE

3 = SEVERE

**Pain**

**Grade Description**

0 = NONE

1 = MILD

2 = MODERATE

3 = SEVERE

Source: Study SB16-1001 protocol, version 5, Appendix I, page 64, submitted to DARRTS November 17, 2021, under IND 141802

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/s/  
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