CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761392Orig1s000
761392Orig2s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary Review Addendum
Assessment Number: First Round
Assessment Date: 11/13/2024
Addendum Date: 02/07/2025
Revised to incorporate the final inspection recommendation to the Quality Executive Summary of November 13, 2024

BLA number	761392
Drug name/Dosage Form	Ospomyv and Xbryk (denosumab-dssb) injection
Strength	60 mg/mL (PFS); 120 mg/1.7 mL (Vial)
Route of Administration	Subcutaneous injection
Rx/OTC	Rx
Indication	All indications currently approved for US-licensed Prolia and US-licensed Xgeva
Applicant	Samsung Bioepis Co., Ltd.

Quality Executive Summary Review Addendum

The Integrated Quality Assessment (IQA) filed on November 13, 2024, provided a preliminary recommendation pending the outcome of the pre-license inspection (PLI) for the drug substance manufacturer at Samsung Biologics Co. (FEI#3010479596), and drug product manufacturing site at (b) (4) (FEI# (b) (4)) as well as the CGMP inspection at Samsung Bioepis (FEI# 3010031951). This IQA Addendum summarizes the outcome of the PLI and CGMP inspection, summarizes the final Facilities recommendation, and provides a final **approval recommendation** from the OPQ team. The updated review sections are below, with key changes highlighted in red text. Refer to the November 13, 2024, Quality Executive Summary memo for all other review sections and recommendations for the action letter.

1. **Recommendation and Conclusion on Approvability**
   Recommendation: Approval

   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 pure and potent. The comparative analytical data support a demonstration that SB16 is highly similar to US-licensed Prolia (US Prolia) and US-licensed Xgeva (US 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.

Establishment Information:

Functions	Site information	FEI Number	Inspectional Observation	Final Recommendation
Manufacturing of DS QC release testing	Samsung Biologics Co. Ltd 300, Songdo bio-daero, Yeonsu-gu, Incheon, 21987, Republic of Korea	3010479596	8-item FDA Form 483 was issued	Approve based on inspection
Manufacturing of cell banks (MCB and WCB)	(b) (4)		N/A	Approve - Based on Previous History
MCB and WCB storage			N/A	No evaluation necessary
MCB and WCB storage			N/A	Approve - Based on Previous History
In-process testing	Samsung Bioepis Co., Ltd 76, Songdogyoyuk-ro, Yeonsu-gu, Incheon, 21987 Republic of Korea	3010031951		Approve based on inspection
QC release testing (DS and DP)	(b) (4)		N/A	Approve - Based on Previous History
DS storage			N/A	No evaluation necessary
Drug Product (DP)				
DP (Prefilled syringe)				
Manufacturing of bulk DP and QC release testing of bulk DP	(b) (4)		9-item FDA Form 483 was issued	Approve based on inspection
Labeling, assembly, and packaging			N/A	No evaluation necessary
DP (Vial)				
Manufacturing of bulk DP, QC release testing, Storage, Labeling and packaging	Samsung Biologics Co. Ltd. 300 Songdobaiodae-Ro, Yeonsu, 21987, Republic of Korea,	3010479596	8-item FDA Form 483 was issued	Approve based on inspection
Storage of bulk DP	(b) (4)		N/A	No evaluation necessary
Labeling and packaging			N/A	Approve - Based on Previous History

Facilities: Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for the proposed DS manufacturing (Samsung Biologics, FEI# 3010479596), PFS DP manufacturing ([redacted] (b) (4) FEI# [redacted] (b) (4)), vial DP manufacturing (Samsung Biologics, FEI# 3010479596), and QC testing (Samsung Bioepis, FEI# 3010031951). All proposed manufacturing and testing facilities are acceptable based on pre-license inspection, acceptable CGMP compliance status, and recent relevant inspectional coverage, as applicable.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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/s/

SAMUEL MINDAYE
02/07/2025 11:36:14 AM

BLA Executive Summary
Assessment Date: 11/13/2024

1. Application/Product Information

BLA number	761392
Submission Type	Original submission
Regulatory Pathway	Interchangeable Biosimilar Application 351(k)
Associated IND/BLA	PIND 141802 Refer to meeting minutes dated Mar 21, 2019, Nov 18, 2021, and Oct 23, 2023, for BPD Type 2 and 4 meetings held between the applicant and the Agency.
Review Designation	Standard review
Applicant	Samsung Bioepis Co., Ltd.
Indication	All indications currently approved for US-licensed Prolia and US-licensed Xgeva
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** OSPOMYV and XBRYK (Proposed)
	Non-proprietary Name: Denosumab-xxxx
	Code name: SB16
	OBP Naming: MAB HUMAN (IGG2) ANTI TNF11_HUMAN [SB16]

Drug Product Description	SB16 is a human monoclonal immunoglobulin G2 antibody (IgG2) is produced in a Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology. SB16 targets and binds to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts, thereby decreasing bone resorption in cortical and trabecular bone. 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). • Each single dose vial contains 120 mg ((b) (4) /1.7mL) SB16, 0.44 mg histidine, 6.53 mg histidine hydrochloride monohydrate, 0.17 mg polysorbate 20, 74.8 mg sorbitol, Water for Injection (USP), pH 5.2. • Each single dose prefilled syringe (PFS) contains 60 mg/1.0mL denosumab-xxxx, 0.28 mg histidine, 3.81 mg histidine hydrochloride monohydrate, 0.1 mg polysorbate 20, 44.00 mg sorbitol, Water for Injection (USP), pH 5.2.		
Dosage Form	Injection (solution)		
Strength	60 mg/mL (PFS); 120 mg/1.7 mL (Vial)		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	**Vial:** (b) (4) glass vial (2mL), a 13 mm rubber stopper and 13 mm aluminum flip-off cap **PFS:** glass syringe with staked needle, rigid needle shield, and a plunger stopper.		
Device Information	Needle safety device ((b) (4)) assembled with PFS		
Co-packaged Product Information	N/A		
	Discipline	**Primary**	**Secondary**

OPQ Review Team	Drug substance	Xuhong Li	Samuel Mindaye
	Drug product		
	Comparative Analytical Assessment (CAA)		
	Immunogenicity Assay	Gunther Boekhoudt	
	Facility/Microbiology	Liqun Zhao (Drug Substance) Andrea Franco (Drug Product)	Zhong Li (facility) Maxwell Van Tassell (Microbiology)
	RBPM	Kristine Leahy	
	ATL	Samuel Mindaye	
OPQ Issued Consults	CDRH consult ICCR# 00974458		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval pending the outcome of pre-license inspection

Pending the outcome of the pre-license inspection (PLI), 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 pure and potent. The comparative analytical data support a demonstration that SB16 is highly similar to US-licensed Prolia (US Prolia) and US-licensed Xgeva (US 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, following recommendation of the PLI, for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:**

  Samsung Biologics (FEI: 3010479596)

300, Songdo bio-daero,
Yeonsu-gu, Incheon, 21987, Republic of Korea

- **Drug Product:**
  - **PFS:** (b) (4)
  - **Vial:** Samsung Biologics (FEI: 3010479596)
    300, Songdo bio-daero,
    Yeonsu-gu, Incheon, 21987,

b. Fill size and dosage form:

- Single dose vial: supplied as a 120 mg/1.7 mL solution in a single dose vial.
- PFS: supplied as a 60 mg/mL solution in a single dose prefilled syringe assembled with a needle safety device.

c. Dating Period:

- **Drug Product:** Vial: 36 months when stored at 5 ± 3°C protected from light.
  PFS: 36 months when stored at 5 ± 3°C protected from light.
- **Drug Substance:** (b) (4) when stored at ≤ (b) (4) °C (b) (4)
- **Stability Option:**
  - For stability protocols:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the process performance qualification lots.
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes, SB16 is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments (PMCs), Requirements, Agreements, and/or Risk Management Steps, as applicable: None

4. Basis for Recommendation

a. Summary:

SB16 PFS and vial (denosumab-xxxx) are developed as a proposed interchangeable biosimilar to US Prolia and US Xgeva (denosumab), respectively, for the same strength, dosage form, indications, and route of administration as for the 60 mg/mL solution PFS (US Prolia) and 120 mg/1.7 mL solution single use vial (US Xgeva). SB16 is a recombinant human monoclonal antibody IgG2 that targets and binds with high affinity and specificity to the transmembrane or soluble protein receptor activator of nuclear factor-κB-ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. RANKL is essential for the formation, function and survival of osteoclasts, the sole cell type responsible for bone resorption. Therefore, prevention of the RANKL/RANK interaction inhibits osteoclast formation,

function, and survival, thereby decreasing bone resorption and cancer-induced bone destruction.

Potency of the SB16 in PFS and vial is assessed using two bioassays: (i) ELISA to measure its RANKL binding activity and (ii) cell-based RANKL neutralization assay to measure its blockade activity. ELISA measures the relative binding of SB16 to RANKL coated on a plate. SB16 bound to RANKL are detected using anti-human IgG (Fc specific)-peroxidase antibody. The cell-based RANKL neutralization assay uses an ProRANK cell line that are genetically engineered to overexpress RANK and to have luciferase reporter gene system. In the cell-based assay system, when RANK signaling pathways are activated by RANKL, luminescence signal can be detected by luciferase reporter gene expression. The relative RANKL neutralization activity of SB16 can be determined by measuring the expression level of luciferase using a luminescent based detection system. All potency results are reported as percentage relative to a qualified reference material.

The totality of the CAA evidence supports that SB16 is highly similar to US Prolia and US Xgeva, notwithstanding minor differences in clinically inactive components. The analytical component of the scientific bridge was established to support the use of EU Prolia as a comparator in clinical studies supporting this application. The strength of 60 mg/mL SB16 PFS and 120 mg/1.7 mL single dose SB16 vial demonstrated the same strength as that of US Prolia and US Xgeva, respectively in the same presentation. Refer to the Appendix for a summary of the CAA.

Manufacturing of SB16 drug substance (DS) by Samsung Biologics is initiated by

The overall SB16 process control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The manufacturing

processes and overall control strategies for SB16 as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for the proposed DS manufacturing (Samsung Biologics, FEI# 3010479596)), PFS DP manufacturing (b) (4) FEI# (b) (4)), and vial DP manufacturing (Samsung Biologics, FEI# 3010479596). The proposed DS and DP manufacturing and testing facilities are under review based on the recent relevant inspectional coverage. Pending the outcome of the pre-license inspection, the BLA is approvable from product quality, facility, microbiology, and sterility assurance perspectives. Individual assessments for each discipline are located in separate documents in panorama.

In addition, CDRH recommends approval for the device constituent parts of the combination product (see review by Papatya Kaner in panorama).

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assays	**-**	**Adequate**
CAA	**-**	**Adequate**
Facilities	**-**	**Pending**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for SB16 PFS and vial DP (i.e., there is no specific test method described in regulation for SB16 that establishes an official standard of potency). We next considered whether potency is a factor for SB16 within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for SB16 for purposes of § 610.61(r) because lot variability is not a concern for SB16 as SB16 manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

1. (b) (4)
2.
3.
4.
5.
6.

ii. Residual risk: None
iii. Future inspection points to consider: Refer to PLI recommendation.

c. Drug Product:

i. Protocols approved:
   - Post-approval annual stability protocol and stability protocol for the extension of drug product shelf-life

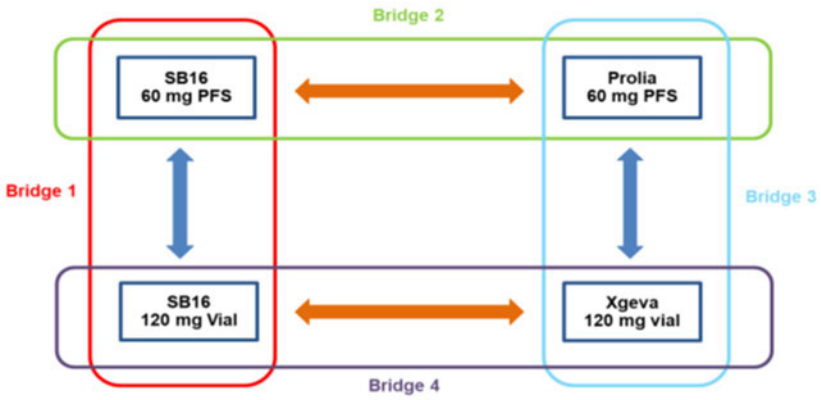
ii. Residual risk: None
iii. Future inspection points to consider: Refer to PLI recommendation.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

APPENDIX. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

Samsung Bioepis proposed SB16, provided in both a single-dose PFS (60 mg/mL) and a single-dose vial (120 mg/1.7 mL) presentations, as an interchangeable biosimilar to the US Prolia and US Xgeva (denosumab) reference products, respectively. SB16 has the same strength, dosage form and route of administration to the reference products. To demonstrate that SB16 is highly similar to US Prolia and US Xgeva, notwithstanding minor differences in clinically inactive components, and to support the relevance of clinical data generated using EU Prolia to the assessment of biosimilarity, Samsung Bioepis submitted the comparative analytical assessment (CAA) that includes similarity assessment between SB16, US Prolia and EU Prolia and between SB16 and US Xgeva. The supporting quality bridging studies summarized below was incorporated in the CAA design to address the comparability between SB16 PFS and SB16 vial presentations, and the absence of clinical studies between SB16 vial and US-Xgeva.



Bridge 1: Comparability studies with SB16 PFS and SB16 vial
Bridge 2: Similarity studies with SB16 PFS and Prolia
Bridge 3: Comparability studies with Prolia and Xgeva
Bridge 4: Similarity studies with SB16 vial and Xgeva

The CAA design was consistent with the FDA Guidance for Industry, *Development of Therapeutic Protein Biosimilar: Comparative Analytical Assessment and Other Quality-Related Considerations, May 2019*. As part of the assessment, an extensive analytical characterization of SB16 (PFS and vial), EU Prolia and US Prolia and US Xgeva was performed, which included comparisons of primary structure, post-translational modifications, glycan profiles, purity, product-related variants, higher order structure, protein concentration, and biological function properties of quality attributes (Table 1). Samsung Bioepis used a risk-based approach for the analysis of the CAA results: high risk quality attributes (e.g., RANKL binding assay and anti-differentiation assay) and moderate risk quality attributes (e.g., protein concentration, primary structure, charge variants, aggregates, and fragments) were evaluated using quality ranges (QRs) of mean ± standard deviation with multipliers 2.6 and 3, respectively, established from US Prolia and EU Prolia, or US Xgeva. The multipliers have been scientifically justified. The analytical similarity is considered to have been demonstrated if 90% or greater of data points for the test products were within the quality range of US Prolia and EU-Prolia, or US-Xgeva. The

raw data/graphical comparisons were evaluated when those quality attributes cannot be quantitatively measured. Each attribute was assessed to support a demonstration that SB16 is highly similar to US Prolia and US Xgeva.

For PFS presentation, seven independent SB16 batches (one DS, three PPQ, and three clinical DP batches), 35 US Prolia batches, and 68 EU Prolia batches were used in the CAA. For the vial presentation, seven independent SB16 batches (one DS, three PPQ, and three clinical DP batches) and 17 US Xgeva batches were included in the CAA. The lots were selected from a range of expiration dates and product ages to adequately capture lot-to-lot variability. SB16 lots were manufactured between February 2020 and September 2023. The expiration dates for US Prolia lots were between Jun 2018 to Jul 2024, US Xgeva have expiry dates ranged from Jun 2019 to May 2024, and EU Prolia lots expire between Oct 2017 to May 2025. All tests were performed before the labeled expiry date. All SB16 and EU-Prolia lots used in the clinical studies were also included in the CAA. When necessary, results are reported relative to a reference standard and data were provided to adequately qualify and bridge the reference standards.

In addition, the CAA included comparative stability studies, which evaluated the stability profile (i.e., degradation pathways and rates) between SB16 PFS, US Prolia, and EU Prolia as well as between SB16 vial and US-Xgeva under stress conditions (heat, basic, acidic, oxidative, and photo-stress) using orthogonal stability-indicating methods. The quality attributes and stress conditions were supported by development studies and risk assessments. The comparative stability studies demonstrate that SB16 (PFS and vial presentation) has similar degradation profile to that of US Prolia and US Xgeva or EU- Prolia.

In conclusion, Samsung Bioepis performed an adequate CAA that evaluated a comprehensive array of quality attributes relevant to SB16, US Prolia, EU-Prolia and US Xgeva by appropriate methods. They employed an appropriate data analysis plan and selected appropriate lots for the assessment. Although some differences are observed in a limited number of quality attributes, the results from this assessment, which are described below, these do not preclude a demonstration that SB16 is highly similar to US Prolia and US-Xgeva, notwithstanding minor differences in clinically inactive components.

Additionally, the pairwise comparisons of SB16, US Prolia, EU Prolia were used to establish the analytical component of the scientific bridge to support the relevance of the data generated from clinical studies using EU Prolia as the comparator to the assessment of biosimilarity. Samsung Bioepis supported the establishment of the analytical component of the scientific bridge using the same methods and statistical approaches used to support the demonstration that SB16 is highly similar to US-Prolia and US-Xgeva. Based on review of the data, we conclude that the analytical component of the scientific bridge was established.

Refer to Section E – Same Strength(s) below for addition comments regarding the comparison of strength, dosage form, and route of administration between SB16 and US- Prolia and US-Xgeva.

B. Results of Comparative Analytical Assessment

The results from the CAA are summarized in Table 1 below. While not illustrated in the table below, the stability profile of SB16 was demonstrated to be similar to US Prolia and US Xgeva.

Table 1. Quality Attributes Analyzed in the Comparative Analytical Assessment

Physico-chemical/Functional Characteristics	Quality Attribute Assessed		Test Method	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
Primary Structure and post-translational modifications	Molecular weight		LC-ESI-MS	Yes	Yes
	Amino acid sequence			Yes	Yes
	peptide mapping			Yes	Yes
	N-terminal sequence			Yes	Yes
	C-terminal sequence			Yes	Yes
	Oxidation			Yes	Yes
	Deamidation			Yes	Yes
	Extinction coefficient		SEC-MALS	Yes	Yes
Glycation & Glycosylation	N-linked glycosylation site		LC-ESI-MS	Yes	Yes
	N-linked glycan identification		Procainamide labeling by LC-ESI-MS	Yes	Yes
	N-Glycan profile	Charged glycan		Yes	Yes
		Galactosylated		Yes	Yes
		High Mannose		Yes	Yes
Purity and product-related variants	Size heterogeneity	Monomer	SE-HPLC	Yes	Yes
		HMW species		Yes	Yes
		%IgG	Non-reduced CE-SDS	Yes	Yes
		%2H1L		Yes	Yes
		%LC+%HC	reduced CE-SDS	Yes	Yes
		%NGHC		Yes	Yes
		%Main	RP-UPLC	Yes	Yes
		%Post-main		Yes	Yes
	Charge heterogeneity	Main species	icIEF/ CEX-HPLC	Yes	Yes
		Acidic species		Yes	Yes
		Basic species		Yes	Yes
Higher order structure and biophysical properties	Disulfide bonds		LC-ESI-MS	Yes	Yes
	Free sulfhydryl group quantification		Measure-IT Thiol assay	Yes	Yes
	Secondary and tertiary structure Thermal stability, and aggregate characterization		CD	Yes	Yes
			ITF	Yes	Yes
			FTIR	Yes	Yes
			DSC	Yes	Yes
			SEC-MALS	Yes	Yes
			H/DX-MS	Yes	Yes
			DLS	Yes	Yes

Physico-chemical/Functional Characteristics	Quality Attribute Assessed	Test Method	Supports a Demonstration of Highly Similar	Supports the Analytical Component of the Scientific Bridge
		Micro-Flow Imaging (MFI)	Yes	Yes
		SV-AUC	Yes	Yes
Quantity	Protein concentration	SoloVPE	Yes	Yes
Biological properties/ Fc Binding	RANKL binding	ELISA	Yes	Yes
	Anti-differentiation assay	Cell-based assay	Yes	Yes
	RANKL neutralization assay		Yes	Yes
	FcRn binding affinity		Yes	Yes
	FcγRIa Binding Affinity	SPR	Yes	Yes
	FcγRIIa Binding Affinity		Yes	Yes
	FcγRIIb binding		Yes	Yes
	FcγRIIIa binding		Yes	Yes
	Membrane bound (mRANKL) binding activity	Cell-based assay	Yes	Yes
	C1q binding	ELISA	Yes	Yes
	ADCC activity	Cell-based assay	Yes	Yes
	CDC activity		Yes	Yes

Comparative assessment of the forced degradation stability studies was performed to evaluate potential differences in the degradation profiles between SB16 PFS, US Prolia and EU Prolia, and between SB16 Vial and US Xgeva lots when stored under thermal stress (40 ± 2 °C/75 ± 5% RH for 3 months), acidic stress (pH 4.0, 25±2ºC for up to 3 days), basic stress (pH 7.0, 25 ± 2ºC for up to 3 days), oxidative stress (Hydrogen peroxide 0.05 %, 2-8 °C 6 hours), and photo stress (UV >200 w/m2·hr, 25 ± 2.5 °C, 60 ± 5 % RH and cool white fluorescent light > 1.2 million lux hours). Considering the data and justifications for the minor differences observed, the results do not preclude a demonstration that SB16 is highly similar to US- Prolia and US Xgeva.

C. Analytical Studies to Support the Use of a Non-US Licensed Comparator Product

The clinical development program to support the interchangeability of SB16 included the following clinical studies:

- Study SB16-1001: Randomized, double-blind, three-arm, parallel group, single-dose (60 mg), PK similarity study in healthy adult subjects comparing SB16, US-Prolia and EU-Prolia.
- Study SB16-3001: Randomized, double-blind, multi-center, active-controlled comparative clinical study comparing efficacy, safety, and immunogenicity in female subjects with postmenopausal osteoporosis comparing SB16 with EU-Prolia.

Based on the data provided to support pairwise analytical similarity between SB16, US Prolia, and EU Prolia, based on comparative structural, physicochemical, and biological studies, an adequate analytical component of the scientific bridge between the pairs, which justifies the

relevance of the clinical data generated using EU- Prolia as the comparator product. For the CAA studies, the same analytical methods used for all the paired assessments. The differences observed in a subset of quality attributes in the CAA (See section D below) do not preclude a demonstration that the analytical component of the scientific bridge is established.

D. Assessment of Comparative Analytical Study Results

Of the quality attributes listed in Table 1 above, some physicochemical test results did not meet the pre-determined similarity acceptance criteria for the attribute (i.e., at least 90% of SB16 lots must be within the quality range) or showed variable results in qualitative assessments Section 3.2.R.4 in eCTD Module 3; however, adequate justification has been provided that the differences observed do not preclude a demonstration that SB16 is highly similar to US Prolia and US Xgeva, or the establishment of the analytical component of the scientific bridge. These instances are described below:

Molecular weight: based on UPLC-MS analysis of intact (glycosylated) and deglycosylated SB16, US and EU Prolia, slight difference observed in molecular weight of the glycosylated forms between SB16 PFS and US Prolia. Similar observation was noted for paired assessment of SB16 vial and US Xgeva. The slight difference was because SB16 does not have 2 G0F and 2 Galactose that were detected in US Prolia, US Xgeva, and EU Prolia. However, as discussed below the relative contents of galactosylation have not been specifically associated with adverse safety or efficacy outcomes and thus this small difference in intact molecular weight is clinically insignificant to preclude a demonstration that SB16 is highly similar to US Prolia and US Xgeva, or the establishment of the analytical component of the scientific bridge.

C-terminal Sequence: The C-terminal posttranslational modifications were assessed by LC-ESI-MS and the detected masses of C-terminal peptides in the HC and LC were consistent with theoretical masses in SB16, US Prolia, US Xgeva and EU Prolia. Denosumab has predominantly intact C-terminus (>97%) in all the tested samples. However, the level of the C-terminal lysine in SB16 PFS was slightly higher than in Prolia (2.1-2.6% in SB16 PFS vs 0.2-0.4% in US and EU Prolia). Similarly, the relative content of the Lys variant for SB16 vial was higher than in Xgeva (1.8-2.7% in SB16 vs 0.2-0.3% in US Xgeva). It has been widely reported that C-terminal lysine variants do not generally have an impact on safety and efficacy as the residual C-terminal lysine is shown to get rapidly cleaved off by carboxypeptidase present in the bloodstream. Furthermore, since Fc effector functions are not relevant to the biological activities of denosumab, the small difference in C-terminal lysine variant level is deemed not to impact on biological activities of SB16, which is also demonstrated by the biological activity comparison. In addition, α-amidated form on the C-terminal end was only detected in SB16 (0.2-0.4%). This is a minor variant and the α-amidated form is observed in endogenous human IgGs, indicating that small amount of the variant present in therapeutic IgGs does not pose a safety concern. Overall, the difference observed in C-terminal sequence variants was not considered significant and do not preclude a demonstration that SB16 is highly similar to US Prolia and US Xgeva, or the establishment of the analytical component of the scientific bridge.

Oxidation: The relative oxidation contents of methionine (Met) residues in SB16, US Prolia, US Xgeva, and EU Prolia were analyzed by LC-ESI-MS. Seven Met residues in the heavy chain

(Met34, Met83, Met106, Met253, Met359, Met398 and Met429) were detected as major oxidation sites. The oxidation level of Met253 for SB16 was slightly lower than those for US and EU Prolia (2.1-2.9% in SB16 while 4.9-6.4% Met253 oxidation observed in US and EU Prolia). Similarly, the oxidation level of Met253 for the SB16 was slightly lower than those for US Xgeva. Specifically, 2.1-4.1% Met253 oxidation in SB16 and 5.0-5.7% Met253 oxidation observed in US Xgeva. Overall, the oxidation level and magnitude of difference is not substantial and there was no statistical difference in RANKL binding activity between SB16, US Prolia, EU Prolia and US Xgeva. Thus, the slight difference observed in oxidation contents was not considered clinically significant and does not preclude a demonstration that SB16 is highly similar to US Prolia and US Xgeva, or the establishment of the analytical component of the scientific bridge.

N-Glycans: the glycan moieties were assessed from digested samples using LC-ESI-MS following procainamide labeling. The comparative analysis revealed there is overwhelmingly comparable profiles (total of 29 N-glycan peaks). The overall high mannose content (M5, M6, M7‘, M7, M8’’, M8’, M8) between SB16, US and EU Prolia, and US Xgeva is comparable, for example, SB16 (6.9-10.3%), US Prolia (6.8-9.5%) and EU Prolia (6.2-10.2%). Nevertheless, the M9 species were detected only in SB16, albeit in small amount, but not in US Prolia, US Xgeva and EU Prolia. Given there was no statistically significant difference in FcRn binding activity between SB16 and US Prolia, US Xgeva, and EU Prolia and M9 form is cleaved by the mannosidase in the cell, the small difference in the N-glycan species in M9 is unlikely to have any clinical significance or to preclude a demonstration that SB16 is highly similar to US Prolia and US Xgeva, or the establishment of the analytical component of the scientific bridge.

Galactosylation: assessment of SB16, US Prolia, US Xgeva, and EU Prolia treated using PNGase F followed by labeling with 2-aminobenzamide (2-AB) revealed all evaluated N-glycan species of SB16 (%High mannose, %Charged glycan, and %Galactosylation) were within the similarity ranges of US Prolia, EU Prolia and US Xgeva although there were some differences in the content of %Galactosylation. Specifically, the %Galactosylation for SB16 were lower (ranges 10.5 – 11.6%) than US Prolia range (15.2-33.8) and EU Prolia range (12.8-35.8). Similarly, %Galactosylation for SB16 were lower than the US Xgeva range (difference of about 0.8-1.7%). Overall, the observed Galactosylation difference (<5% below the QR) is not expected to have clinically meaningful impact in activity for reasons including, (a) Fc effector function is not part of MOA of denosumab; and (b) the FcRn binding activity of the SB16 is confirmed to be similar to US and EU Prolia.

In addition, recent studies[1] indicate that galactosylation may play a role in antibody clearance. Antibodies containing lower galactosylation are cleared more rapidly than those containing more galactosylation. There is currently no known bioactivity assay that can assess the impact of differences in galactosylation on the PK of mAbs. The results from the PK similarity study SB16-1001, considered in the context of other information submitted by the Applicant and the publicly

[1] Literature reference is made to the following two articles:
i. David Falck et al. Glycoform-resolved pharmacokinetic studies in a rat model employing glycoengineered variants of a therapeutic monoclonal antibody. MABS 2020, VOL. 13, NO. 1, e1865596.
ii. David Falck et al. Clearance of therapeutic antibody glycoforms after subcutaneous and intravenous injection in a porcine model. MABS 2022, VOL. 14, NO. 1, e2145929.

available literature, have provided a framework for evaluating the acceptable range of the differences observed in the comparative analytical assessment.

Taken together, the observed difference in galactosylation is not expected to have significant impact on product quality and do not preclude a demonstration that SB16 is highly similar to US Prolia and US Xgeva, or the establishment of the analytical component of the scientific bridge.

Hydrophobicity and disulfide bond variants: the purity of SB16, US Prolia, EU Prolia or US Xgeva was comparatively assessed side-by-side using CE-SDS (non-reduced) electropherograms and RP-HPLC chromatograms. Overall, the main peak area of SB16 is similar (within the QR) of US Prolia, EU Prolia or US Xgeva, although there were some differences in the peak shape of the main peak in the profiles between samples. The applicant confirmed the difference in peak shape was due to differences in IgG2 isoform distribution within SB16, US Prolia, EU Prolia or US Xgeva caused by differences in disulfide linkages in the interchain hinge region. The disulfide variants in IgG2 have been reported in the literature and the variants were designated as IgG2-A, IgG2-B and IgG2-A/B variants.

IgG2-B accounted for less proportion in SB16 compared to that in US Prolia, EU Prolia or US Xgeva, while IgG2-A/B variant appear to be more in SB16 than US Prolia, EU Prolia or US Xgeva. The initial CAA considered the total area of the main peak, which % main peak in SB16 fell within the QR of US Prolia, EU Prolia or US Xgeva. There was no difference in the higher order structure, thermal stability, and biological activities between SB16 and US Prolia, EU Prolia or US Xgeva. However, this did not inform the contribution of individual variants to the overall activity or whether the difference in variants (SB16 vs US Prolia and US Xgeva or EU Prolia) has any impact on the biosimilarity conclusion. Upon FDA's request, the applicant performed further investigation on the fractionated variants and provided additional data collected using enriched fractions. The biological impact of disulfide isoforms in the whole sample and enriched fractions were analyzed using bioassays including RANKL binding and RANKL neutralization assays. The results shows %Relative binding activities of all samples were within release acceptance criteria (80-120%) but the %Relative binding activity for RANKL binding is relatively higher (10-15%) in the IgG2-A/B enriched sample. The RANKL neutralization was comparable (summarized below).

Table 3: Biological Analysis Results of Redox Treatment

Sample			RP-UPLC					RANKL Binding Activity	RANKL Neutralization Activity
			%Peak 1	%Peak 2	%Peak 3	%Peak 4	%Main (Total)[a]	%Relative Binding Activity	%Relative Potency
IRS-SB16-02		Whole	32.5	44.0	4.8	5.0	86.3	103	103
		Enriched IgG2-B	54.3	20.1	3.6	5.0	83.0	101	99
		Enriched IgG2-A/B	16.2	57.8	6.1	4.7	84.7	116	102
EU Prolia	1088503A	Whole	40.9	36.7	3.3	6.1	86.9	97	100
		Enriched IgG2-B	53.7	19.7	3.7	5.8	83.0	103	92
		Enriched IgG2-A/B	14.5	57.5	6.3	5.6	83.8	115	97
Major species[c]			IgG2-B	IgG2-A/B	IgG2-A	IgG2-A	N/A[b]	N/A	N/A

[a] %Main (Total): Sum of %Peak 1, %Peak 2, %Peak 3, and %Peak 4
[b] Not applicable
[c] According to the literature [Lacher, 2010], the corresponding isoform is the major species in each RP fraction.

To further support the conclusion, the applicant cited a literature that shows IgG2 isoforms shift *in vivo*[2], which means the difference in distribution of IgG2 isoforms is expected to decrease in the physiological condition. Therefore, the potential impact caused by difference in IgG2 isoform distribution is considered negligible in physiological condition.

Overall, their additional investigation revealed that the variants have somewhat moderate differences in the RANKL binding activity (10-15%) although that was not translated into the overall difference in RANKL binding or RANKL neutralization activities. Further, the *in vitro* binding differences will likely minimize once the products are administered. Taken together, the observed differences in disulfide variants between SB16 and US Prolia, EU Prolia or US Xgeva do not cause clinically significant impact or preclude a demonstration that SB16 is highly similar to US Prolia and US Xgeva, or the establishment of the analytical component of the scientific bridge.

E. Same Strength

SB16 in PFS and vial presentations have the same dosage form and route of administration as US Prolia and US Xgeva, respectively. Samsung Bioepis is seeking licensure of the 60 mg/mL SB16 in a single dose PFS assembled with a needle safety device (NSD) as an interchangeable biosimilar to US Prolia. They are also seeking licensure of the 120 mg/1.7 mL SB16 in a single dose vial as an interchangeable biosimilar to US-licensed Xgeva. Comparative protein concentration (mg/mL) was assessed as part of the CAA. (b) (4) Based on the comparative protein concentration data and manufacturing data, the proposed presentations of SB16 have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in unit of mass per unit volume as US-Prolia (60 mg/mL) and US-Xgeva (120 mg/1.7 mL). The strength of SB16 PFS assembled with a NSD and SB16 vial is the same as that of US Prolia and US Xgeva, respectively.

[2] Literature reference is made to the following article: Lui YD et al. 2013 IgG2 disulfide isoform conversion kinetics, Mol Immunol. 54:217-26. doi: 10.1016/j.molimm.2012.12.005

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