CDER Clinical, CDTL, and Division Summary Memo

Date	See Electronic Stamp Date
From	Hamid Tabatabai, M.D.
Subject	Clinical, Cross-Discipline Team Leader, and Division Summary Review
BLA # and Supplement#	BLA 761373 S-001 and BLA 761425 S-001
Applicant	Samsung Bioepis Co., Ltd.
Date of Submission	July 29, 2024
BSUFA Goal Date	January 29, 2025
Division/Office	Division of Dermatology and Dentistry (DDD)/Office of New Drugs (OND) in collaboration with the Division of Rheumatology and Transplant Medicine (DRTM)/OND and Division of Gastroenterology (DG)/OND
Code Name / Proprietary Name (proper name)	SB17 / Pyzchiva (ustekinumab-ttwe)
Reference Product Proprietary Name (proper name)	Stelara (ustekinumab)
Approved Indication(s)	Adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis (PsA). • moderately to severely active Crohn's disease (CD). • moderately to severely active ulcerative colitis (UC). Pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy. • active psoriatic arthritis.
Purpose of the Submission	Seeking licensure for the following presentations: • 45 mg/0.5 mL in a single-dose autoinjector (AI) for subcutaneous (SC) use as biosimilar to and interchangeable with US-Stelara 45 mg/0.5 mL single-dose prefilled syringe (PFS) for SC use • 90 mg/mL single-dose AI for SC use as biosimilar to and interchangeable with US-Stelara 90 mg/mL single-dose PFS for SC use

New Indication(s) and/or Population(s)	None
New Dosing Regimen(s)	None
Recommendation on Regulatory Action	Approval

1. Introduction

PYZCHIVA (ustekinumab-ttwe), also referred to as SB17, is a human interleukin-12 and -23 antagonist.

On June 28, 2024, the Agency approved Pyzchiva (SB17) as biosimilar to US-Stelara under Original 1 of the following BLAs as follows:

- BLA 761373: Pyzchiva (ustekinumab-ttwe) 45 mg/0.5 mL and 90 mg/mL injection in single-dose prefilled syringes (PFS) for subcutaneous (SC) use, as biosimilar to US-Stelara 45 mg/0.5 mL and 90 mg/mL injection for subcutaneous use in PFSs, respectively and
- BLA 761425: Pyzchiva (ustekinumab-ttwe)130 mg/26 mL injection in single-dose vial for intravenous (IV) use as biosimilar to US-Stelara 130 mg/26 mL injection in single-dose vial for IV use.

In addition, on June 28, 2024, FDA made provisional determinations under Original 2 of the following BLAs that:

- BLA 761373: Pyzchiva (ustekinumab-ttwe) 45 mg/0.5 mL and 90 mg/mL injection in a single-dose prefilled syringe (PFS) for SC use, would be interchangeable with US-Stelara 45 mg/0.5 mL and 90 mg/mL injection for subcutaneous use in a PFS, respectively and
- BLA 761425: Pyzchiva (ustekinumab-ttwe) 130 mg/26 mL injection in single-dose vial for IV use would be interchangeable with US-Stelara 130 mg/26 mL injection in single-dose vial for IV use.

On December 20, 2024, the Agency approved under supplement 761373/002 Pyzchiva (ustekinumab-ttwe) 45 mg/0.5 mL injection in a single-dose vial for SC use as biosimilar to US-Stelara (ustekinumab) 45 mg/0.5 mL injection in a single-dose vial for SC use and provisionally determined, under supplement 761373/004, that Pyzchiva (ustekinumab-ttwe) 45 mg/0.5 mL injection in a single-dose vial for SC use would be interchangeable with US-Stelara (ustekinumab) 45 mg/0.5 mL injection in a single-dose vial for SC use.

On April 30, 2025, the following interchangeable products were approved. For details, refer to Action Package dated April 30, 2025 in DARRTS:

- BLA 761373:
  - Pyzchiva (ustekinumab-ttwe) 45 mg/0.5 mL injection in a PFS for SC use, as interchangeable with US-Stelara 45 mg/0.5 mL injection for SC use in a PFS,
  - Pyzchiva (ustekinumab-ttwe) 90 mg/mL injection in a PFS for SC use, as interchangeable with US-Stelara 90 mg/mL injection for SC use in a PFS,
  - Pyzchiva (ustekinumab-ttwe) 45 mg/0.5 mL injection in a single-dose vial for SC use as interchangeable with US-Stelara (ustekinumab) 45 mg/0.5 mL injection in a single-dose vial for SC use.
- BLA 761425: Pyzchiva (ustekinumab-ttwe) 130 mg/26 mL injection in single-dose vial for IV use as interchangeable with US-Stelara 130 mg/26 mL injection in single-dose vial for IV use.

The "Biosimilar Multidisciplinary Evaluation and Review" (BMER) documenting the Agency's review of the original application (Original 1) dated June 28, 2024, and the CDTL memos documenting the Agency's review of Supplement 002 and Original 2 dated December 20, 2024 and April 30, 2025, respectively, are incorporated herein by reference. Refer to them for additional information.

On July 29, 2024, the Applicant submitted Prior Approval Supplement (PAS) 001 seeking approval of :[1]

- A Pyzchiva 45 mg/0.5 mL injection in a single-dose autoinjector (AI) for SC use as biosimilar to and interchangeable with US-Stelara 45 mg/0.5 mL injection in a single-dose PFS for SC use
- Pyzchiva 90 mg/mL injection in a single-dose AI for SC use as biosimilar to and interchangeable with US-Stelara 90 mg/mL injection in a single-dose PFS for SC use

In addition, with this submission, the Applicant proposed to introduce Chemistry Manufacturing and Control (CMC) changes to BLA 761373 and BLA 761425 as follows:

- Change of Drug product (DP) (PFS) maximum storage condition in room temperature ((b) (4) days to 35 days), and DP (PFS) maximum storage condition when refrigerated ((b) (4) days to 60 days) after storage in room temperature (BLA 761373 only)
- Update of DP stability protocol for the final long-term stability timepoint of 48-month to 42-month or 44-month (BLA 761373)
- Update of CCIT method description of DP stability in align with BLA 761425 information request response (Seq 0010) (BLA761373)
- Addition of a new shipping system, (b) (4) for the ocean shipment (BLA 761373 and BLA 761425)

[1] The proposed proprietary name for the autoinjector is "PYZCHIVA AUTOINJECTOR".

- Update of non-compendial incoming test item and acceptance criteria (b) (4) (BLA 761373 and BLA 761425)
- Change of raw material grade (b) (4) (b) (4) (BLA 761373 and BLA 761425)

A Comparative Use Human Factors (CUHF) Study was not submitted for the AI presentation on this date.

On October 15, 2024, the Applicant submitted a CUHF study, which constituted a major amendment to these supplements. Therefore, we extended the goal date by two months to January 29, 2025 to provide time for a full review of the submission.

2. Background

July 28, 2023: Samsung requested a meeting under IND 136959 to discuss Samsung's planned strategy for the licensure of the 45 mg/0.5mL and 90 mg/mLSB17 AIs as interchangeable biosimilars to the US-licensed Stelara PFS products, respectively.

Samsung discussed plans to submit a PAS for a single-dose AI containing 45 mg/0.5 mL or 90 mg/mL of SB17 to be administered via SC injection. SB17 AI is a (b) (4) (b) (4) (b) (4) The Agency provided Written Responses for the BPD Type 2a meeting regarding the SB17 AI. The (b) (4) AI was not approved at the time and Agency responses were predicated on the approval of the (b) (4) AI. Advice provided included:

> From a human factors perspective, in order for the Agency to assess whether there are any clinically meaningful differences between SB17 AI products and US-licensed Stelara [PFS] products, Samsung would need to submit the results of a human factors validation study to support a future 351(k) BLA. In addition, subject to the Agency's ongoing consideration of whether a determination of interchangeability could be made between a proposed product in an AI presentation and a reference product in a vial or PFS presentation, the Agency recommended that Samsung submit a CUHF study to support approval of the SB17 AI products as interchangeable with the Stelara PFS products, respectively.

December 11, 2023: Under IND 136959, the Agency provided Written Response for BPD Type 2a meeting for the planned PAS addition of single-dose AI device presentation for SB17. The Agency noted that the Applicant's proposal to not conduct a PK comparability study between the SB17 PFS and SB17 AI appeared reasonable.

[2] The Applicant did not provide further information about the terminology used in the naming of the (b) (4) (b) (4) is not included in the proposed proprietary name for the SB17 AI, which is "PYZCHIVA AUTOINJECTOR".

February 22, 2024: Under IND 136959 (SDN 16), the Applicant submitted the summary of the use-related risk analysis (URRA) for SB17AI and comparative analyses between:

1. SB17 AI and (b) (4) AI and
2. SB17 AI and Stelara PFS

This document applied to both 45 mg and 90 mg SB17 AI.

September 9, 2024: The Agency sent an Information Request (IR) for the Applicant to confirm if the use-related risk analysis (URRA) submitted on October 19, 2023, and the task comparison portion of the comparative analyses (CA) submitted on February 22, 2024, for IND 136959, are the same as the URRA and task comparison portion of the CA submitted on July 29, 2024, for BLA 761373/S-01. The Applicant was requested to specify if changes were made after the April 26, 2024, Agency URRA advice letter for SB17 (ustekinumab-ttwe) AI injections under IND 136959.

November 12, 2024: The Agency issued an IR to the Applicant requesting the study dataset and data definition file for the SB17 Autoinjector CUHF Study.

November 15, 2024: The Applicant submitted the study dataset for the SB17 Autoinjector CUHF Study.

November 26, 2024: The Agency issued an IR requesting Samsung to submit the following:

- A comprehensive URRA.
- The average injection completion time for the lot of autoinjectors tested in the CUHF study (time required for the autoinjector to complete the delivery of the drug).
- The time for the AI Window to turn completely yellow and hear a 2nd "click" in Step 11 "*Continue to press down onto the skin until the yellow indicator stops moving"* → *"Your injection could take up to 10 seconds*" → "*You may hear a second click. This means the injection is finished*."
- The injection hold time for the 5 participants who did not complete the "Wait until injection completion" task.
- Data on the participant ID number, their age group (adult or adolescent participant), AI they used (i.e., 45 mg/0.5 mL or 90 mg/mL), and the associated use errors with the particular AI.

January 29, 2025*:* On the goal date, the Agency was still considering novel issues raised by these supplements; therefore, the Agency did not take action. The Agency continued to work diligently on these supplements and communicated frequently with the Applicant.

3. Summary of Conclusions of Other Review Disciplines

3.1 Product Quality

The Office of Product Quality Assessment (OPQA) III provided a Memorandum of Assessment. Reviewer, Barry Gertz, reviewed sBLA 761373 S-001, as amended (Refer to memo in Panorama from February 19, 2025, amended April 29, 2025). The conclusions were:

- The use of non-compendial material with the vendor and DS manufacturer testing and specifications is acceptable.
- PQ validation of the (b) (4) system for DP shipment is acceptable. Shipping qualification using the (b) (4) container system and shipping routes within the validated shipping times is acceptable.
- The long-term stability protocol has been updated for the 45 mg and 90 mg PFS for the final timepoint from 48 months to 42 months (44 months for PFS batches TT447 and TT448).

The OPQ team has determined that the Applicant has provided adequate data and information in the BLA, including this supplement, to support a demonstration that Pyzchiva 45 mg/0.5 mL and 90 mg/mL in single-dose AIs are highly similar to US-Stelara 45 mg/0.5 mL and 90 mg/mL in single-dose PFSs, respectively.

OPQA recommended that the supplement be approved with a post marketing commitment (PMC). (See PMR/PMC section)

The Office of Pharmaceutical Manufacturing Assessment (OPMA) provided a Memorandum of Review. OPMA's Dr. Esther Broner reviewed BLA 761373 S-1 and BLA 761425 S-1 from a sterility assurance perspective and recommended for Approval. Also, the Manufacturing Facility Assessment Recommendation is for Approval. Refer to memo in Panorama from January 22, 2025.

3.2 Devices

Center for Devices and Radiological Health (CDRH)

CDER consulted CDRH requesting review of the subject combination product that includes an autoinjector device. Office of Product Evaluation and Quality (OPEQ), Office of Health Technology (OHT) 3 reviewer Bingjie Liang completed the memorandum.
An IR was sent to the Applicant on December 23, 2024, to which Samsung responded on December 31, 2024.

The CDRH final recommendation is that the proposed device constituent parts of the combination product are Approvable for the approved indications. Refer to memo in Panorama from January 29, 2025.

Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA 1 reviewed Samsung's comparative use human factors (CUHF) study for the autoinjector (AI) device. Among the materials Dr. Lisa Huang reviewed were CMC supplement and amendments, CUHF study report, and other pertinent reviews.

The CUHF study utilized a paired study design where each participant was randomized to one of two sequence groups (RT and TR), and the participants used either R (Stelara PFS) or T (SB17 AI, packaged as AB17 for the study) first followed by the presentation that they did not use previously. The randomization list was generated by Samsung Bioepis and included in the study protocol. Forty participants used the 45 mg dose for both products (R and T), and forty participants used the 90 mg dose for both products. Additionally, as part of running the study, the Applicant assigned participants a binary value of 0 and 1 for each critical task performed, where 1 is success and 0 is task failure.

According to the protocol, the primary endpoint for the CUHF study was the overall use success rate, defined for a given participant and a given product (T or R) as successfully completing all the critical tasks (i.e., making no error on any of those tasks) that were affected by the differences in external critical design attributes between the test and reference products.

DMEPA reviewer, Dr. Lisa Huang, considered whether CUHF study results support a determination that each Pyzchiva AI product can be expected to produce the same clinical result as the respective Stelara PFS product in any given patient, and the risk in terms of safety or diminished efficacy of alternating or switching between use of the Pyzchiva AI product and the respective Stelara PFS product is not greater than the risk of using the reference product without such alternation or switch. DMEPA also evaluated whether patients and caregivers who have experience with subcutaneous injection technique using a Stelara PFS product could successfully use a Pyzchiva AI product without the intervention of the healthcare provider and/or without additional training prior to use.

Based on the totality of evidence considered, DMEPA determined that the CUHF study results support a demonstration that the proposed Pyzchiva AI products are interchangeable with the respective Stelara PFS products.

Additionally, DMEPA concluded that the CUHF study results showed that each Pyzchiva AI product could be substituted for its respective Stelara PFS reference product without the intervention of the healthcare provider who prescribed the reference product and/or without additional training (other than self-directed review of the proposed Pyzchiva labeling) prior to use.

Based on the review of the available participants' subjective feedback and root cause analyses, DMEPA also identified additional labeling risk controls to address the use errors. Recommendations were provided which could be implemented without submitting additional CUHF testing data for Agency review.

Refer to DMEPA's review in DARRTS from June 18, 2025.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this sBLA. There are no nonclinical pharmacology/toxicology issues that would preclude the approval of these supplements.

5. Clinical Pharmacology

The SB17 AI device is a (b) (4) (b) (4) (b) (4) During the development of the SB17 AI (IND 136959), the Applicant proposed not to conduct a pharmacokinetic (PK) comparability study between the AI and the PFS and submitted a justification which included aspects like comparability assessment of drug product quality such as viscosity; device characteristics such as needle length, injection depth, delivered volume, etc. between the current formulation (b) (4) (b) (4) primary container closure in direct contact with drug product for the AI and PFS presentations of this product (b) (4) (b) (4) and prior experience of PK comparability establishment between the AI and PFS (b) (4)

The Clinical Pharmacology review team has completed their review and concludes that overall, the comparability assessment is acceptable, and a PK comparability study to establish a bridge between SB17 PFS and SB17 AI is not deemed necessary to support a demonstration of biosimilarity or interchangeability. Additionally, the comparability data was presented at the Office of Clinical Pharmacology Biologics Oversight Board Weekly Meeting on April 18, 2024, where the Board concurred that a PK comparability study of SB17 between the AI and PFS was not necessary. For detailed information, see Clinical Pharmacology Review and addendum authored by Dr. Pan in DARRTS (Reference ID of 5534068 dated 02/19/2025 and Reference ID of 5612195 dated 06/20/2025).

In summary, the supplemental application (BLA 761373/S-001 & BLA 761425/S-001) for adding a new AI presentation of SB17 is recommended for approval from a Clinical Pharmacology perspective.

6. Clinical

No new clinical information is submitted under BLA Supplements 761373-001 and

761425-001, and there are no clinical/Statistical efficacy issues that would preclude their approval.

7. Safety

No new clinical information is submitted under BLA supplements 761373-001 and 761425-001, and there are no clinical safety issues that would preclude their approval.

8. Pediatrics

Under 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.

The recommended regulatory action is approval. On June 24, 2025, the Pediatric Review Committee (PeRC) considered this supplement and found that the BLA is fully assessed. At this time, no pediatric studies are needed for this supplement.

Refer to the BMER dated June 28, 2024 and the CDTL memo dated December 20, 2024 for more information on the applicability of PREA for this BLA.

9. Other Relevant Regulatory Issues

The Applicant seeks licensure of Pyzchiva 45 mg/0.5 mL and 90 mg/mL AIs as biosimilar to and interchangeable with Stelara 45 mg/0.5 mL and 90 mg/mL prefilled syringes, respectively. Stelara is not licensed in an AI presentation.

FDA guidance recommends that "[a] sponsor developing an interchangeable product generally should not seek licensure for a presentation for which the reference product is not licensed. For example, if the reference product is only marketed in a vial and a prefilled syringe, a sponsor should not seek licensure for the proposed interchangeable product for a different presentation, such as an auto-injector. However, if a sponsor is considering the development of a presentation for which the reference product is not licensed, this should be discussed with FDA. In such cases, FDA will evaluate whether the proposed presentation could support a demonstration of interchangeability."[3]

On two prior occasions, the Agency has approved a biosimilar product in an autoinjector when the reference product was not approved in an autoinjector, but the Agency has

[3] FDA Guidance for Industry, *Considerations in Demonstrating Interchangeability with a Reference Product* (May 2019).

not previously approved an interchangeable biosimilar with this difference in presentation from a reference product. As such, and as previously communicated to the Applicant, these supplements raised novel issues regarding whether the proposed AIs could be approved as interchangeable with their respective reference products in a PFS presentation.

Based on the data and information in BLAs 761373 and 761425 and in these supplements, including the CUHF study results, the Agency concluded that this difference in presentation does not preclude approval of these supplements and that the standards for biosimilarity and interchangeability have been met.

10. Labeling

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1), Office of Medication Error Prevention and Risk Management (OMEPRM) conducted a proprietary name review of the proposed name PYZCHIVA AUTOINJECTOR. Reviewer Dr. Madhuri R. Patel evaluated the proposed name and concluded that this proprietary name is conditionally acceptable on October 23, 2024.

The Applicant provided updated labeling for Pyzchiva (ustekinumab-ttwe) to include the 45 mg/0.5 mL and the 90 mg/mL single-dose autoinjectors for SC use. The conditions of use in the labeling for the Pyzchiva 45 mg/0.5 mL and 90 mg/mL autoinjectors have been previously approved for the Stelara 45 mg/0.5mL and 90 mg/mL PFSs, respectively.

Labeling consultants, including Office of Therapeutic Biologics and Biosimilars (OTBB) labeling, OPQAIII labeling, DMEPA, the Office of Prescription Drug Promotion (OPDP), and the Division of Medical Policy Programs (DMPP) reviewed the proposed labeling and found the proposed revisions acceptable. All labeling changes were agreed upon with the Applicant. The final labeling will be included with the approval letter.

Other Labeling Recommendations

It has been 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.

11. Postmarketing Requirements (PMR) and Commitments (PMC)

There are no PMRs associated with these supplements. The Applicant committed to a PMC for long-term stability study of the AI (product quality and device functionality attributes) using one 45 mg/0.5 mL AI lot and one 90 mg/mL AI lot to support the proposed shelf-life.

PMC 4796-1:

- Samsung Bioepis commits to conduct stability studies for one lot each of the Ustekinumab-ttwe 45 mg autoinjector (AI) and ustekinumab-ttwe 90 mg AI presentations stored under long-term conditions. The AI shelf life supported by the stability study (b) (4)
- Stability testing will be performed periodically through the end of shelf life following the PFS commercial long-term stability protocol in CTD Section 3.2.P.8.1 and using all tests in the PFS specifications in addition to the AI specifications.
- The stability data will be provided in the post marketing commitment (PMC) report at the completion of the studies.

12. Risk Evaluation and Mitigation Strategies

There are no REMS associated with these supplements.

13. Recommended Regulatory Action

The data and information in BLA 761373 and BLA 761425, including the information submitted by the Applicant with these supplements, are sufficient to demonstrate that Pyzchiva 45 mg/0.5 mL and 90 mg/mL injection in single-dose AIs for SC use are highly similar to US-Stelara 45 mg/0.5 mL and 90 mg/mL single-dose PFSs for SC use, respectively, notwithstanding minor differences in clinically inactive components. FDA has further determined that the data and information provided by the Applicant support a demonstration of no clinically meaningful differences between Pyzchiva 45 mg/0.5 mL and 90 mg/mL injection in single-dose AIs for SC use and the respective US-Stelara 45 mg/0.5 mL and 90 mg/mL injection in single-dose PFSs for SC use. In addition, Pyzchiva 45 mg/0.5 mL and 90 mg/mL injection in single-dose AIs can be expected to produce the same clinical result as the respective US-Stelara 45 mg/0.5 mL and 90 mg/mL injection in single-dose PFSs in any given patient, and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Pyzchiva products in single-dose AIs and US-Stelara products in single-dose PFSs is not greater than the use of US-Stelara products in single-dose PFSs without such alternation or switch. FDA concludes that the standards for biosimilarity and interchangeability have been met.

We conclude that the information submitted by the Applicant, including data from a CUHF study, demonstrated that:

- Pyzchiva (ustekinumab-ttwe) 45 mg/0.5 mL injection in a single-dose AI for SC use is interchangeable with US-Stelara 45 mg/0.5 mL injection in a single-dose PFS for SC use
- Pyzchiva (ustekinumab-ttwe) 90 mg/mL injection in a single-dose AI for SC use is interchangeable with US-Stelara 90 mg/mL injection in a single-dose PFS for SC use

The Division of Dermatology and Dentistry recommends approval of Pyzchiva (ustekinumab-ttwe) 45 mg/0.5 mL and 90 mg/mL injection AIs for SC use as biosimilar to and interchangeable with Stelara (ustekinumab) 45 mg/0.5 mL and 90 mg/mL injection PFSs for SC use, respectively.

14. DDD Designated Signatory Comments

I concur with the review team's assessment of the data and information submitted in these supplemental BLAs and support the regulatory action.

15. Appendix

FDA Guidance for Industry, *Considerations in Demonstrating Interchangeability with a Reference Product* (May 2019) https://www.fda.gov/media/124907/download

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/s/

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