CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761059Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Indication/First Biosimilar/Expedited or Breakthrough Assessment: No

Recommendation: Approval

BLA/NDA Number: 761059
Assessment Number: 2
Assessment Date: 7/12/2019

Drug Name/Dosage Form	Hadlima- adalimumab-bwwd
Strength/Potency	40 mg/0.8 mL
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps), Juvenile idiopathic arthritis (JIA) in patients 4 years of age and older
Applicant/Sponsor	Samsung Bioepis Co, Ltd
US agent, if applicable	Cardinal Health 127, Inc

Note: This updated version of the Integrated Quality Assessment (IQA) memo for BLA 761059 reflects that stability protocols for the purpose of extending the expiration dating of drug substance and drug product are not approved as part of this license application because the sponsor did not request these protocols be approved.

Product Overview

Hadlima is a fully human anti-TNF-α IgG1 monoclonal antibody produced in (b) (4) cells using recombinant DNA technology. It is proposed as a biosimilar to US-licensed Humira. Hadlima binds to TNF-α, blocks its interaction with the p55 and p75 cell surface TNF receptors and neutralizes its biological function.
Hadlima is supplied as a prefilled syringe and an autoinjector as a sterile liquid solution for subcutaneous injection. Samsung seeks licensure of Hadlima for the following indications: rheumatoid arthritis, juvenile idiopathic arthritis (4 years of age and older), ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

Quality Assessment Team

Discipline	Assessor	Branch/Division
Drug Substance	Joao Pedras-Vasconcelos	Division of Biotechnology Review and Research (DBRR) III
Drug Product	Tracy Denison	DBRR III
Analytical similarity	Joao Pedras-Vasconcelos	DBRR III
Immunogenicity	Joao Pedras-Vasconcelos	DBRR III
Validation of analytical methods	Merry Christie	DBRR III
Labeling	Vicky Borders-Hemphill	Office of Biotechnology Products
Facility	Viviana Matta	Division of Inspectional Assessment (DIA)
Facility Team Lead	Peter Qui	DIA
Microbiology Drug Substance	Bo Chi	Division of Microbiology Assessment (DMA)
Microbiology Drug Product	Jessica Hankins	DMA
Microbiology Team Lead	Reyes Candau Chacon	DMA

Regulatory Business Process Manager	Oumou Barry	Office of Program and Regulatory Operations
Application Team Lead	Maria Cecilia Tami	DBRR III
Tertiary Assessor	Susan Kirshner	DBRR III

Multidisciplinary Assessment Team

Discipline	Assessor	Office/Division
RPM	Brandi Wheeler	OND/DPARP
Cross-disciplinary Team Lead	Nikolay Nikolov	OND/DPARP
Medical Officer	Raj Nair / Nikolay Nikolov Roselyn Epps / David Kettl Anil Rajpal / Jessica Lee	OND/DPARP OND/DDDP OND/DGIEP
Pharm/Tox	David Klein / Tim Robison	OND/DPARP
Clinical Pharmacology	Lei He / Anshu Marathe	OCP/DCPII
Statistics	Becky Rothwell / Lei Nie	OB/ DB II
CMC Statistics	Yu-Ting Weng / Meiyu Shen	OB/ DB IV

1. Names:
    a. Proprietary Name: Hadlima
    b. Trade Name: Hadlima
    c. Non-Proprietary Name/USAN: adalimumab-bwwd
    d. INN Name: adalimumab-bwwd
    e. Company Code: SB5
    f. CMO code: BIIB606
    g. OBP Systematic Name: MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [SB5]

Submissions Assessed:

Submission(s) Reviewed	Document Date
STN 0012/resubmission	7/23/2018
STN 0014/OPF	8/17/2018
STN 0015/revision of module 3	9/10/2018
STN 0016/DMA	9/14/2018
STN 0022/OBP	11/5/2018
STN 0023/OBP	11/6/2018
STN 0025/DIA	11/21/2018
STN 0027/OBP	12/31/2018
STN 0029/DMA/DIA	1/10/2019
STN 0031/OBP	1/15/2019
STN 0032/DMA	1/25/2019
STN 0035/mid cycle minutes	2/5/2019
STN 0036/OBP	2/12/2019
STN 0037/OBP Immunogenicity	2/21/2019
STN 0038/DIA	2/21/2019
STN 0041/OBP	3/06/2019
STN 0042/ DMA/DIA	3/08/2019

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STN 0043/OBP	3/13/2019
STN 0044/OBP/DMA	3/14/2019
STN 0045/OBP	3/18/2019
STN 0048/OBP	4/8/2019
STN 0049/DMA	4/17/2019
STN 0050/OBP	4/19/2019
STN 0051/OBP	4/29/2019
STN 0054/OBP	5/14/2019
STN 0055/OBP	5/21/2019
STN 0056/OBP	5/24/2109
STN 0057/OBP	6/07/2019

Quality Assessment Data Sheet

1. Legal Basis for Submission: 351(k)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed
(b) (4)	V		(b) (4)	2	Adequate	N/A
	V			2	Adequate	N/A
	III			3	Adequate	N/A
	III			3	Adequate	N/A
	III			1	Adequate	N/A
	II			2	Adequate	N/A
	510 (k)			3	Adequate	Assessed by CDRH

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			needle Guard Syringe			
(b) (4)	N/A	(b) (4)		3	Adequate	Assessed by CDRH. No LOA provided. No review of DMF required because sufficient information provided in the application.

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.
None

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
CDRH ODE/OC	August 9, 2018	Complete	Approval. Recommendation to perform a post approval inspection of (b) (4)	Sarah Mollo/Stevens Alan & Carolyn Dorgan

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Products, OPQ, CDER, recommends approval of STN 761059 for Hadlima manufactured by Samsung Bioepis Co., Ltd. For the purposes of this review, the proposed product is referred to by the Sponsor's descriptor SB5, which was the name used to refer to this product during development. The data submitted in this application are adequate to support the following conclusions:

- The manufacture of SB5 is well-controlled and leads to a product that is pure, potent and safe.
- SB5 is highly similar to US-licensed Humira (hereinafter, US-Humira) notwithstanding minor differences in clinically inactive components
- SB5 prefilled syringe and autoinjector have the same strength as that of US-Humira.
- The analytical component of the scientific bridge between SB5, US-Humira, and EU-approved Humira (hereafter EU-Humira) was established to support the relevance of the data generated from studies using EU-Humira as the comparator to the assessment of biosimilarity.

It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance:
  (b) (4)
- Drug Product:
  (b) (4)

- Fill size and dosage form:
  40 mg/0.8 mL prefilled syringe and autoinjector

- Dating period:
  - Drug Product: 36 months: 5 ± 3 °C
  - Drug Substance: (b) (4) months: (b) (4) °C

- Exempt from lot release
  - Yes

- Rationale, if exempted: specified product
  Note: Per FR notice 95-29960 well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products are exempted from 21 CFR 601.2a lot release requirements.

Samsung requests categorical exclusion from the preparation of an environmental assessment requirement under 21 CFR Part 25.31(g): "Establishment of bioequivalence requirements for a human drug or a comparability determination for a biologic product subject to licensing". Samsung developed SB5 as a proposed biosimilar to US-licensed Humira and considers that establishment of analytical similarity is conceptually similar to establishing comparability between pre- and post-change products.
Approval of this submission will not increase the overall use of the active moiety. Therefore, exclusion may be granted.

C. Assessment Summary:

SB5 is a proposed biosimilar to US-Humira (40 mg/0.8 mL).
Samsung seeks licensure for the indications listed below, for which US-Humira is licensed:

- Rheumatoid Arthritis (RA)
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Adult Crohn's Disease (CD)
- Ulcerative Colitis (UC)
- Plaque Psoriasis (Ps)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients 4 years of age and older

The overall control strategy includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The control strategy combined with in-process, release, and stability testing ensure that the drug substance and drug product manufacturing processes are well controlled and lead to a product with the expected quality attributes and free of adventitious agents.

The data support the demonstration that SB5 is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components (refer to Section II of this memo for further details and discussion of the differences observed).

Analytical similarity between SB5 and US-Humira was evaluated using a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of SB5 and US-Humira. The numbers of lots tested and the statistical analyses were appropriate to allow for a meaningful evaluation of the results of the analytical studies.

EU-Humira was used as a comparator to SB5 in study SB5-G31-RA. To justify the relevance of the clinical comparative data generated using EU-Humira as a comparator product, Samsung established the analytical component of the scientific bridge between SB5, US-Humira, and EU-Humira.

SB5 has the same dosage form, and route of administration as US-Humira, but has a different formulation. Samsung is seeking approval of two 40 mg/0.8 mL presentations of SB5: 40 mg/0.8 mL SB5 in a single-dose prefilled glass syringe and 40 mg/0.8 mL SB5 in a single-dose prefilled auto-injector. US-Humira is available at this strength (40 mg/0.8 mL) in a single-dose prefilled glass syringe and in a single-dose prefilled auto-injector. Comparative protein concentration (mg/mL) was assessed as part of the analytical similarity assessment. The deliverable volume (mL) and fill weight data were assessed [redacted] (b) (4) The proposed presentations of SB5 have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as U.S-Humira (40 mg/0.8 mL). The strength of SB5 prefilled syringe and autoinjector is the same as that of US-Humira.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective.

The DIA assessor is recommending approval of [redacted] (b) (4) [redacted], for commercial manufacture of SB5 DS and [redacted] (b) (4) for commercial manufacture of DP.

Secondary packaging of the Safety Prefilled Syringe is performed at [redacted] (b) (4)
Secondary packaging of the Autoinjector is performed at [redacted] (b) (4)
CDRH recommends approval based on assessment of device constituent with a post-approval inspection of [redacted] (b) (4), the autoinjector manufacturing site.

The OBP assessments including DS, DP, analytical similarity and validation of immunogenicity assays, DMA DS and DP microbiological assessments, and DIA facility technical assessment are located as separate documents in Panorama.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

1- To implement an SB5 derived assay control reference material for the potency assays and establish acceptance criteria for the assay control relative to the reference standard (RS)
2- To implement a system suitability criterion [redacted] (b) (4) and establish a tighter limit for %difference in the peak areas [redacted] (b) (4) [redacted].
3- To implement [redacted] (b) (4) monitoring [redacted] (b) (4) of the SB5 drug product.

II. Analytical Similarity Assessment and Evaluation of the Analytical Component of the Scientific Bridge

A. Analytical Assessment Overview and Conclusions

The analytical assessment consisted of three studies that included:

- US-Humira, EU-Humira, and SB5 material used in clinical and non-clinical studies,

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- SB5 drug substance (DS) and drug product (DP) manufactured at different sites or using different manufacturing processes, including the proposed commercial process.

Data from the three studies were used to assess whether SB5 was highly similar to US-Humira. The analytical assessment included a total of 53 DP batches each of US-Humira and EU-Humira, 9 independent SB5 DP batches, and one additional SB5 DS batch not used for DP production. The analytical assessment was performed with SB5 in PFS. This approach is acceptable because the Sponsor provided adequate data to show that assembly of the PFS into the secondary packaging component of the autoinjector does not impact product quality attributes. The analytical assessment included:

- extensive comparative physicochemical and functional assessment of quality attributes,
- comparative assessment of the degradation profiles under forced degradation conditions,
- comparative assessment of the stability profile under long-term, accelerated, and stress temperature conditions.

Samsung used a risk-based approach for statistical evaluation of analytical results. Highest-ranked risk attributes tested using quantitative assays were evaluated using equivalence testing. Moderate to high risk attributes tested using quantitative assays were evaluated using quality ranges calculated to account for reference product manufacturing variability and assay variability. Low risk attributes or attributes tested using qualitative assays were evaluated using visual display comparisons. Results from method validation or qualification studies support the suitability of the methods used in the analytical assessment.

Based on our assessment of the SB5 and US-Humira data, we determined that SB5 is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components. SB5 has the same strength, dosage form, presentations, and route of administration as US-Humira, but has certain formulation differences. The applicant used a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of SB5 and US-Humira to support the demonstration that the products are highly similar. Numbers of lots tested and statistical analyses were appropriate to allow for a meaningful evaluation of the results of the analytical studies. Observed differences do not preclude a determination that SB5 and US-Humira are highly similar.

In addition, three-way pairwise comparisons of SB5, US-Humira, and EU-Humira were used to establish the analytical component of the three-way scientific bridge between SB5, US-Humira, and EU-Humira to support the relevance of the data generated from studies using EU-Humira as the comparator to the assessment of biosimilarity.

Based on our review of the data, we conclude that the Sponsor established the analytical portion of the scientific bridge between SB5, US-Humira, and EU-Humira, using the same methods and statistical approaches used to evaluate high similarity between US-Humira and SB5. The analytical portion of the scientific bridge was established to support the relevance of the data generated from studies using EU-Humira as the comparator to the assessment of biosimilarity.

B. Analytical Similarity Results

Table A. Quality Attributes Analyzed to Assess Analytical Similarity

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Comparative Analytical Attributes		
Physico-chemical/Functional Characteristics	**Quality Attribute Assessed**	**Supports a Demonstration of Highly Similar**
Primary Structure and sequence variants	*Amino acid sequence*	*Yes*
	N-terminal sequencing	*Yes**
	C-terminal sequencing	*Yes**
	Peptide Mapping	*Yes*
	Disulfide bonds	*Yes*
	Free sulfhydryl group quantification	*Yes**
	Methionine Oxidation (Met 256 and 34)	*Yes**
	Asparagine Deamidation (peptides LH27 and LH30)	*Yes*
	Molecular Mass (intact and deglycosylated)	*Yes*
Glycosylation	*N-linked glycosylation site occupancy*	*Yes*
	N-glycan identification	*Yes*
	non-fucosylated + high mannose N-glycan	*Yes**
	N-glycan non-fucosylated	*Yes**
	N-glycan high mannose	*Yes**
	N-glycan galactosylated	*Yes**
	Charged glycans (sialylated)	*Yes**
	%G0F	*Yes**
	%G1F	*Yes**
	%G2F	*Yes**
Purity and product related variants or impurities	*HMW species*	*Yes*
	LMW species	*Yes*
	Antibody fragments	*Yes**
	Monomer, Intact IgG	*Yes*
	Charged variants	*Yes**
High Order structure	*Secondary structure*	*Yes*
	Tertiary structure	*Yes*
	Folding analysis	*Yes*
	Thermal stability	*Yes*
	Extinction Coefficient	*Yes*
Bioactivity	*Tumor neutralizing factor (TNF)-alpha binding and neutralization*	*Yes*
	Binding and stimulation of mTNF-α induced apoptosis	*Yes*
	Antibody-dependent cell-mediated cytotoxicity (ADCC)	*Yes*
	Complement Dependent cytotoxicity (CDC)	*Yes*
	Regulatory Cell Induction (reverse signaling)	*Yes*

	Neonatal Fc receptor (FcRn) binding	*Yes*
	Binding to Fcγ Receptors	*Yes**
Drug Product Attributes	*Protein concentration*	*Yes*
	Particulates	*Yes*

"*Yes*"Differences between SB5 and US-Humira were noted. However, these differences do not preclude a determination of highly similar. See section IV for additional information

The comparative evaluation of the stability of SB5, US-Humira, and EU-Humira under long-term, accelerated, and stressed temperature storage conditions and under oxidative, basic, acidic, and light forced degradation conditions show minor differences attributable to the differences in formulation, and therefore, these differences do not preclude a determination that SB5 is highly similar to US-Humira.

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

The clinical development of SB5 included two pivotal clinical studies:

- Study SB5-G11-NHV: a randomized, single-blind, three-arm, parallel group, single-dose study to compare the PK, safety/tolerability and immunogenicity of a single 40 mg administration of each SB5, US-Humira, and EU-Humira in healthy subjects.
- Study SB5-G31-RA: a randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy, safety, tolerability, PK, and immunogenicity of SB5 compared to EU-Humira in subjects with moderate to severe RA despite methotrexate (MTX) therapy.

Samsung used EU-Humira as a comparator to SB5 in study SB5-G31-RA. To support the relevance of this clinical comparative data generated using EU-Humira as a comparator product to the assessment of biosimilarity, Samsung performed a three-way analytical assessment of SB5, US-Humira, and EU-Humira using a comprehensive array of analytical methods. The analytical component of the three-way scientific bridge included comparison of SB5 to US-Humira, SB5 to EU-Humira, and EU-Humira to US-Humira. The same analytical methods used for the assessment of high similarity between SB5 and US-Humira were used for comparison of SB5 and EU-Humira and US-Humira and EU-Humira. The differences observed in the analytical studies do not preclude a determination that the three-way analytical component of the scientific bridge is acceptable. See section IV below. The results of the assessment establish a robust analytical component of the three-way scientific bridge.

D. Assessment of Analytical Study Results

Comparative analytical acceptance criteria were met for all attributes evaluated with quality ranges with the following exceptions:

1- The %Non-glycosylated heavy chain content of all SB5 lots (NGHC; 1.5-4.2%) was above the quality range of US-Humira (1.0-1.4%), and EU-Humira (0.8-1.5%) and %main peak content was correspondingly lower. Glycan structures may impact binding to Fcγ receptors, such as FcγRIIIa. Binding to FcγRIIIa is the primary mechanism that can lead to ADCC activity. Therefore, differences in glycan structures may result in differences in ADCC activity. The Sponsor performed structure-activity relationship (SAR) studies with %NGHC-enriched samples and showed that an NGHC increase of ~3.5% may result in ~10% decrease in ADCC activity. However, analytically, no differences in ADCC activity were observed between SB5 and US-Humira, SB5 and EU-Humira, or US-Humira and EU-Humira. In addition, differences in %NGHC and %main peak did not impact binding to TNF-α or FcRn or biological activity measured by the NF- κβ Reporter Gene assay. Furthermore, the %NGHC levels were below 2% in the three DP batches manufactured at the proposed commercial sites. Therefore, the observed differences in %NGHC do not preclude a determination that SB5 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.

2- Three SB5 batches had %Afucose + %high mannose (HM) content (8.4 to 11.9%) slightly above the quality range of US-Humira (6.2 to 11.4%) but were within the quality range for EU-Humira. However, FcγRIIIa binding and ADCC activity, which correlate with afucosylated + HM glycans content, were similar between SB5 (90-116% and 81%-114%), US-Humira (82-126% and 71-145%) and EU-Humira (95-118% and 80-141%). Therefore, the slight difference observed in the content of %Afucose + %HM is unlikely to affect biological activity and does not preclude a determination that SB5 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.

3- Afucosylation in most SB5 batches (2.0-3.6%) was above the quality ranges of US-Humira (1.6-2.3%) and EU-Humira (1.6-2.7%). Afucosylation in two EU-Humira batches was above the quality ranges of US-Humira. Afucosylation impacts binding affinity to FcγRIIIa. Binding to FcγRIIIa is the primary mechanism that can lead to ADCC activity. Therefore, differences in afucosylation may result in differences in ADCC activity. However, no differences were observed in ADCC activity or FcγRIIIa binding. Therefore, the observed differences in afucosylation do not preclude a determination that SB5 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.

4- Two SB5 batches had %HM content (5.2-9.9%) slightly above the quality ranges of US-Humira (4.4-9.3%) and EU-Humira (4.1-9.4%). These were clinical batches manufactured using an early process. High mannose content may impact the PK of antibodies by increasing uptake of antibodies through mannose receptor in the liver. However, the slight differences observed here are not expected to impact the pharmacokinetics of SB5 because liver clearance is not the predominant clearance mechanism of antibodies. HM is also known to increase FcγRIIIa binding and ADCC activity, as well as to decrease C1q binding and CDC activity. Increased %HM in the SB5 batches, did not impact FcγRIIIa binding, C1q binding, ADCC activity, or CDC activity. Therefore, the differences in %HM content do not preclude a determination that SB5 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established. Additionally, we conferred with the clinical pharmacology reviewers, and the PK data are consistent with these conclusions.

5- The %Charged glycans content in all batches of SB5 (2.1-3.5%) was above the quality ranges of US-Humira (0.0-0.6%) and EU-Humira (0.0-1.2%). The increase in SB5 charged glycans is due to higher terminal sialylated glycan levels, which may increase serum half-life and impact Fc effector function. However, no differences were observed in ADCC. In addition, removal of sialic acid did not result in measurable differences in FcRN binding, which is a factor in determining serum half-life, TNF-α binding, or ADCC activity. Based on these clearance mechanisms of antibodies, the increased levels of terminal sialylation in SB5 are not expected to impact the pharmacokinetics of SB5. Therefore, the observed differences in %Charged glycans do not preclude a determination that SB5 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established . Additionally, we conferred with the clinical pharmacology reviewers, and the PK data are consistent with these conclusions.

6- The galactosylation content in several SB5 batches (19.3-28.3%) was above the quality ranges of US-Humira (18.3-21.4%) and EU-Humira (16.7-22.2%). Increased galactosylation may increase C1q binding and CDC activity.. However, this difference did not result in differences in CDC or C1q binding. Therefore, the observed differences in %galactosylation do not preclude a determination of highly similar or a determination that the analytical part of the scientific bridge was established.

7- Differences are seen between SB5, US-Humira, and EU-Humira for G0F, G1F and G2F:

- Content of G0F in all SB5 batches (59.1-63.7%) was below the quality ranges US-Humira (65.8-71.2%) and EU-Humira (64.5-72.9%).

- Several SB5 batches (12.4-21.1%) fall outside the US-Humira (12.8-16.4%) and EU-Humira (12.9-15.9%) quality ranges for G1F.

- Several SB5 batches (0.7-1.9%) fall outside the US-Humira (0.9-1.5%) and EU-Humira (0.8-1.4%) quality ranges for G2F.

The data indicate that the differences in %galactose observed between SB5, US-Humira and EU-Humira are mostly due to the lower content of G0F in SB5. As explained above, increased galactosylation may increase binding of C1q and CDC activity. However, these differences did not result in differences in CDC or C1q binding. Therefore, the observed differences in G0F, G1F, and G2F do not preclude a determination that SB5 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.

8- Levels of basic variants in all SB5 batches (8.6-10.9%) were below the quality ranges of US-Humira (17.5-30.2%) and EU-Humira (18.1-27.8%). Levels of acidic variants in all SB5 batches (22.6-25.6%) were above the quality ranges of US-Humira (11.9-18.7%) and EU-Humira (11.4-19.5%). The Sponsor provided characterization and biological activity data showing that acidic variants were enriched in sialylated N-glycans, which are discussed under bullet 3. Basic variants had high levels of C-terminal Lys and α-amidated C-terminal proline residues of the heavy chain, which are not CQAs because C-terminal lysine is cleaved in serum and proline amidation of the C-terminus of monoclonal antibodies does not impact the Fc-mediated effector function. Acidic and basic variants had similar activities to the main product in both the TNF-α binding assay and the ADCC assay. Therefore, the differences seen in acidic and basic variants do not preclude a determination that SB5 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.

9- Several SB5 batches showed binding affinity to FcγRIIIb below the quality ranges of US-Humira and EU-Humira. However, it is likely that the ranges were not accurate because they were established using only 5 batches of US-Humira and 6 batches of EU-Humira. Indeed, when quality ranges were recalculated using data from additional US-Humira and EU-Humira lots, then all batches of SB5 tested fell within the US-Humira and the EU-Humira quality ranges. The inclusion of additional lots of US-Humira and EU-Humira in the analysis is more representative of the actual variability of the US-Humira and EU-Humira indicating that the original quality ranges were too narrow. In addition, the FcγRIIIb affinity differences are not reflected in functional assays such as ADCC, and, therefore, do not preclude a determination of highly similar or a determination that the analytical part of the scientific bridge was established.

Comparative analytical acceptance criteria were met for all attributes evaluated using visual display with the following exceptions:

10- SB5 batches show deamidation levels in position Asn 319. However, levels are low, up to 1.7% in SB5, 1.1 % in US-Humira, and 0.7% in EU-Humira. Because Ans 319 is located in the HC framework region, away from the regions of the molecule implicated in functional activities, the observed difference does not preclude a determination that SB5 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.

11- All SB5 batches have higher free thiol content (0.5-3.1%) than US-Humira (0.1-1.1%) and EU-Humira (0.1-0.3%). The relative percentage of free thiol was low (< 3.1%) in all SB5, US-Humira, and EU-Humira batches suggesting that most of the 32 Cys residues are forming disulfide bonds, and that there are no free Cys residues. Thiol content could impact structural integrity and stability; however, no differences were observed between SB5, US-Humira, and EU-Humira batches when evaluated in orthogonal higher order structure assays, suggesting that the differences in thiol content do not impact conformation or stability. Therefore, the observed differences in free thiol do not preclude a determination of highly similar or a determination that the analytical part of the scientific bridge was established.

12- All SB5 batches show lower levels of C-terminal lysine (1.3-3.1%) than US-Humira (5.7-9.6%) and EU-Humira (6.8-8.1%). The Sponsor provided data showing that C-terminal lysine variation has no effect on TNF-α binding and ADCC. Refer to discussion point 8. In addition, C-terminal lysine variants do not impact pharmacokinetics of monoclonal antibodies, when administered intravenously, and have little impact on the biological activity of monoclonal antibodies in general, due to their distal location from the antigen-binding domain and from the sites involved in interactions with Fc receptors. Therefore, the decreased levels of SB5 C-terminal lysine do not preclude a determination that SB5 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established.

13- SB5 showed higher oxidation (3.0-6.4%) than US-Humira (2.3-3.9%) and EU-Humira (2.9-3.5%) at Met 256 residue, primarily in the three clinical batches, which were manufactured using an early process. This is the most oxidized of the 5 methionine residues in SB5, US-Humira and EU-Humira (HC 34, 83, 256 and 432; LC 4). Met 256 is located in the FcRn binding region, and its oxidation can potentially affect Fc-related biological activity. However, FcRn binding affinity was shown to be similar between SB5 (85-111% n=10), US-Humira (81-115%, n=39) and EU-Humira (80-120%, n=40). Therefore, the observed differences do not preclude a determination that SB5 and US-Humira are highly similar or a determination that the analytical part of the scientific bridge was established. No evident differences in the level of oxidation were observed in the other Met residues.

E. Same Strength(s)

Samsung is seeking approval of two 40 mg/0.8 mL presentations of SB5: 40 mg/0.8 mL SB5 in a single-dose prefilled glass syringe and 40 mg/0.8 mL SB5 in a single-dose prefilled auto-injector. U.S.-Humira is available at this strength (40 mg/0.8 mL) in a single-dose prefilled glass syringe and in a single-dose prefilled auto-injector. Samsung is seeking approval of SB5 for the same strength as U.S-Humira. Comparative protein concentration (mg/mL) was assessed as part of the analytical similarity assessment. The deliverable volume (mL) and fill weight data were assessed (b) (4) . The proposed presentations of SB5 have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as U.S-Humira (40 mg/0.8 mL). The strength of SB5 prefilled syringe and autoinjector is the same as that of US-Humira.

III. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management (see example in Attachment 1)

CQA (type)	Risk	Origin	Control Strategy	Other
Potency	Direct link to Efficacy	Intrinsic to the molecule	(b) (4)	Stability-indicating data show that the NRGA assay is more sensitive to potency changes than the

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				Apoptosis inhibition assay. The current control over the potency assay is acceptable. Establishment of an assay control derived from SB5 and implementation of additional assay controls post marketing will improve long term assay robustness.
ADCC (Potency)	Direct link to Efficacy	Intrinsic to the molecule	(b) (4)	Data support a correlation between levels of afucosylation + high mannose and ADCC activity.
CDC (Potency)	Direct link to Efficacy	Intrinsic to the molecule		CDC rejection limits were provided in the response to IR dated March 22, 2019 and deemed acceptable.
HMW species	Efficacy and safety	Introduced during manufacturing process and storage		Stability-indicating. No or reduced activity in TNF-α reporter gene assay.
LMW species	Efficacy and safety	Introduced during manufacturing process and storage		Stability-indicating. No or reduced activity in TNF-α reporter gene assay.
Fragments	Efficacy and safety	Introduced during manufacturing process and storage		Stability-indicating. No or reduced activity in TNF-α reporter gene assay.
Charge variants (product related variants)	Efficacy and safety	Intrinsic to the molecule		Stability-indicating lysine variants or deamidated variants.
High order structure (potency)	Direct link to efficacy and MOA	Intrinsic to the molecule		
Glycosylation (potency, PK)	Directly linked to efficacy and safety	Introduced during manufacturing process		

			(b) (4)	
Deamidation	Efficacy and safety	Introduced during manufacturing process and storage		Stability-indicating. Most susceptible deamidation sites in the Fc-part of the molecule. (b) (4)
Oxidation	Efficacy and safety	Introduced during manufacturing process and storage		Stability-indicating. Most susceptible oxidation sites in the Fc-part of the molecule, (b) (4) No effect on FcRN binding activity.

B. Drug Substance [adalimumab-bwwd] Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management. (see example in Attachment 2)

CQA (type)	Risk	Origin	Control Strategy	Other
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing	(b) (4)	
Endotoxin	Safety and purity	Raw materials or contamination during manufacturing		
HCP	Safety and immunogenicity	Process; during cell disruption		The proposed control strategy provides an

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			(b) (4)	acceptable assurance of safety.
HCDNA	Safety and immunogenicity	Process; during cell disruption		The proposed control strategy provides an acceptable assurance of safety.
Viruses (process related impurity)	Safety	Contamination of raw materials or during manufacture		
(b) (4) (Process related impurity)	Safety	(b) (4		
(b) (4)	Safety	Added during cell culture		
	Safety	Added during cell culture		
	Safety	Added during cell culture		
	Safety	Added during detergent viral inactivation step		
	Safety	Added during cell culture		
	Safety	Added during cell culture		
	Safety	Added during cell culture		
	Safety	Formulation		The current control (b) (4) acceptable. Additional system suitability criteria will be implemented

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				post marketing to improve the control over the assay.
Leachables and extractables	Safety	Entire process	(b) (4)	

- Description:

SB5 is a recombinant human monoclonal antibody consisting of two kappa light chains, each with a molecular weight of approximately 24 kDa (214 amino acids), and two IgG1 heavy chains, each with a molecular weight of approximately 49 kDa (451 amino acids). The total molecular weight of SB5 is approximately 148 kDa. One N-linked glycosylation site is located at Asn301 on each heavy chain. Glycans include, afucose, high mannose, galactose, and sialylated species.

- Mechanism of Action (MoA):

SB5 specifically binds to soluble and transmembrane TNF-α and neutralizes its biological function by blocking its interaction with the p55 and p75 cell surface TNF-α receptors. In addition, antibody dependent cell mediated cytotoxicity, complement dependent cytotoxicity, antibody mediated reverse signaling, and induction of regulatory macrophages have been identified in the scientific literature as potential mechanisms of action for anti-TNF monoclonal antibody products.

- Potency Assay:

The primary mechanism of action (MOA) of adalimumab is binding to soluble TNF-α. Samsung assessed two activities relevant to the MOA of the product:

1- TNF-α activity neutralization measured using an NF- κβ Reporter Gene Assay (NRGA) and
2- Inhibition of TNF-α binding measured by fluorescent resonance transfer (FRET)

The NRGA assay evaluates early steps in the TNF-α signaling cascade when compared to the cell-based inhibition of apoptosis bioassay.

The assay uses a HEK 293 cell line transfected with NF-κβ binding sequence upstream of the luciferase reporter gene. The binding of TNF-α to the cell surface TNF receptor leads to a signal cascade that results in activation of NF-κβ, which then activates the expression of the luciferase reporter gene. The luciferase assists oxidation of luciferin which then emits light. Luciferase activity (luminescence) is measured in the presence or absence of adalimumab. Decrease in luminescence is proportional to TNF-α neutralization. Potency is reported relative to the reference standard.

Apoptosis is a downstream event to NF-kβ induction, and it involves activation of caspases such as Casp 3 and Casp 7. Apoptosis occurs primarily when inflammation reaches excessive levels and the NF-κβ pathway is overwhelmed leading to caspase activation and DNA fragmentation and nuclear collapse. To support the use of the NRGA assay (b) (4), Samsung provided data showing that the NRGA and the cell-based inhibition of apoptosis bioassay have comparable performance with regards to precision, accuracy, and linearity over a concentration range of 75-125% of primary reference standard (PRS), which are the assay acceptance criteria. However, the data showed that the NRGA assay is more sensitive to potency changes than the apoptosis inhibition assay. Therefore, the

TNF NRGA potency assay is an acceptable alternative to the cell-based inhibition of apoptosis assay (b) (4)

The inhibition of TNF-α binding measured by FRET assay uses Europium-labelled SB5 and Cy5 fluorophore-labelled TNF-α. When Europium-SB5 is bound to Cy5-TNF-α and excites Cy5 via the emission wavelength of Europium, a detectable fluorescent signal from Cy5 can be measured. Binding is competed by unlabeled SB5 and the measured fluorescence is inversely proportional to the binding of unlabeled drug.

Additional potential mechanisms of action proposed for SB5 are ADCC and CDC. (b) (4)

The potency assays currently include an assay control in addition to the RS. This approach is adequate as it improves control over the performance of the assay. However, the assay control is currently a commercially sourced U.S.-licensed Humira lot. This approach limits the control o the Sponsor over this critical control. The Sponsor committed to implement an SB5 derived assay control for the potency assays and to establish acceptance criteria for the assay control relative to the reference standard (RS). This approach will improve control over assay variability and provide additional assurance that the RS is performing as expected during routine testing. The implementation of the SB5 assay control and additional system suitability criteria for the potency assays will be a PMC.

- Reference Materials:

(b) (4)

- Critical starting materials or intermediates:

(b) (4)

(b) (4)

- Manufacturing process summary:

(b) (4)

- Container closure:

The drug substance is filled and stored in (b) (4) The container closure system and stability sample storage containers are adequate.

- Dating period and storage conditions: (b) (4) months: (b) (4) °C

The commercial expiration dating for SB5 is (b) (4) months when stored at (b) (4) °C. (b) (4) A (b) (4) month shelf life is supported by real time stability data for the three process validation batches at (b) (4) the DS manufacturing site in the original BLA application. The manufacturing process at (b) (4) is representative of the proposed commercial DS manufacturing process at (b) (4), is stored in the same container closure system, and the data provided in the submission support comparability of DS material manufactured at (b) (4). Therefore, these data can be leveraged to establish the DS shelf life.

The stability data were collected at -20± 5°C. However, the proposed long-term storage condition for the DS is (b) (4) °C. This is acceptable (b) (4)

The stability testing program is adequate and consistent with ICH Q5C recommendations.

C. Drug Product [Hadlima] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management (see example in Attachment 3)

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process	(b) (4)	Sterility (contaminant)
Container closure integrity (maintenance of sterility during shelf-life)	Safety	Container closure breaches during storage		
Endotoxin (contaminant)	Safety, purity, and immunogenicity	Raw materials or contamination during manufacturing		
Appearance Clarity and color)	Safety and Efficacy	(b) (4)		
pH	Stability			
Osmolality	Stability and Safety	Formulation		
Deliverable volume	Essential for dosing	Manufacturing process		
Identity	Safety and efficacy	Intrinsic to the molecule		

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Protein concentration	Efficacy	(b) (4)	(b) (4)
Particulate matter (Sub-visible particles (SVP)) (product or process related impurities)	Safety and immunogenicity	Manufacturing process and Container Closure System	
Polysorbate	Safety	Formulation	(b) (4)
Visible particles	Safety and immunogenicity	Manufacturing process and Container Closure System	

- Potency and Strength:

Hadlima is supplied as a 40 mg/0.8 mL solution of adalimumab- bwwd

- Summary of Product Design:

Hadlima is supplied in a Safety prefilled syringe (PFS) and autoinjector (AI). The primary container of the Safety PFS and AI is a PFS

- List of Excipients:

16 mg Sodium citrate dihydrate, 0.544 mg Citric acid monohydrate, 0.96 mg L-Histidine, 8.64 mg L-Histidine hydrochloride monohydrate, 20.0 mg Sorbitol, 0.64 mg Polysorbate 20

- Reference Materials:

The same reference material is used for DS and DP

- Manufacturing process summary:

(b) (4)

(b) (4)

- Container closure:

The primary container closure system is a 1mL clear (b) (4) glass prefilled syringe stainless steel staked needle, rigid needle shield, and a rubber plunger stopper. The Safety PFS consists of a PFS assembled into the secondary packaging components: safe-shield body, finger flange, and plunger rod.
The AI consists of a PFS assembled into device components, front and rear subassemblies, which have no contact with the product and are not sterile.

- Dating period and storage conditions:

The proposed 36-months commercial dating period for Hadlima when stored at 5 ± 3 °C is supported by 36 months stability data from three clinical and three PV DP batches manufactured at (b) (4) . The manufacturing process at (b) (4) is representative of the proposed commercial DP manufacturing process at (b) (4) DP is stored in the same container closure system, and the data provided in the submission support comparability of DP manufactured at (b) (4). Therefore, data from DP manufactured at (b) (4) can be leveraged to establish the DP shelf life.

The stability testing program is adequate and consistent with ICH Q5C recommendations.

The Sponsor commits to place in the stability program one lot of the safety PFS and one lot of AI per year.

- List of co-package components, if applicable: None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: None

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacturing and packaging QC release testing (appearance, protein concentration, endotoxin, and microbial enumeration) In-process testing (all	(b) (4)		VAI	A six-item FDA Form 483 was issued on February 12, 2019. Deficiencies were adequately addressed in the firm's responses to the FDA-483, Inspectional Observations.	Approve

tests except (b) (4)					
Analytical Similarity data In-process testing (b) (4)	Samsung Bioepsis Co, Ltd. 107 Cheomdan-daero, Yeonsu-gu, Incheon, South Korea	3010031951	NAI	No Form 483 was issued on November 15, 2018.	Approve
Master cell bank (MCB) and working cell bank (WCB) manufacture	(b) (4)		Facility adequate	N/A	Approve
MCB and WCB storage In-process testing (b) (4)			Facility adequate	N/A	Approve
MCB and WCB storage			Facility adequate	N/A	Approve

QC release testing (all tests except appearance, protein concentration, endotoxin, and microbial enumeration) Stability testing (all tests)	(b) (4)		Facility adequate	N/A	Approve
QC release testing (all tests except appearance, protein concentration, endotoxin, and microbial enumeration) Stability testing (all tests)			Facility adequate	N/A	Approve
DS Storage			Facility adequate	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of bulk prefilled syringe QC release testing (sterility and endotoxin) In-process testing (all tests)	(b) (4)		VAI	A five-item 483 form was issued on February 15, 2019. Deficiencies were adequately addressed in the firm's responses to the FDA-483, Inspectional Observations.	Approve
QC release testing (all tests except sterility)			Facility adequate	N/A	Approve

Stability testing (all tests)	(b) (4)			
QC release testing (all tests except sterility and endotoxin) Stability testing (all tests except sterility and endotoxin)		Facility adequate	N/A	Approve
Stability testing (sterility and endotoxin)		Facility adequate	N/A	Approve
Secondary packaging		Facility adequate	N/A	Approve
Secondary packaging Release test for functionality of AI Functional stability testing of AI (all tests except container closure integrity test (CCIT))		Facility adequate	N/A	Approve/ Post-Approval Inspection Requested
Functional stability testing of AI and PFS (CCIT)		Facility adequate	N/A	Approve

	(b) (4)			

G. Facilities:

(b) (4) is responsible for DS manufacturing. A PLI was conducted from (b) (4). This inspection was system-based and covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 6-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. Refer to the EIR or the Form FDA 483 for a list of the 483 observations. Deficiencies were adequately addressed in the firm's responses to the Form FDA-483, Inspectional Observations. The inspection was classified as VAI. Approval of BLA STN 761059 was recommended.

Samsung Bioepis Co., Ltd. (FEI: 3010031951) in South Korea is responsible for DS Drug substance QC in-process testing on (b) (4). A PLI was conducted from 11/12/2018 to 11/14/2018. The pre-license inspection covered the in-process testing of adalimumab drug product. The profile covered was CTL. No Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. The inspection was classified as NAI. Approval of BLA STN 761059 was recommended.

(b) (4) is responsible for DP manufacturing. A PLI was conducted from (b) (4). This inspection was a system-based covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 6-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. Refer to the EIR or the Form FDA 483 for a list of the 483 observations.

Deficiencies were adequately addressed in the firm's responses to the Form FDA-483, Inspectional Observations. The inspection was classified as VAI. Approval of BLA STN 761059 was recommended.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
- Qualification of new WCB
- Requalification of MCB and WCB
- Qualification of new primary and working RS
- Requalification of primary and working RS
- Concurrent validation of (b) (4) at full manufacturing scale
- Concurrent validation of (b) (4) at full manufacturing scale

ii. Outstanding assessment issues/residual risk:
See list of PMCs in section I. Recommendations

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved: None

ii. Outstanding assessment issues/residual risk:
See list of PMCs in section I. Recommendations

iii. Future inspection points to consider:

(b) (4)

[redacted]

Maria Cecilia Tami

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Maria Gutierrez Lugo

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

BLA STN 761059
Drug Product Assessment

Drug Product Addendum

Product: SB5
Proposed Trade Name: Hadlima
Manufacturer: Samsung Bioepis Co, Ltd

Primary Assessor: Tracy Denison

ATL: Maria Cecilia Tami, Ph.D.

Division of Biotechnology Review and Research III
Office of Biotechnology Products

OVERALL ASSESSOR CONCLUSION

All outstanding drug product quality issues were satisfactorily addressed. No additional issues were identified in the information provided in the responses to information requests sent from March 22nd to June 3rd, 2019. From a CMC DP perspective, 351 (k) BLA 761059 is recommended for approval.

BACKGROUND

The product quality reviews for BLA 761059 were completed and uploaded into Panorama on March 22, 2019. However, at that time the responses to the information request dated March 22, 2019, were outstanding. This addendum provides an evaluation of all outstanding responses that pertain to the drug product quality assessment. The responses for all requests that are reviewed in this memo were received by the Agency on April 8, 2019.

The assessment section of this addendum memo is organized by each numerical information request and the response to that request provided by the sponsor. Each section is formatted as follows:

a) In **bold font** is the numbered FDA information request (only those pertaining to DP).
b) In normal font is a summary of the sponsor's response to the information request.
c) In *italic font* is the assessor's evaluation of the sponsor's response.

For some information requests, the response was relevant to both drug substance and drug product review. The reader is also referred to the addendum of the drug substance review by Dr. Joao Pedras-Vasconcelos for additional assessment of the information in the context of drug substance for those responses where this is applicable.

ASSESSMENT

<u>Drug Product Related Items in the Information Request Sent on March 22, 2019</u>

FDA'S QUESTION 4:
In our information request dated 3/8/2019, we requested you update the release and stability specifications for Drug Substance (DS) and Drug Product (DP) to include:

a. **For purity by icIEF include Delta pI: Main peak within (b) (4) pI units of corresponding peak in the RS, %acidic (b) (4), % main (b) (4) or %Basic (b) (4)**
b. **For identity by icIEF, update the specifications section to describe the criteria that need to be met for the sample to conform to RS. You could provide this information as a footnote to the specifications Tables.**
c. **For purity by CE-SDS (NR), include % Total purity (b) (4) and "%other highest single impurity (b) (4)" to monitor additional LMW impurities.**
d. **Purity by SE-HPLC, revise acceptance for HMW impurities to (b) (4)**

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We note that these revisions were not updated in the pertinent sections of you 351 (k) BLA submission. Update sections 3.2.S.4.1 and 3.2.P.5.1 to reflect the updates to the DS and DP specifications.

Sponsor's Response: The sponsor updated the drug product specifications to the version shown in the table below.

Table 1: SB5 DP Release and Shelf-life Specifications

Test Item			Release Acceptance Criteria	Shelf-life Acceptance Criteria
General test	Appearance	Clarity	(b) (4)	
		Colour		
		Visible particles		
	pH			
	Osmolality			
Identity	icIEF			
	Competitive inhibition binding assay to TNF-α by FRET			
Quantity	Protein concentration (A_{280})			
	Extractable volume			
Biological activity	Competitive inhibition binding assay to TNF-α by FRET			
	TNF-α neutralisation assay by NF-κB reporter gene			
Purity and impurity	CE-SDS (non-reducing)	%Total purity		
		%2H1L		
		%Other highest single impurity		
	SE-HPLC	%Monomer		
		%HMW		
	icIEF	pI of main peak		
		%Acidic		
		%Main		

Assessor Comment: The sponsor updated the icIEF purity specifications to include the acceptance criteria proposed in the amendment dated November 5, 2018 . The Sponsor also updated the icIEF identity test to indicate it must also meet the same criteria as the icIEF test as applied for purity. The wider icIEF acceptance criteria for DP stability were discussed in the original DP memo for the BLA. The proposed changes for CE-SDS (NR) and for SE-HPLC specifications were also updated in the 351 (k) BLA submission. The changes are acceptable.

FDA'S QUESTION 5:
In response to question 2a of an IR received 11/05/2018 (eCTD sequence 0022), you concluded that, compared to SE-HPLC, non-reducing (NR) CE-SDS is the "more appropriate method to monitor main peak." However, we do not agree with your conclusion because:

a. **Method validation data provided to support suitability of the NR CE-SDS and SE-HPLC methods indicate that SE-HPLC is more sensitive to changes in main peak (monomer). Specifically, SE-HPLC detected a 50% decrease in monomer in drug substance samples heated at (b) (4). However, no significant difference in monomer was detected by NR CE-SDS in drug substance samples heated at (b) (4)**

b. **NR CE-SDS separates based on the mobility of mass-to-charge ratio of denatured protein species. On the other hand, SE-HPLC does not require denaturation and separates based on the hydrodynamic radius and shape. Therefore, SE-HPLC provides more relevant information on the molecule because it requires less sample manipulation and may also provide additional information on higher order structure.**

Therefore, we conclude that compared to NR CE-SDS, SE-HPLC provides better control of monomeric SB5. Revise your drug substance and drug product release and stability specifications to include a quantitative lower limit for monomer. Update your 351 (k) BLA accordingly.

Sponsor's Response: As shown in the updated DP specification table from the response to question #4, the Sponsor included a lower limit for monomer for the SE-HPLC test of (b) (4)% on release and of (b) (4)% on stability. While the stability specification limits HMW species to be less than (b) (4)%, the proposed stability specification leaves (b) (4)% material that is not controlled. It is expected that this (b) (4)% represents low-molecular weight species based on stability studies performed under real time, accelerated and stress conditions. LMW species are not expected to be active. However, to support the proposed stability specifications for SE-HPLC, the Sponsor showed that a decrease in monomer of (b) (4)% does not impact biological activity. Therefore, impurities in the range of (b) (4)% are not expected to impact product activity and quality.

Assessor Comment: The changes are in agreement with the request and the acceptance criteria are acceptable.

FDA'S QUESTION 13:
You noted in your IR response received 2/12/2019 that three materials are used in the (b) (4) DP process that are not used in the (b) (4) process and were therefore, not included in the extractable studies. These three materials are (b) (4) Provide data to indicate what compounds are extractable from these materials. Provide a risk assessment for any identified extractable compounds that may leach into the product regarding the risk to both SB5 product quality and patient safety.

Sponsor's Response: The Sponsor performed extractable studies on the three new materials at (b) (4) under the conditions and durations shown in the following table. The studies included the components of these materials exposed to the extraction solutions of (b) (4)

Table 1: Extraction Condition

(b) (4)

(b) (4)

[redacted]

Assessor Comment: The Sponsor tested the three new materials from [redacted] (b) (4) *at low and high pH and with* [redacted] (b) (4) *for durations equal to or exceeding those expected during manufacturing and using harsher conditions of temperature and solvent than would be expected during routine manufacturing. The risk of leachables from these three materials that could impact patient safety or product quality is low and is acceptable.*

FDA'S QUESTION 14:
In a previous information request, you were asked to indicate your commitment to test identity of Safety PFS and AI lots after final labeling in Section 3.2.P.5.1. Instead, in amendment 0043 dated 03/13/2019, you indicated this intention in Section 3.2.P.5.2.1.2 around the description of the identity test. This is not a clear place to include this information. Either update specification tables in Section 3.2.P.5.1 with an identity specification and footnote that identity testing is performed on labeled product for both Safety PFS and AI, or alternatively, update Section 3.2.P.3.3 to indicate that samples are taken for identity testing following labeling for both Safety PFS and for AI, in their respective sections.

Sponsor's Response: The Sponsor updated Section 3.2.P.3.3.4.12 (for Safety PFS) and Section 3.2.P.3.3.5.7 (for AI) Description of Manufacturing Process and Controls, to indicate that samples for identity release testing are collected after labeling.

Assessor Comment: The Sponsor's update is adequate as it addresses our request to comply with the requirement to perform identity testing after labeling as per 21 CFR 610.14 .

FDA'S QUESTION 15:
To help establish the dating period for DP provide the following updates if available:

a. **Stability data from your on-going container closure leachable studies, as well as from the on-going [redacted] (b) (4) compatibility studies, as described in Section 3.2.P.2.4.**
b. **Results from ongoing real-time stability studies with DP manufactured at [redacted] (b) (4)**

Sponsor's Response: For Part a, the Sponsor provided updated results to the container closure leachable study and the [redacted] (b) (4) compatibility study. The additional data support the stability of the product in the container closure and that the risk of product quality concerns from [redacted] (b) (4) is low.

For Part b, the Sponsor provided the additional stability time point data indicated in the following table to Section 3.2.P.8.1 and 3.2.P.3.

Table 1: Summary of SB5 DP Stability Study Time Point Updates

Manufacturing Site	Manufacturing Phase	Lot Numbers	Stability Condition	Updated Time Points (Months)
[redacted] (b) (4)	PVR	028G15, 029G15, 030G15	Long-term	30, 36
		SB5PV01, SB5PV02, SB5PV03		9, 12, 18
		SB5PV05, SB5PV06, SB5PV07	Long-term	6, 9, 12
			Accelerated	6

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Assessor Comment: The updated stability results were assessed. The real-time leachable study supports the stability out of SB5 DP for 36 months for the lots from (b) (4)*. The updated data at accelerated conditions support the product stability also, except that acidic species in icIEF do increase and correlated with a decrease in main peak, which was previously observed in other available data in the original submission. The additional data from the container closure leachable study and* (b) (4) *compatibility study support that residual* (b) (4) *in SB5 DP does not negatively impact DP quality and the product shelf-life of 36 months is acceptable.*

FDA'S QUESTION 16:
You assess extractable volume by converting to volume the measured weight of expelled volume using the density of formulated SB5. Provide the calculated density of SB5 used for this assessment. Provide data to show that expected density of SB5 is consistent between lots to rely on the calculation of volume by using density.

Sponsor's Response: The Sponsor provided a tabular summary of density testing from four PVR DS lots and three PVR DP lots, as shown below. (b) (4)

(b) (4)

Assessor Comment: The data support a consistent density, when rounded up, of (b) (4) *g/mL, which is the value the Sponsor is using for density of SB5. The data support that the calculation of volume using density is acceptable because density is consistent between lots.*

FDA'S QUESTION 17:
Table 1 in Section 3.2.P.7 provides a generic description of your container closure parts but does not specify the supplier part numbers. Provide an updated table(s) in Section 3.2.P.7

that indicate all specific supplier part numbers for every component of your container closure. Include applicable DMF numbers in the table(s) also.

Sponsor's Response: The Sponsor provided an updated table in Section 3.2.P.7 that included the part numbers and DMF numbers for the container closure parts.

Assessor Comment: The updated table is adequate in that it provides the requested information.

FDA'S QUESTION 18:
In your IR response provided on 03/6/2019, you indicate a PQ shipping validation study was performed for a shipping lane between (b) (4) to a (b) (4) Indicate if this (b) (4) will be a storage and distribution location for commercial SB5 DP. If it will be, update Section 3.2.P.3.1 to reflect all intended locations.

Sponsor's Response: The (b) (4) will not be used during commercial distribution of the SB5 under the BLA.

Assessor Comment: The response is acceptable and clarifies that this facility will not be used.

Tracy Denison

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Maria Cecilia Tami

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GUID: 508da6d9000264e1912653dd7f25aae4

U.S. FOOD & DRUG ADMINISTRATION

BLA 761059
Addendum to DS Quality Assessment
Product: SB5
Proposed Trade Name: Hadlima
Manufacturer: Samsung Bioepis Co, Ltd

João Pedras-Vasconcelos: DS
Merry Christie: Validation of Analytical methods
Maria Cecilia Tami: ATL
Susan Kirshner: Tertiary Assessor/Review Chief

Division of Biotechnology Review and Research III

Reference ID: 4466647

U.S. FOOD & DRUG ADMINISTRATION

OBP CMC Assessment Data Sheet

1. BLA#: 761059

2. Assessment Date: June 17, 2019

3. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request (OBP X)	March 22, 2019
Information Request (OBP XI)	April 23, 2019
Late Cycle Meeting	April 25, 2019
OBP Teleconference	May 02, 2019
Information Request (OBP XII)	May 20, 2019
Information Request (OBP XIII)	May 20, 2019

4. Submissions Assessed:

Submission:	Date Received:	Assessment Completed (yes or no)
761059/0048 response to IR X	April 8, 2019	Yes
761059/0050 pending responses to IR IV and IR X	April 19, 2019	Yes
761059/0051 pending responses to IR IV	April 29, 2019	Yes
761059/0054 response to OBP Teleconference	May 14, 2019	Yes
761059/0055 pending responses to IR XI	May 21, 2019	Yes
761059/0056 response to IR XII	May 24, 2019	Yes
761059/0057 response to IR XIII	June 7, 2019	Yes

Assessor note: *By the time the primary review memo was uploaded in Panorama, the responses to IR X had not be received. During the review of the responses to this IR, additional information was requested in IRs dated April 23, 2019 (IR XI), May 20, 2019 (IR XII) and May 29, 2019 (IR XIII). The responses to IR X-XIII are reviewed and discussed in this addendum to the primary review memo.*

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U.S. FOOD & DRUG ADMINISTRATION

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation

We recommend approval of 351 (k) BLA 761059. Samsung Bioepis provided satisfactory responses to all information requests sent from March 22nd to June 3rd, 2019. The Sponsor adequately addressed all outstanding CMC issues.

II. List of Deficiencies to be Communicated

There are no CMC-Product Quality deficiencies identified that may preclude approval of this BLA.

III. List of Post-Marketing Commitments/Requirements

The following CMC items will be addressed post marketing. This is draft PMC language. For the final PMC language agreed with the Sponsor, please refer to the action letter for this application.

1- To implement an SB5 derived assay control for the complement-dependent cytotoxicity (CDC), TNF-α reporter gene potency, and TNF-α FRET binding potency assays and to establish acceptance criteria for the assay control relative to the reference standard (RS). The final study report(s) will be submitted in accordance with 21 CFR 601.12.

2- To implement a system suitability criterion [redacted] (b) (4) and establish a tighter limit for %difference in the peak areas [redacted] (b) (4) The final study report(s) will be submitted in accordance with 21 CFR 601.12.

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The following information request responses were assessed by JPV

Amendment 48 (04/08/2019)

Drug Substance:

(b) (4)

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Joao Pedras Vasconcel

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Comments: DS addendum

Merry Christie

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Maria Cecilia Tami

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351(k) BLA IMMUNOGENICITY ASSAYS ASSESSMENT

Application Type	BLA
Application Number	761059 STN 12
Submit Date	July 23, 2018
Received Date	July 23, 2018
BsUFA Goal Date	July 23, 2019
Division/Office	DBRR3/OBP
Assessment Completion/Revision Date	June 3, 2019
Product Code Name	SB5 (company code) BIIB606 (CMO code)
Proposed Nonproprietary Name[1]	Adalimumab-bwwd
Proposed Proprietary Name[1]	Hadlima and Hadlima PushTouch
Pharmacologic Class	TNF-α inhibitors
Applicant	Samsung Bioepis Co, Ltd.
Applicant Proposed Indication(s)	Rheumatoid Arthritis (RA); Psoriatic Arthritis (PsA); Ankylosing Spondylitis (AS); Adult Crohn's Disease (CD); Ulcerative Colitis (UC); Plaque Psoriasis (Ps); Juvenile idiopathic arthritis (JIA) (4 years of age and older)
Recommended Regulatory Action	Approval

Immunogenicity Assessors

Primary Assessor(s)	Joao Pedras-Vasconcelos, Ph. D.
Secondary Assessor(s)	Maria Cecilia Tami, Ph.D
Tertiary Assessor(s)	Susan Kirshner, Ph. D.

[1] The proposed nonproprietary and proprietary names are conditionally accepted until such time that the application is approved.

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1. Summary Basis of Recommendation/Executive Summary

1.1 Immunogenicity Executive Summary and Recommendation

US-licensed Humira (adalimumab) (hereafter referred to as US-Humira) is a fully human IgG1kappa therapeutic mAb specific for human TNF-α which is capable of neutralizing inflammatory effects of this acute-phase cytokine in vitro and in vivo. US-Humira is licensed for the following indications: rheumatoid arthritis (RA), juvenile idiopathic arthritis (in patients 2 years and older), ankylosing spondylitis, adult Crohn's disease, pediatric Crohn's disease, ulcerative colitis, plaque psoriasis, psoriatic arthritis, hidradenitis suppurativa, and uveitis. SB5 (proposed proprietary name Hadlima) is Samsung Bioepis' proposed biosimilar to US- Humira. Samsung is seeking approval of SB5 for the following indications, for which US-Humira has previously been licensed: RA, juvenile idiopathic arthritis (in patients 4 years and older), ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, plaque psoriasis, and psoriatic arthritis. Samsung proposes two presentations of SB5, a 40mg/0.8 ml prefilled syringe and a 40mg/0.8 ml single use-auto-injector; both presentations are previously licensed for US-Humira; the proposed biosimilar has formulation differences from US-Humira.

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Samsung performed two clinical studies where immunogenicity rates were assessed- 1) a three- way single dose cross-over PK/PD clinical study SB5-G11-NHV in healthy volunteers comparing SB5 to US-Humira and EU-approved Humira (hereafter referred to as EU-Humira) ; 2) a comparative, parallel arm, multi-dose clinical safety study SB5-G31-RA in patients with RA using SB5 and EU-Humira. Samsung followed a recommended tiered immmunogenicity assessment approach of screening, confirmatory, and titering steps, followed by neutralizing antibody assessment in the confirmed ADA+ study samples. The primary supportive study for comparative immunogenicity is study SB5-G31-RA.

Samsung contracted the development and validation of anti-drug antibody (ADA) and neutralizing anti-drug antibody (NAb) assays to contract research organization (b) (4) . (b) (4) developed screening, confirmatory, and titer ADA assays as well as Nab assays using a single assay approach based on the proposed biosimilar and using MesoScale Discovery electrochemiluminescent (ECL) platform. (b) (4) performed study-specific ADA and Nab assay validations using baseline sera to establish *in study* cutpoints. A summary of the immunogenicity assays used in supportive clinical studies is provided in Table 1 below, compiled by the assessor. The developed ADA and NAb assays are suitable for intended purpose, and so resulting immunogenicity data can be regarded as valid.

Assessor Table 1: Summary of immunogenicity a s s a y s used in supportive clinical studies.

Clinical Study	SB5-G11-NHV	SB5-G31-RA
ADA assay **MSD platform: biotin SB5/sTag-SB5** **Commercial PC: human anti-Humira mAb**	Reports: 8295677/8295864 • Drug tolerance = 10 µg/mL each drug • Sensitivity = 5.4 ng/ml NHS • SCP FP ~7.6% (43/567) • CCP: ≥18% (1% FP) • MRD: 1/10 **Suitable for intended purpose post-amendment 37**	Reports: 8306911/8295856 • Drug tolerance = 20 SB5; 40 µg/mL EU-Humira • Sensitivity = 63 ng/mL RA sera • SCP FP ~7.8% (323/4124) • CCP: ≥44% (1% FP) • MRD: 1/50 **Suitable for intended purpose post-amendment 21**
NAb assay **MSD platform: biotin SB5/Humira /sTag-TNF-α** **Commercial PC: human anti-Humira mAb**	Reports: 8297981/8295864 • *Drug Tolerance: <0.5ug/ml* • TNF tolerance = 0.5 ng/ml • Sensitivity = 132 ng/ml in NHV serum • NCP (fixed): 0.873 (1% FP) • MRD: ¼ • Poor drug tolerance but still able to detect NAbs in Healthy subjects (>80%) **Suitable for intended purpose post-amendment 37**	Reports: 8306921/8295856 • *Drug Tolerance: <0.5ug/ml* • TNF tolerance = 0.5 ng/ml • Sensitivity = 148 ng/mL in RA serum • NCP (fixed): 0.863 (1% FP) • MRD: ¼ • Poor drug tolerance but still able to detect NAbs in RA subjects (>50%) **Suitable for intended purpose post-amendment 37**

PC: positive control; SCP: Screening Cut point; CCP: Confirmatory cut point; NCP: Neutralization cut point; FP: false positive rate; MRD: minimum required dilution. MSD: MesoScale Discovery

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1.2 Deficiencies and Other Recommended Comments to Applicant

None. ADA and NAb assays supporting comparative clinical safety study SB5-G31-RA and clinical PK/PD cross over study SB5-G11-NHV can be considered suitable for intended purpose.

2. Assessment

Document Reviewed	Submission Date
BLA 761059 SN 01	08/28/2016
BLA 761059 SN 12	7/23/2018
BLA 761059 SN 21	10/29/2018
BLA 761059 SN 37 Response to IR 1	2/21/2019

2.1 Background Immunogenicity Information

SB5, US-Humira, and EU-Humira are administered by subcutaneous injection. Subcutaneous routes of administration could result in ADA of the IgM and IgG isotype, with IgG isotype ADA dominating a persistent response.

Assessor comment*: The Sponsor used a bridging assay format for the screening and confirmatory assays. Bridging assays can detect all antibody isotypes therefore, this is an acceptable approach.*

2.2 Validation of Anti-Drug Antibody Assay

Samsung used a tiered approach for ADA assay development including screening, confirmatory, titering, and neutralizing assays. To detect the ADA in the serum samples, Samsung contracted the development of a MesoScale Discovery (MSD) platform electrochemiluminescence (ECL) bridging ELISA to (b) (4) [redacted]. Following initial development work with various assay formats involving SB5, US-Humira and EU-Humira, Samsung opted for a single-assay approach based on the proposed biosimilar for capture and detection. The single assay was demonstrated during development to have similar antigenic equivalence for SB5, US-Humira, and EU-Humira through cold competition experiments. The NAb assay is discussed in section 2.3 below.

Assessor comment*: The tiered approach to ADA assessment is consistent with FDA recommendations in FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products-Developing and Validating Assays for Anti-Drug Antibody Detection (2019) and is acceptable. The use of a single assay that uses the proposed biosimilar for capture and detection is consistent with FDA recommendations in FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2015) and is acceptable.*

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2.2.1 Method Principle

To conduct the screening assay, serum samples are first subjected to an acid treatment to dissociate the pre-formed ADA-drug complexes. Samples are then incubated Biotin-SB5 + Sulfo-Tagged SB5, and the complexes are added to a streptavidin-coated MesoScale Discovery (MSD) plate. The chemiluminescent signal readout is obtained from an ECL reaction (sTag/ tripropylamine) and measured by a MSD plate reader. The higher the level of ADAs present in the sample, the higher the ECL signal will be in the assay.

If the sample signal is higher than the screening cut-point (SCP), the specificity of the sample for the analyte is confirmed using a confirmatory assay. The confirmatory assay is a competitive inhibition test in which the signal from a sample spiked with an excess amount of SB5 is compared with the signal from an unspiked sample. Specific ADAs will bind to the spiked SB5, resulting in a signal reduction compared to the signal from unspiked samples. If the % signal reduction is equal to or greater than the confirmatory cut-point (CCP), the sample is reported as confirmed positive for ADAs.
An ADA titer assay is performed by preparing a dilution series of test samples. The fold dilution of the most diluted sample that exhibits a signal above the SCP is defined as the ADA titer. Titer cut points (TCP) were mathematically derived from resulting dilution curves.

Two sets of ADA assays were developed to support immunogenicity assessment of the two clinical studies with an immunogenicity component in their design- one for PK/PD cross-over study SB5-G11-NHV (validation report 8295853) and one for comparative safety study SB5-G31-RA (validation report 8306911). Validations were performed in a study-specific manner, using pre-study clinical samples to set up *in-study* screening, confirmatory, and titer cut-points. The clinical ADA data along with clinical NAb data (sect 2.2 below) were provided in integrated reports 8295864 (study SB5-G11-NHV) and 8295856 (study SB5-G31-RA), respectively.

2.2.2 Validation Exercises

Assessor comment*: The validation results for ADA assays used in each clinical study and a reviewer assessment are provided in Summary Table 2.1 below. Raw validation data are not provided unless necessary to discuss identified validation issues.*

Table 2.1: Validation Results and Assessor Assessment for ADA assays used in Phase 1 SB5-G11-NHV ((b) (4) validation reports 8295853/8295864) and Phase 3 SB5-G31-RA ((b) (4) Validation Reports 8306911/8295856)

Validation Parameter	Clin Study SB5-G11-NHV Val Reports: 8295853/8295864	Clin Study SB5-G31-RA Val Reports: 8306911/8295856	Assessor Comment
Contract Research Org	(b) (4)		*Bioanalytical inspection waived by OSIS as* (b) (4)

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	Validation performed by at least 2 analysts on 3 separated days	Validation performed by at least 2 analysts on 3 separated days	*had been recently inspected*
Assay principle	• MSD (ECL) based Single Bridging ELISA with Biotin-SB5 + sTagged-SB5 onto streptavidin coated MSD plates. • The higher the ADA the higher the ECL signal (Relative Light Units) detected • Blocking is performed with SuperBlock buffer.	Same	*Applicant used single assay approach based on the proposed biosimilar, consistent with 2015 FDA Guidance* ***Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry***
Sample Pretreatment (Acid dissociation)	1 in 5 in 300 mM acetic acid followed by a 1:1 dilution in neutralization buffer	1 in 25 in 300 mM acetic acid followed by a 1:1 dilution in neutralization buffer	*Acid dissociation is a common approach to reduce drug interference. A single round of acid dissociation was performed. Results were acceptable.*
Positive control (PC)	Commercial Serotec AbD 18655_hIgG1 anti - adalimumab mAb (Bio-Rad) is a neutralizing ultra-high affinity anti-idiotypic antibody that specifically recognizes adalimumab and inhibits the binding to its TNFα target.	Same	*PC used in validation of ADA and NAb assays, including LPC and HPC preparation.* *Use of commercial antibody for validation and system suitability is acceptable if Samsung demonstrates antigenic equivalence between SB5 and US-Humira and/or EU-Humira*
PC Dose Curve and Hook Effect	0.32, 1.6, 8, 40, 200, 1000, 5000, 10000, 15000, 20000 ng/ml R2>0.99 PC Hook Effect observed > 10 ug/ml	1.22,2.44, 4.88, 9.77, 19.5, 39.1, 78.1, 156.25, 312.5, 625,1250, 2500, 5000 10000, 25000 ng/ml R2>0.99 No PC Hook Effect observed	*Dose Ranges are sufficient to establish 4 PL curve fits.* *No hook effect for RA sera. Hook effect detected for NHV sera at higher PC concentrations.*
LPC	6.5ng/ml LPC calculated to fail ~1%	74 ng/ml LPC calculated to fail ~1%	*Both LPC concentrations were suitably determined*
HPC	10,000 ng/ml	25,000 ng/ml	*Both HPC tested 100% positive for all tested conditions, as expected.*
Matrix and NC	Normal Human Serum pool	Normal Human Serum pool	*The signals of blank samples must be below*

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			SCP. The use of healthy human serum pool as the matrix control is acceptable.
MRD	1:10 final	1:50 final MRD higher for RA serum to reduce matrix effects due to auto-antibodies	*Correctly includes acid dissociation and buffer neutralization steps to determine MRD.*
NC system suitability range	Expected response of ≤ 113 ECL RLU	Expected response of ≤ 100 ECL	*Acceptable for MesoScale Discovery ECL assays*
LPC system suitability range	Expected response of ≥ 79 and ≤ 163 ECL RLU	Expected response of ≥ 160 and ≤ 349 ECL	*Acceptable for MesoScale Discovery ECL assays*
HPC system suitability range	Expected response of ≥ 74271 and ≤ 102593 ECL RLU	Expected response of ≥ 38485 and ≤ 87007 ECL	*Acceptable for MesoScale Discovery ECL assays*
Antigenic Equivalence testing (Competitive DOE)	PC conc. (0, 6.5, 50, 250 and 10000 ng/ml) competed with unlabeled SB5 (Clin lot 002K13), US-Hum (lot 250732E) or EU-Hum (29396XH10) at 0, 5, 10, 20, 40 ug/ml *Curves overlapped at all concentrations tested*	PC conc. (0, 74, 250, 1000, 5000, and 10000 ng/ml) competed with unlabeled SB5 (Clin lot 012C14) or EU-Hum (lot 38466XD03) at 0, 5, 10, 20, 40 ug/ml) *Curves overlapped at all concentrations tested*	*Data show that a single ADA assay approach based on SB5 is acceptable as the resulting competition curves overlapped at all concentrations tested*
Screening cut- point (SCP) Floating CP: Mean NC response × normalization factor [1.15]	Used 110 In study pre-dose NHV samples *In study* FP ~7.6% (43/567) Floating CP: Mean 6 NC × 7 CP Data determined to be normally distributed. No outliers found.	Used 99 In study pre-dose RA samples *In study* FP ~7.8% (323/4124) Floating CP: Mean 6 NC × 2.3 CP Data determined to be normally distributed once outliers were statistically removed.	*Both assays used in study baseline samples to establish study-specific cut points. This is acceptable as both in-study FP rates fell within 2-11%, statistical range for a screening assay.* *RA sera are expected to have some degree of auto-antibodies and thus a larger number of outliers that should be removed following outlier analysis.*
Confirmatory cut-point (CCP) Floating	≥ 24.0% (based on 30 pre-dose NHV study samples; 99.9% CI; 0.1%FP) ≥ 18.0% (based on 30 pre-dose NHV study samples; 99% CI; 1%FP) *Originally Samsung used 99.9 CI, 0.1% FP (SN 12) but reanalyzed data using 99% CI; 1%FP in SN37 following Jan 21, 2019 IR. This is acceptable.*	≥ 54.3% (based on 50 pre-dose samples; 99.9% CI; 0.1%FP) in STN01/12 ≥ 44% (based on 50 pre-dose samples; 99% CI; 1%FP) following reanalysis provided in STN21. *Samsung included both 0.1% (SN 12) and 1% FP rate (SN 21) analysis in their submission which is acceptable*	*Applicant initially used 0.1% FP for both studies, but in amendment 21 reanalyzed RA study data using the recommended 1% FP (44% CCP). In amendment 37 applicant reanalyzed NHV study data using recommended 1% FP (18% CCP).* *The additional confirmed positive samples were not reanalyzed by either ADA*

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			titer assay nor NAb assay because ADA and NAb assays are inactive. For titer estimate the Applicant performed data simulations correlating S/N ratios with known titers to estimate titers of the additional samples (see additional comments below).
Titer Cut Point (TCP)	≥3.71 (99.9% CI, 0.1% FP) Parametrically estimated from PC dose curve	≥3.72 (99.9% CI, 0.1% FP) Parametrically estimated from PC dose curve	*TCP was similar for both studies. The cut points were set appropriately.*
Assay Drug tolerance	LPC tolerant to 10ug/ml of SB5, US-Humira and EU-Humira	LPC tolerant to 20ug/ml of SB5, and 40ug/ml EU-Humira	*Mean Drug C trough <10 ug/ml. 0.3% (3/865) RA study samples had drug at 22-32 ug/ml.*
Target (TNF-α) tolerance	Not Reported	LPC and HPC spiked with 500 pg/ml TNF-α all screened positive (100%)	*TNF-α is not expected to impact ADA assay, but could impact NAb assay, as it uses Sulfo-tagged TNFα as detection reagent*
Sensitivity	5.37 ng/mL in NHS Back-calculated from dose curves	63.38 ng/mL in RAS Back-calculated from dose curves	*Sensitivities for both studies are within current recommendations ≤100ng/ml*
Repeatability/Intra-assay variability	NC %CV 3.5-6.2 LPC %CV 1.3-7.6 HPC %CV 0.7-4.7	NC %CV 3.8-10.8 LPC %CV 1.5-7.6 HPC %CV 1.0-6.2	*Repeatability for both studies are <15% and are acceptable*
Intermediate Precision (IP)/inter-assay variability	NC %CV 16.6 LPC %CV 12.4 HPC %CV 6.1	NC %CV 9.4 LPC %CV 12.4 HPC %CV 12.9	*IP for both studies are <20% and are acceptable*
Selectivity	10 NHV sera spiked with LPC and HPC all screened positive (100%)	10 RA sera spiked with LPC and HPC all screened positive (100%)	*Selectivity suitably demonstrated for both studies*
Stability	LPC and HPC: 6 freeze/thaw cycles with 80-120% accuracy LPC and HPC: stable at RT for 24 hours with 80 –120% Accuracy	LPC and HPC: 7 freeze/thaw cycles with 80-120% accuracy LPC and HPC: stable at RT for 24 hours with 80 –120% Accuracy	*Stability testing shows PC remain stable for up to 6-7 freeze thaw cycles when stored at ≤ -20 ℃, and up to 24hrs at RT. This is acceptable.*
Lipemia	3 lipemic sera spiked with LPC and HPC screened positive (100%), while testing negative if unspiked	3 RA sera spiked with 300 mg/dL of triglyceride and LPC and HPC screened positive (100%), while testing negative without PCs	*Data indicate that increased levels of triglycerides do not impact the ADA assay. Testing is acceptable.*
Hemolysis	Matrix spiked 2, 5 and 10% lysed whole blood tested negative, but were positive	Matrix spiked 2% and 5% lysed whole blood tested negative, but were 100%	*Data indicate that up to 10% sera hemolysis does not impact the NHV assay,*

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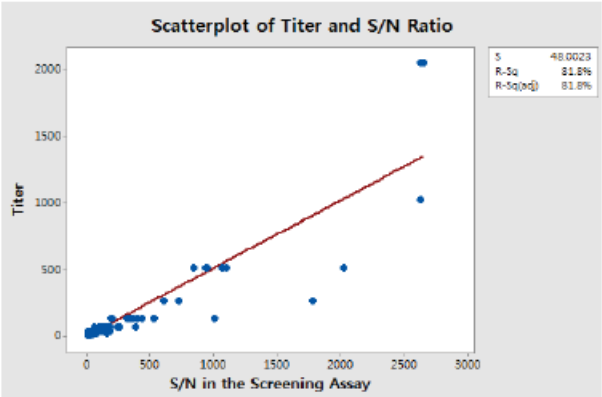
	when spiked with LPC and HPC	positive when spiked with LPC and HPC	*and that 5% sera hemolysis does not impact the RA assay. Testing is acceptable*
ADA Assay Assessment	**Suitable for Intended purpose following reanalysis of CCP using 1%FP rate (Amendment 37).**	**Suitable for Intended purpose following reanalysis of CCP using 1%FP rate (Amendment 21)**	**Individual clinical study ADA assays are suitably validated**

Additional Assessor Comments:
Samsung initially used 0.1% FP for the CCP, but subsequently analyzed RA study data using the recommended 1% FP (44% CCP) and provided reanalysis data in amendment 21. The resulting screening, confirmatory, and titering ADA assays are suitable for intended purpose.

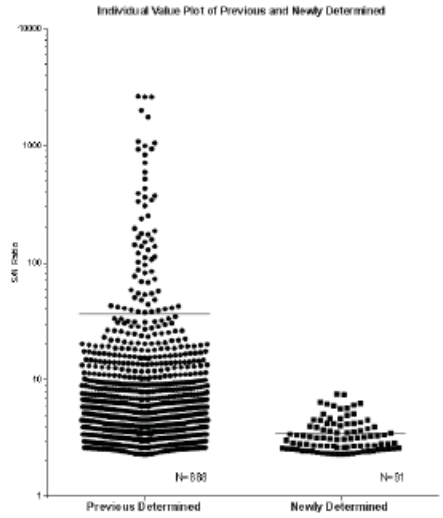
The Applicant's Integrated Summary of Safety and Integrated Summary of Efficacy were updated with the new data in amendment 37 (Jan 21, 2019) and Section 5.3.5.3 ISE and ISS Attachment 13 (for Study SB5-G11-NHV) and Attachment 14 (for Study SB5-G31-RA).

The CCP used in study SB5-G11-NHV initially included only the 0.1% FP rate. Samsung provided results from their reanalysis of the data using a 1% FP in amendment 37. The assay table above contains the updated CCPs for both studies.

Samsung was unable to titer additional confirmed positive samples for safety study SB5-G31-RA as Samsung no longer has active ADA assays for SB5. To estimate the titers of the 91 newly identified positive samples Samsung chose to correlate ECL signal/negative control (S/N ratios) from the screening assay with ADA titers of the 888 study samples tested using CCP 99.9% CI and 0.1% FP rated (left figure below). Based on this correlation, Samsung subsequently plotted the distribution of S/N ratio of the original 888 study samples with that of the 91 newly identified positive samples (right figure below). Based on the S/N distributions, the titers of the newly identified positive samples are likely close to MRD of 1/50.



Correlation between S/N Ratio in the Screening Assay and Titer from the ADA-positive Samples Determined by a Confirmatory Cut Point Based on 0.1% False Positive Rate



Distribution of S/N Ratio in the Screening Assay of Previous (0.1% False Positive Rate) and Newly Determined (1.0% False Positive Rate) ADA-positive Clinical Samples

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The S/N approach followed by Samsung is an exploratory alternative to formal titer determination, that was acceptable for the current situation, i.e. when assessing samples where ADA titers are low and will not exceed the upper linear range of the assay.

2.3 Validation of Neutralizing Antibody Assay

Study sera samples confirmed as ADA positive are further tested for neutralizing ADAs. The method described in validation report 829798 was used to test samples from healthy volunteers (HV) from clinical study SB5-G11-NHV while the method described in validation report 8306921 was used to test samples from patients with RA from clinical study SB5-G31-RA.

The NAb assay uses a competitive ligand binding assay (CLBA) format to evaluate the ability of ADAs to SB5, US-Humira, or EU-Humira to prevent binding of the drug to its cognate target, TNF-α receptor. The assays were developed by (b) (4)), using a single assay MSD platform. Other NAb assay formats were also explored, including a TNF-α-neutralization cell-based assay (CBA) based on the current NF-kb Reporter Gene Assay used for potency, but Samsung opted for CLBA because it showed better drug tolerance than the CBA at concentration ranges higher than LPC (150-170ng/ml). Both assay types showed low drug tolerance (<0.5ug/ml) at LPC.

The NAb assay clinical data along with ADA clinical data (sect 2.1 earlier in report) were provided in integrated reports 8295864 (study SB5-G11-NHV) and 8295856 (study SB5-G31-RA), respectively.

2.3.1 Method Principle

Serum samples are first subjected to an acid treatment to dissociate the pre -formed antibody complexes as in the ADA assays. Subsequently, samples are added to Biotin-SB5/Streptavidin coated MSD plate to anchor down ADAs. During validation Biotin-US-Humira and Biotin-EU-Humira/SA coated were also assessed for comparison. Samples are then incubated with sulfo-tagged (sTag) TNF-α. If ADAs do not exhibit neutralizing ability, SB5- biotin can bind to TNF-α and result an ECL signal due to the reaction between tripropylamine and sTag. If anti-drug NAbs are present in the sample, a reduction of ECL assay signal is observed when compared to a negative control sample. The sample is reported as NAb positive when the inhibition -signal is equal to or greater than the assay cut-point.

2.3.2 Validation Exercises

Assessor comment: *The assay validation results for the NAb detection assays used in each clinical study along with the reviewer assessment are provided in Summary Table 2.2 below, which was compiled by the assessor. Raw validation data are not provided unless necessary to discuss identified validation issues.*

Table 2.2: Validation Results and Assessor Assessment for NAb Detection assays used in Phase 1 SB5-G11-NHV ((b) (4) validation reports 8297981/8295864) and Phase 3 SB5-G31-RA ((b) (4) Validation Reports 8306921/8295856)

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Validation Parameter	Clin Study SB5-G11-NHV Val Reports: 8297981/8295864	Clin Study SB5-G31-RA Val Reports: 8306921/8295856	Assessor Comment
Contract Research Org	(b) (4)		*Bioanalytical inspection waived by OSIS as (b) (4) had been recently inspected*
Assay principle competitive ligand binding assay (CLBA)	• MSD (ECL) based competitive ligand binding assay (LBA) • Biotin-SB5 + sTagged TNF-α onto streptavidin coated plates. • NAbs inhibit binding of labelled drug to ligand, decreasing ECL signal (RLU). • Blocking is performed with SuperBlock buffer	Same	*Applicant used single assay approach based on the proposed biosimilar, consistent with 2015 FDA Guidance* ***Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Guidance for Industry*** *, which is acceptable.* *The choice of competitive LBA format instead of a bioassay is acceptable.*
Sample Pretreatment (Acid dissociation)	1 in 2 in 0.5 M glycine HCl followed by a 1:1 dilution in neutralization buffer. *Different from ADA assay.*	1 in 2 in 0.5 M glycine HCl followed by a 1:1 dilution in neutralization buffer. *Different from ADA assay.*	*Acid dissociation is a common approach to reduce drug interference. The acid solution is different from the ADA assays, but a single round was used as well.*
Positive control (PC)	Commercial Serotec AbD 18655_hIgG1 anti - adalimumab mAb is a neutralizing ultra-high affinity anti-idiotypic antibody that specifically recognizes Adalimumab and inhibits the binding to its TNF-α target.	Same	*PC used in validation of ADA and NAb assays, including LPC and HPC preparation.* *Use of commercial antibody for validation and system suitability is acceptable if Samsung demonstrates antigenic equivalence between SB5, US-Humira, and EU-Humira*
PC Dose Curve and Hook Effect	39.06,78.13, 312.5, 625, 1250, 2500, 5000, 10000, 20000 ng/ml R2>0.99 NO PC Hook Effect observed	0.61, 1.22,2.44, 4.88, 9.77, 19.5, 39.1, 78.1, 156.25, 312.5, 625,1250, 2500, 5000 10000, 25000 ng/ml R2>0.99 NO PC Hook Effect observed	*Dose Ranges are sufficient to establish 4 PL curve fits.* *No PC hook effect observed in either study*

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LPC	150 ng/ml LPC calculated to fail ~1%	170 ng/ml LPC calculated to fail ~1%	*Both LPC concentrations were determined mathematically and failed ~1/20 runs for RA assay.*
HPC	10,000 ng/ml	25,00 ng/ml	*Both HPC tested 100% positive for all tested conditions, as expected.*
Matrix and NC	Normal Human Serum pool	Normal Human Serum pool	*The signals of blank samples must be below SCP. The use of healthy human serum pool as the matrix control is acceptable.*
MRD	1:4 final *MRD lower than for ADA assay to increase detection of NAbs.*	1:4 final *MRD lower than for ADA assay to increase detection of NAbs.*	*Correctly includes acid dissociation and buffer neutralization steps to determine MRD.*
NC system suitability range	Expected response of ≥ 726 ECL	Expected response of ≥ 1844 ECL	*Acceptable for MesoScale Discovery ECL assays*
LPC system suitability range	Expected response of ≥ 565 and ≤ 2323 ECL	Expected response of ≥ 1099 and ≤ 2337 ECL	*Acceptable for MesoScale Discovery ECL assays*
HPC system suitability range	Expected response of ≥ 157 and ≤ 460 ECL	Expected response of ≥ 298 and ≤ 510 ECL	*Acceptable for MesoScale Discovery ECL assays*
Antigenic Equivalence testing (Competitive DOE)	PC conc. (0, 150, 250, 2500 and 10000 ng/ml) competed with unlabeled SB5 (Clin lot 002K13), US-Hum (lot 250732E) or EU-Hum (29396XH10) at 0, 0.5, 1.0, 2.0, 5.0, 10 ug/ml *Curves overlapped at all concentrations tested*	PC conc. (0, 170, 500, 1000, 2500, and 10000 ng/ml) competed with unlabeled SB5 (Clin lot 012C14) or EU-Hum (lot 38466XD03) at 0, 0.5, 1.0, 2.0, 5.0, 10 ug/ml. *Curves overlapped at all concentrations tested*	*Data show that single ADA assay approach based on SB5 is acceptable as the resulting curves overlapped at all concentrations tested*
NAb assay cut- point (NACP) Normalized CP: mean S/N-3.09*SD	Used 50 In study pre-dose (baseline) NHV samples SN 12: 99.9% CI; 0.1%FP Fixed CP: 0.844 SN 37: 99 % CI; 1%FP Fixed CP: 0.873 CP Data determined to be normally distributed. No outliers were statistically identified (Q1-1.5IQR or Q3+1.5IQR) *Use of a fixed cut point although not typical, is acceptable as validation was performed in-study, and number of baseline*	Used 100 In study pre-dose (baseline) RA samples SN 12: 99.9% CI; 0.1%FP Fixed CP: 0.828 SN 37: 99 % CI; 1%FP Fixed CP: 0.863 CP Data determined to be normally distributed once outliers were statistically removed (Q1-1.5IQR or Q3+1.5IQR) *Use of a fixed cut point although not typical, is acceptable as validation was performed in-study, and number of samples used*	*Both assays used in-study samples to establish study specific fixed cut points. The use of fixed NACPs is acceptable as these were study-specific CPs calculated from 50-100 baseline samples per study. As was the initial case for CCP, NACP was initially assessed using 99.9% and 0.1% FP, rather than the recommended 1% FP rate. An IR was sent on Jan 21, 2019 requesting reanalysis using 1%, and the data for additional samples confirmed ADA+ at readjusted 1%FP.*

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	samples used for CP assessment (N=50) followed recommendations in 2016 immmunogenicity guidance	*for CP assessment (N=100) exceeded recommendations in 2016 immmunogenicity guidance*	*In amendment 37, Samsung reanalyzed both data sets using recommended 1% FP but the additional confirmed positive samples were not tested by NAb assay because NAb assays are inactive. Samsung performed data simulations assuming worst case scenario where all newly confirmed positive samples in both studies were NAb+. This is acceptable.*
Assay Drug tolerance	LPC NOT tolerant to 0.5ug/ml of SB5, US-Humira or EU-Humira HPC tolerant to 2ug/ml of each drug	LPC NOT tolerant to 0.5ug/ml of SB5 or EU-Humira. HPC tolerant to 2ug/ml of each drug.	*NAb Assay is not tolerant to drug levels expected at Ctrough (8-15 ug/ml). However, this is likely a function of the anti-idiotypic PC mAb as both assays can detect NAbs > 80% for NHV and >50% for RA, respectively (see 2.4.3).*
Target (TNF-α) tolerance	LPC and HPC spiked with 500 pg/ml TNFα all screened positive (100%)	LPC and HPC spiked with 500 pg/ml TNFα all screened positive (100%)	*TNF-α up to 500pg/ml did not impact NAb assays in either study. Sera TNF-α levels <10pg/ml for patients with RA.*
Sensitivity	132 ng/mL in NHS Back-calculated from dose curves	147.73 ng/mL in RAS Back-calculated from dose curves	*Sensitivities for both studies are within current recommendations ~100ng/ml.*
Repeatability/Intra-assay variability	NC %CV 3.1-6.8 LPC %CV 0.7-10.9 HPC %CV 0.3-11.9	NC %CV 2.4-4.4 LPC %CV 1.1-5.0 HPC %CV 2.1-3.9	*Repeatability for both studies are <15% and are acceptable.*
Intermediate Precision/inter-assay variability	NC %CV 20.1 LPC %CV 20.3 HPC %CV 16.7	NC %CV 15.1 LPC %CV16.8 HPC %CV 15.5	*IP for both studies are ≤20% and are acceptable.*
Selectivity	10 NHV sera spiked with LPC and HPC all screened positive (100%)	10 RA sera spiked with LPC (80% positive; 20% negative) and HPC (100% positive.	*Selectivity suitably demonstrated for both studies.*
Stability	LPC and HPC: 6 freeze/thaw cycles with 80-120% accuracy LPC and HPC: stable at RT for 24 hours with 80 –120% Accuracy	LPC and HPC: 6 freeze/thaw cycles with 80-120% accuracy LPC and HPC: stable at RT for 24 hours with 80 –120% Accuracy	*Stability testing shows PC remain stable for up to 6 freeze thaw cycles when stored at ≤ -20 ℃, and up to 24hrs at RT. Testing is acceptable.*

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Lipemia	3 lipemic sera spiked with LPC and HPC screened positive (100%), while testing negative without PCs	3 RA sera spiked with 300 mg/dL of triglyceride and LPC and HPC screened positive (100%), while testing negative without PCs	*Data indicate that increased levels of triglycerides up to 300 mg/dL do not impact the ADA assay. This is acceptable.*
Hemolysis	Matrix spiked 2 or 5% lysed whole blood tested negative but was positive when spiked with LPC and HPC. Matrix spiked 10% whole blood tested positive with or without LPC.	Matrix spiked with 2% and 5% lysed whole blood tested negative, but were 100% positive when spiked with LPC and HPC	*Data indicate that up to 5% sera hemolysis does not impact the NHV assay or the RA assay.* *NHV assay is impacted with 10% sera hemolysis, leading to false positives. Therefore, results from samples with greater that 10% hemolysis should be excluded.*
NAb Assay Assessment	**Able to detect NAbs despite poor drug tolerance by PC. Suitable for Intended purpose following reanalysis of using 1%FP rate (Amendment 37).**	**Able to detect NAbs despite poor drug tolerance by PC. Suitable for Intended purpose following reanalysis of using 1%FP rate (Amendment 37).**	**Individual clinical study ADA assays are suitably validated.**

Additional Assessor Comments:
In-study NAb assay validations used 99.9% CI, 0.1% FP, rather than the recommended 99% CI, 1.0 % FP samples for both clinical studies SB5-G31-RA and SB5-G11-NHV. An IR was sent to Samsung on Jan 21, 2019 requesting data reanalysis using the recommended 1% FP for both studies. In addition, Samsung was requested to provide NAb testing results for all newly determined ADA-positive clinical samples for both clinical studies and to update the ISE and ISS with these data, as appropriate.

In amendment 37, Samsung provided the requested data in Section 5.3.5.3 ISE and ISS Attachment 13 (for Study SB5-G11-NHV) and Attachment 14 (for Study SB5-G31-RA). While Samsung submitted both reanalyzed data sets with recommended 1% FP rate, the additional confirmed positive samples were not tested by NAb assay because, according to the submission, Samsung does not currently have active immunogenicity assays for SB5. Instead Samsung performed data simulations assuming worse-case scenario where all newly confirmed ADA positive samples in either study were considered NAb+. Assessment of these data is deferred to Clinical Pharm Assessor Lei He and DPARP Clinical review by Raj Nair.

2.4 Facility Inspection Summary

Assessor comment:
The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) waived the biopharmaceutical inspection for [redacted] (b) (4) *the CRO*

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responsible for developing immmunogenicity assays and performing clinical sample analysis for Samsung under BLA 761059, because the outcome of a December 2017 inspection was voluntary- action-indicated (VAI).

2.5 Assessment of Assay Performance in Clinical Studies

Assessor Comment:
The immunogenicity data provided by Samsung using the validated ADA and NAb assays discussed in earlier sections, confirm that both sets of assays are suitable for intended purpose as they are able to detect and confirm high rates of ADA and NAb+ samples for clinical studies SB5-G31-RA and SB5-G11-NHV.
For a complete analysis of clinical immunogenicity data refer to Clinical Pharmacology review by Lei He and DPARP Clinical review by Raj Nair.

2.6 Information Requests Sent During Assessment

Midcycle Immunogenicity Information Request (1/22/2019):
We are currently reviewing the immunogenicity information submitted to BLA761059 section 5.3.1.4 and provided in validation reports 8297981 (Validation of a method for Detection of Neutralizing Anti-SB5 and Anti-EU/US Humira Antibodies in Human Serum using the MesoScale Discovery (MSD) Platform) used to test samples from clinical PK/PD study SB5-G11-NHV, and 8306921(Validation of a method for Detection of Neutralizing Anti-SB5 and Anti-EU/US Humira Antibodies in Rheumatoid Arthritis Serum using the MesoScale Discovery (MSD) Platform) used to test samples from clinical safety study SB5-G31-RA . Based on this information, you established *in-study* cut points for the Neutralizing antibody (NAb) Assay used to analyze samples from studies SB5-G11-NHV, and SB5-G31-RA using a 99.9% Confidence interval (CI), and a 0.1% False Positive (FP) rate. A similar approach (99.9% CI, 0.1%FP) was initially utilized for Anti-Drug Antibody (ADA) Confirmatory Assays cut points used to analyze samples from study SB5-G11-NHV (validation report 829553) and study SB5-G31-RA (validation report 8306911). However, you subsequently reanalyzed ADA data from study SB5-G31-RA using a cut point calculated using the 99% CI, 1%FP, as per recommendations in the FDA 2016 immmunogenicity draft Guidance ("*Assay development and validation for immunogenicity testing of therapeutic protein products*") and provide these data in SN 21 Annex 2 to Section 2.5. This reanalysis led to increased rates of ADA positive subjects across SB5 and EU-approved Humira groups. However, the newly determined ADA-positive clinical samples were not tested for the presence of NAbs. You also did not provide ADA reanalysis data for study SB5-G11-NHV using the 99% CI, 1%FP cut point. Provide the following immunogenicity data.

1. ADA data for study SB5-G11-NHV samples using a 99% CI, 1%FP cut point.
2. The NAb testing results for all newly determined ADA-positive clinical samples for clinical studies SB5-G31-RA and SB5-G11-NHV.
3. NAb data for studies SB5-G11-NHV and SB5-G31-RA samples using a 99% CI, 1%FP cut point as per recommendations in the FDA 2016 immunogenicity draft Guidance ("*Assay development and validation for immunogenicity testing of therapeutic protein products*").
4. For Study SB5-G31-RA, provide an updated analysis across treatment arms of NAb status with ADA titer and its impact on PK, efficacy and safety.

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5. Update the integrated summary of efficacy (ISE) and integrated summary of safety (ISS) sections of your BLA, where appropriate, to include the immunogenicity data analyzed with the 99% CI, 1%FP ADA confirmatory and NAb cut points.

Reference ID: 4466647

Joao Pedras Vasconcel

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: **4/30/2019**
To: Administrative File, **STN 761059/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/Branch IV
Subject: Addendum to CMC microbiology memo for new 351(k) Biologic License Applications (BLA) STN761059/0 dated 3/21/2019
Applicant: Samsung Bioepis Co., Ltd.
US License: **2046**
Facility: (b) (4)
Product: SB5
Dosage: Single-dose pre-filled syringe, autoinjector, 40 mg, subcutaneous injection
Indication: Rheumatoid Arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps)
BsUFA date: July 23, 2019

Recommendation: The drug substance part of this BLA, as amended, is recommended for approval from quality microbiology perspective.

Assessment Summary

This memo amends the drug substance microbiology product quality memo for Samsung's 351(k) BLA STN761059/0 dated 3/21/2019 with new information and data submitted by the applicant (amendment dated 4/17/2019, sequence 49) pertaining to hold time validation for (b) (4)

Hold time validation study

(b) (4)

(b) (4)

Assessor comment: The hold times for (b) (4) *have been adequately validated at scale from microbiology perspective.*

Satisfactory

Conclusion

I. The drug substance part of this BLA is recommended for approval from quality microbiology perspective.

II. Information and data in this submission not related to microbial control of the drug substance should be evaluated by the OBP assessor.

III. See Panorama for compliance status of the facilities.

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Bo Chi

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Reyes Candau-Chacon

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STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA NO.:	761059
SERIAL NO.:	0000
DATE RECEIVED BY THE CENTER:	July 23, 2018
DRUG NAME:	SB5 (proposed biosimilar to US-licensed Humira)
DOSAGE FORM:	Prefilled vials, 40 mg/0.8 mL
INDICATIONS:	Same indications of use as approved for US-licensed Humira
APPLICANT:	Samsung Bioepis Co., Ltd.
REVIEW FINISHED:	March 23, 2019
NAME OF PRIMARY STATISTICAL REVIEWER:	Yu-Ting Weng
NAME OF SECONDARY STATISTICAL REVIEWER:	Meiyu Shen
NAME OF PROJECT MANAGER:	Brandi Wheeler

_____

Reviewer: Yu-Ting Weng, Ph.D., Mathematical Statistician, CDER/OTS/OB/DB VI
Secondary reviewer: Meiyu Shen, Ph.D., Team Leader, CDER/OTS/OB/DB VI

Concur: _____
Meiyu Shen, PhD CMC stats Team leader, CDER/OB/DBVI
Shein-Chung Chow, Ph.D., Associate Director for Biosimilar, CDER/OTS/OB

Distribution: CDER/OTS/OB/DB VI/Yi Tsong
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CDER/OBP/Joao Pedras-Vasconcelos
CDER/OBP/Cecilia Tami
CDER/OMPT/CDER/OND/ODEII/DPARP/Brandi Wheeler
CDER/TBBS

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1 INTRODUCTION

The FDA refused to file this application on October 28, 2016 because of the lack of scheduled drug substance production during the review cycle. On July 23, 2018, Samsung Bioepis Co., Ltd. (the applicant) resubmitted to the US Food and Drug Administration (FDA) a 351(k) BLA which included analytical similarity assessments of comparing SB5, US-licensed Humira (US), and EU-approved Humira (EU).

Two Tier 1 Quality Attributes (QAs) are relative activities of TNF-α neutralization assay and TNF-α binding assay. The CMC statistical reviewer found out the following review issue related to the reference standard used in Tier 1 QAs and discussed internally with OBP CMC reviewers.

Issue. (b) (4)

On September 13, 2018, OBP CMC reviewer, Dr. Joao Pedras-Vasconcelos, emailed the following response to the CMC statistical reviewer in the message titled "Re: BLA 761059 filing meeting slides":

- Agree with the way the applicant performed their sequential qualification of reference standards for the Tier 1 bioassays.

On October 5, 2018, the FDA sent the applicant the Information Request (IR). The request related to the Tier 1 QAs is described below.

Request. The applicant proposed to measure potency using an NF-κB reporter gene assay to measure TNF-α activity neutralization and a FRET assay to measure competitive inhibition binding to TNF-α at release and stability testing of DS and DP. These assays are insufficient to control potency because both assays measure only the early steps of the TNF-α signaling cascade. The TNF-α induced apoptosis inhibition assay is a more appropriate approach to controlling potency because better reflects a dominant mechanism of action of adalimumab. To improve the control strategy over the potency of SB5, implement a bioassay that assesses the impact of adalimumab on TNF-α-induced apoptosis and establish appropriate DS and DP release and stability specifications.

On November 5, 2018, the applicant responded to the FDA IR dated October 5, 2018 and provided the following justifications to propose to maintain the NF-κB reporter gene assay as the potency assay:

- For MoA of adalimumab and core assay principle, it was confirmed that both assays are measuring neutralization potency of adalimumab against TNF-α, not the apoptotic activity of adalimumab.
- For assay conditions, assay procedure is similar in neutralization steps, the difference lies only in the detecting method of the extent of TNF-α neutralization.

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- Method validation/qualification results demonstrate that two assays are comparable in most of performance factor, but in case of sensitivity, the NF-κB reporter gene-based assay has higher performance than apoptosis-based assay.

On January 4, 2019, Dr. Joao Pedras-Vasconcelos, emailed the following response to the CMC statistical reviewer in the message titled "Re: Question for BLA 761059":

- Agree with the applicant's proposal based on the data they submitted showing that their assay appears to be more sensitive to potency changes than the apoptosis inhibition assay and thus is likely a better assay to monitor potency.

The FDA CMC statistics reviewers carefully evaluated data for the relative activities of TNF-α neutralization assay and TNF-α binding assay provided in the BLA resubmission. The applicant's statistical equivalence testing (Tier 1 approach) is provided in Section 2, and CMC statistical reviewer's independent statistical equivalence testing analyses using modified Wald test are present in Section 3.

2 APPLICANT'S STATISTICAL EQUIVALENCE TESTING

In this submission, the applicant followed the FDA's recommendation to conduct Tier 1 statistical equivalence testing with the margin defined as $1.5\hat{\sigma}_R$, where $\hat{\sigma}_R$ is the sample standard deviation based on the reference product lots, for the relative activities of TNF-α neutralization assay and TNF-α binding assay.

The CMC statistical reviewer performs an independent statistical analysis in the next section.

3 FDA STATISTICAL ANALYSES

To evaluate analytical similarity, the FDA recommended the applicant to apply a tiered approach in the FDA responses to IND meetings with the applicant. That is, product QAs amenable to statistical evaluation are assigned to three tiers based on their criticality. The QAs with potential highest risk in product quality, efficiency, safety, and PK/PD are generally assigned to Tier 1, in which analytical similarity is assessed by statistical equivalence test. QAs with lower impact are generally assigned to Tier 2 and their analytical similarity is evaluated by Quality Range approach. That is, a high percentage of the biosimilar data should be covered by $(\hat{\mu}_R - X\hat{\sigma}_R, \hat{\mu}_R + X\hat{\sigma}_R)$, where $\hat{\mu}_R$ is the sample mean, $\hat{\sigma}_R$ is the sample standard deviation based on the reference product lots, and the multiplier X typically ranges from 2 to 4. The QAs with the lowest risk are generally assigned to Tier 3 and their analytical similarity is evaluated by side-by-side comparison using graphic display.

This review focuses on the equivalence test in Tier 1.

3.1 Data analyzed

The applicant submitted the analytical data on July 23, 2018 and the data is corrected on December 31, 2018. The summary of SB5 lots for Tier 1 analysis is provided in Table 1. The CMC statistical reviewer conducted Tier 1 statistical equivalence testing based on these ten independent lots for each QA.

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Table 1. Summary of SB5 Lots for Tier 1 Analysis

Source	Site	Lot number
PVR DS	(b) (4)	PP5-16-606A-001
Clinical DP		002K13
		007K13
		019A14
PVR DP		028G15
		029G15
		030G15
PVR DP		SB5PV05
		SB5PV06
		SB5PV07

3.2 Statistical method

Let μ_T and μ_R be the population mean of the QA for the test product and the population mean of the QA for the reference product, respectively. Let σ_R be the standard deviation of the QA of interest for the reference product. To conclude the equivalence in the QA of interest between the test product and the reference product, we aim to reject the null hypothesis of the following null and alternative hypotheses (Tsong et al., 2017) [1]:

$$H_0 : \mu_T - \mu_R \le \theta_1 \text{ or } \mu_T - \mu_R \ge \theta_2$$
$$H_1 : \theta_1 < \mu_T - \mu_R < \theta_2$$

where $\theta_1 \quad -1.5\sigma_R$, $\theta_2 \quad 1.5\sigma_R$, θ_1 and θ_2 are equivalence margins.

In the current practice for fixed margin, we reject H_0 if 90% CI for the mean difference in the QA of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. In other words, we conclude that the equivalence in the QA of interest between the test product and the reference product if 90% CI for the mean difference in the QA of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. This specific equivalence margin was set as 1.5 times the standard deviation of the QA for the reference product to ensure an adequate power for the case in which a small but sufficient number of lots are available for testing. For example, the probability of rejecting H_0 in the above two one-sided tests procedure with the equivalence margin being $\pm 1.5\sigma_R$ is 87% if the true mean difference is $0.125\sigma_R$ for a sample size of 10 test product lots and 10 reference product lots.

First, we estimate σ_R by the sample variability of the reference product, and then θ_1 and θ_2 are treated as a constant, but not a random variable in the statistical analysis.

Let X_{Tj} be the observed value of the QA of interest for Lot *j* of the test product (the proposed biosimilar product) and X_{Rj} be the observed value of the QA of interest for Lot *j* of the reference product. Since the two products are manufactured by two manufacturers, two products are

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independent. $\bar{X}_i = \sum_{j=1}^{n_i} X_{ij} \Big/ n_i$, and $S_i^2 = \sum_{j=1}^{n_i} \left(X_{ij} - \bar{X}_i\right) \Big/ \left(n_i - 1\right)$, where n_i is the number of lots in the ith product, $i = T, R$.

Under the unequal variance of the test product and the reference product, the (1-2α)*100% CI of the mean difference in the QA of interest can be calculated as:

$$\left(\bar{X}_T - \bar{X}_R - t_\alpha(\nu)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}}, \bar{X}_T - \bar{X}_R + t_\alpha(\nu)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}} \right).$$

where $t_\alpha(\nu)$ is the 1-α quantile and ν is the degrees of freedom calculated by Satterthwaite's approximation.

If $n_R > 1.5n_T$, the (1-2α)*100% sample size imbalanced adjusted CI of the mean difference in the QA of interest can be calculated as (Dong et al., 2017a):

$$\left(\bar{X}_T - \bar{X}_R - t_\alpha(\nu^*)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}}, \bar{X}_T - \bar{X}_R + t_\alpha(\nu^*)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}} \right).$$

where $n_R^* = \min(n_R, 1.5n_T)$ and $\nu^* = \dfrac{\left(\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R^*}\right)^2}{\frac{1}{n_T - 1}\left(\frac{S_T^2}{n_T}\right)^2 + \frac{1}{n_R - 1}\left(\frac{S_R^2}{n_R^*}\right)^2}$.

If $n_T > 1.5n_R$, we can apply a similar approach as above with $n_T^* = \min(1.5 \times n_R, n_T)$ for the CI calculation. In the following analyses, we use the significance level α=0.05.

However, the current practice for fixed margin results in inflating type I error rate and reducing power when sample size is not sufficiently large, as pointed out by Dong et al. (2017a) [2]. Hence, one needs to consider σ_R as a parameter to be estimated with the study data. We recommend the MWCMLE method for reducing the type I error rate to the significance level (5%) and increasing the power to 86% for the true mean difference is $0.125\sigma_R$ for a sample size of 10 test product lots and 10 reference product lots.

The above null and alternative hypotheses for reference scaled equivalence can be rewritten as the two-one-sided hypothesis testing as follows.

$$H_{0U}: \mu_T - \mu_R \geq f\sigma_R \text{ vs. } H_{aU}: \mu_T - \mu_R < f\sigma_R$$

$$H_{0L}: \mu_T - \mu_R \leq -f\sigma_R \text{ vs. } H_{aL}: \mu_T - \mu_R > -f\sigma_R$$

where μ_T and μ_R are the population means of the test product and the reference product, respectively; σ_R is the Standard Deviation (SD) of the reference product; and f is 1.7.

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The test statistics of the MWCMLE method to test H_{0U} and H_{0L} in (1) are as follows:

$$W_L = \frac{\hat{\mu}_T - \hat{\mu}_R + f\tilde{\sigma}_R}{\sqrt{\frac{\breve{\sigma}^2_{T_L}}{n_T} + \left(\frac{1}{n_R} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_L}}} \text{ and } W_U = \frac{\hat{\mu}_T - \hat{\mu}_R - f\tilde{\sigma}_R}{\sqrt{\frac{\breve{\sigma}^2_{T_U}}{n_T} + \left(\frac{1}{n_R} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_U}}},$$

where $\hat{\mu}_T$, $\hat{\mu}_R$, and $\tilde{\sigma}_R$ denote the MLE for the mean of the test product, the MLE for the mean of the reference product, and the sample estimator for the SD of the reference product, respectively. When X_T follows $N(\mu_T, \sigma_T^2)$ distribution and X_R follows $N(\mu_R, \sigma_R^2)$ distribution, $\hat{\mu}_T = \frac{\sum_{i=1}^{n_T} X_{T_i}}{n_T} = \bar{X}_T$, $\hat{\mu}_R = \frac{\sum_{i=1}^{n_R} X_{R_i}}{n_R} = \bar{X}_R$, $\tilde{\sigma}_R = \sqrt{\frac{\sum_{i=1}^{n_R}\left(X_{R_i} - \hat{\mu}_R\right)^2}{n_R - 1}}$ where n_T and n_R denote the sample sizes of test product lots and reference lots, respectively. σ_T^2 is the variance of the test product. Under the null hypothesis, each test follows an asymptotically standard normal distribution. The overall null hypothesis is rejected by either of the following two criteria: first, $W_L > Z_{1-\alpha}$ and $W_U < -Z_{1-\alpha}$ at significance level α, where Z_p is the 100pth percentile of the standard normal distribution; or second, the intersection (L, U) of two one-sided (1- α)*100% confidence intervals falls within the equivalence margin $(-f\tilde{\sigma}_R, f\tilde{\sigma}_R)$ and is listed as follows.

$$(L, U) =$$

$$\left(\hat{\mu}_T - \hat{\mu}_R - Z_{1-\alpha}\sqrt{\frac{\breve{\sigma}^2_{T_L}}{n_T} + \left(\frac{1}{n_R} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_L}}, \hat{\mu}_T - \hat{\mu}_R + Z_{1-\alpha}\sqrt{\frac{\breve{\sigma}^2_{T_U}}{n_T} + \left(\frac{1}{n_R} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_U}}\right)$$

Following the above same logic of the sample size imbalanced adjustment, the Adjusted MWCMLE statistics for imbalanced sample (AMWCMLE) can be written as follows:

$$W_{L'} = \frac{\hat{\mu}_T - \hat{\mu}_R + f\tilde{\sigma}_R}{\sqrt{\frac{\breve{\sigma}^2_{T_L}}{n_T} + \left(\frac{1}{n_R^*} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_L}}} \text{ and } W_{U'} = \frac{\hat{\mu}_T - \hat{\mu}_R - f\tilde{\sigma}_R}{\sqrt{\frac{\breve{\sigma}^2_{T_U}}{n_T} + \left(\frac{1}{n_R^*} + \frac{f^2 V_{n_R}}{n_R - 1}\right)\breve{\sigma}^2_{R_U}}},$$

where the sample sizes of adjusted reference lots, n_R^* , is equal to $\min(1.5 \times n_T, n_R)$. n_T and n_R denote the sample sizes of test product lots and the sample sizes of reference product lots, respectively.

More details are described in Weng et al. (2018) [3].

3.3 FDA statistical equivalence testing for the relative TNF-α neutralization activity

The relative TNF-α neutralization activity's data points of SB5, US, and EU are displayed in Figure 1. SB5 has the smallest sample mean and sample variability among three products.

Ten SB5 lots, 35 US lots, and 40 EU lots were included for the statistical equivalence testing for the relative TNF-α neutralization activity. Descriptive statistics for the relative TNF-α neutralization activity's data are listed in Table 2.

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From Table 3, the result shows that the three-way pairwise comparisons (SB5 vs. US, SB5 vs. EU, and US vs. EU) for the relative TNF-α neutralization activity, using the current practice for fixed margin, pass equivalence testing.

Figure 1. Scatter plot of the relative TNF-α neutralization activity for SB5, US-licensed Humira, and EU-approved Humira

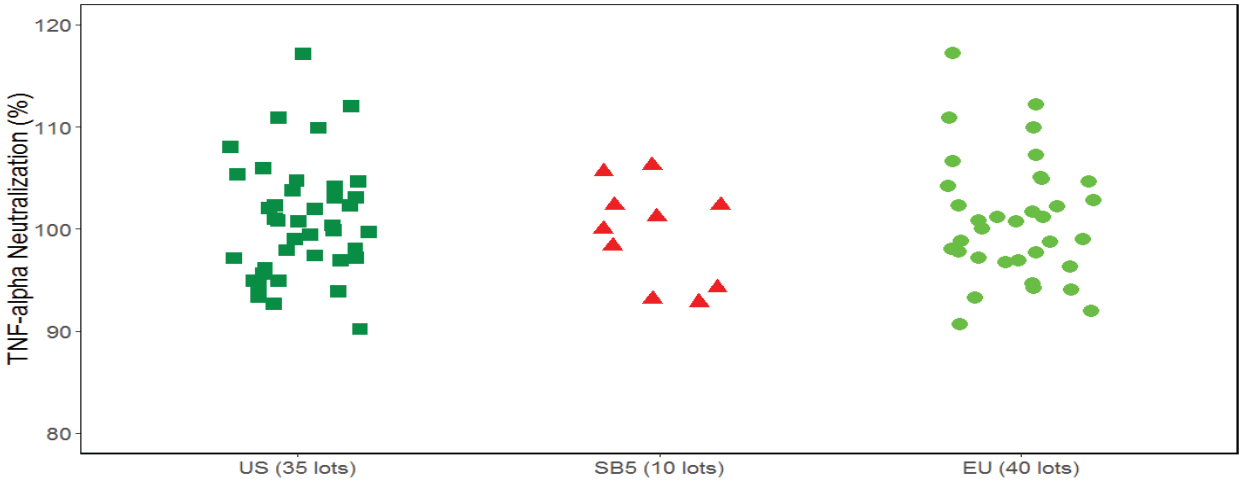


Table 2. Descriptive statistics for the relative TNF-α neutralization activity data

Product	Number of lots	Sample mean, %	Sample standard deviation, %	Minimum, %	Maximum, %
SB5	10	99.5	4.9	93	106
US	35	100.94	5.91	91	117
EU	40	100.8	5.71	90	117

Table 3. Equivalence testing results for the relative TNF-α neutralization activity using the current practice for fixed margin

Comparison	Number of lots	Mean difference, %		Equivalence margin, %	Statistical Equivalence
		Estimate	90% CI [1]		
SB5 vs. US	(10, 35)	-1.44	(-5.14, 2.26)	(-8.86, 8.86)	Yes
SB5 vs. EU	(10, 40)	-1.3	(-4.94, 2.34)	(-8.56, 8.56)	Yes
EU vs. US	(40, 35)	-0.14	(-2.39, 2.10)	(-8.86, 8.86)	Yes

1. The 90% confidence interval is adjusted by the sample size imbalance

From Table 4, the result shows that the three-way pairwise comparisons (SB5 vs. US, SB5 vs. EU, and US vs. EU) for the relative TNF-α neutralization activity, using the MWCMLE method for parameter margin, also pass equivalence testing.

Reference ID: 4466797

Table 4. Equivalence testing results for the relative TNF-α neutralization activity using the MWCMLE for parameter margin

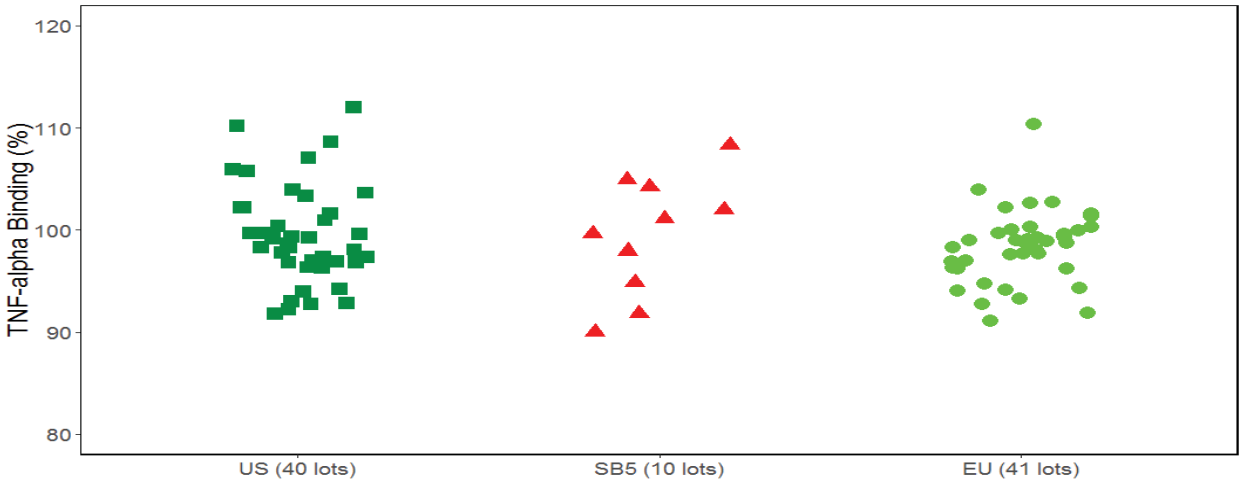
Comparison	Number of lots	Mean difference, %		Equivalence margin, %	Statistical Equivalence
		Estimate	90% CI [1]		
SB5 vs. US	(10, 35)	-1.44	(-6.54, 4.89)	(-10.04, 10.04)	Yes
SB5 vs. EU	(10, 40)	-1.3	(-6.37, 4.88)	(-9.70, 9.70)	Yes
EU vs. US	(40, 35)	-0.14	(-3.02, 2.78)	(-10.04, 10.04)	Yes

1. The 90% confidence interval is adjusted by the sample size imbalance

3.4 FDA statistical equivalence testing for the relative TNF-α binding activity

The relative TNF-α binding activity's data points of SB5, US, and EU are displayed in Figure 2. SB5 has the largest sample mean and largest sample variability among three products.

Figure 2. Scatter plot of the relative TNF-α binding activity for SB5, US-licensed Humira, and EU-approved Humira



Ten SB5 lots, 40 US lots, and 41 EU lots were included for the statistical equivalence testing for the relative TNF-α binding activity. Descriptive statistics for the relative TNF-α binding activity's data are listed in Table 5.

Table 5. Descriptive statistics for the relative TNF-α binding activity data

Product	Number of lots	Sample mean, %	Sample standard deviation, %	Minimum, %	Maximum, %
SB5	10	99.5	5.78	90	108
US	40	98.35	3.60	91	110
EU	41	99.46	4.87	92	112

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From Table 6, the result shows that the three-way pairwise comparisons (SB5 vs. US, SB5 vs. EU, and US vs. EU) for the relative TNF-α binding activity, using the current practice for fixed margin, pass equivalence testing.

Table 6. Equivalence testing results for the relative TNF-α binding activity using the current practice for fixed margin

Comparison	Number of lots	Mean difference, %		Equivalence margin, %	Statistical Equivalence
		Estimate	90% CI [1]		
SB5 vs. US	(10, 40)	1.15	(-2.46, 4.76)	(-5.40, 5.40)	Yes
SB5 vs. EU	(10, 41)	0.04	(-3.80, 3.88)	(-7.31, 7.31)	Yes
EU vs. US	(41, 40)	1.11	(-0.47, 2.70)	(-5.40, 5.40)	Yes

1. The 90% confidence interval is adjusted by the sample size imbalance

From Table 7, the result shows that the three-way pairwise comparisons (SB5 vs. US, SB5 vs. EU, and US vs. EU) for the relative TNF-α binding activity, using the MWCMLE method for parameter margin, also pass equivalence testing.

Table 7. Equivalence testing results for the relative TNF-α binding using the MWCMLE for parameter margin

Comparison	Number of lots	Mean difference, %		Equivalence margin, %	Statistical Equivalence
		Estimate	90% CI [1]		
SB5 vs. US	(10, 40)	1.15	(-3.65, 5.19)	(-6.12, 6.12)	Yes
SB5 vs. EU	(10, 41)	0.04	(-5.24, 5.28)	(-8.29, 8.29)	Yes
EU vs. US	(41, 40)	1.11	(-1.08, 3.03)	(-6.12, 6.12)	Yes

1. The 90% confidence interval is adjusted by the sample size imbalance

4 CONCLUSION AND RECOMMENDATION

The results from the statistical equivalence analyses for the relative activities of TNF-α neutralization and TNF-α binding supported a demonstration that the proposed biosimilar SB5 is highly similar to US. In addition, the results support the analytical portion of the scientific bridge to justify the relevance of EU data from the comparative clinical study.

5 REFERENCE

[1] Tsong Y., Dong X., Shen M. (2017): Development of statistical methods for analytical similarity assessment, Journal of Biopharmaceutical Statistics: 27:2, pages 308-316

[2] Dong X., Weng Y.T., Tsong Y. (2017b). Adjustment for unbalanced sample size for analytical biosimilar equivalence assessment. Journal of Biopharmaceutical Statistics: 27:2, pages 220-232

Reference ID: 4466797

[3] Weng Y.T., Tsong Y., Shen M., Wang C. (2018). Improved Wald Test for Reference Scaled Equivalence Assessment of Analytical Biosimilarity. Accepted by International Journal of Clinical Biostatistics and Biometrics. DOI: 10.23937/2469-5831/1510016

Reference ID: 4466797

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/s/

YU-TING WENG
03/28/2019 08:55:44 AM

MEIYU SHEN
03/28/2019 09:13:31 AM

SHEIN-CHUNG CHOW
03/28/2019 09:32:21 AM

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	March 26, 2019
To	Barry Oumou, Regulatory Project Manager CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Division	OPQ/OPQR
From	Sarah Mollo CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission # BLA 761059 ICCR #2018-03348 ICC#1800665
Recommendation	**Recommending approval based on review of device constituent with a post-approval inspection of** (b) (4) (b) (4) This recommendation is based on the firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and a recent medical device inspection of the firm has not been performed, i.e. it has been (b) (4) years since the last site inspection. CDRH is recommending that the inspection is deferred to a Post-BLA action based on the following rationale: 1) current limited inspectional resources due to shut down 2) the last inspection was a comprehensive inspection that covered the medical device PAC Code, and it was NAI.

Digital Signature Concurrence Table	
Reviewer	
Team Lead	

Branch Chief	

Reference ID: 4466647

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2018-03348 (technical/engineering); ICCR2018-03350 (compliance)
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=3665 http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=3667
ICC tracking # (Lead)	ICC1800665
Submission Number	BLA761059
Sponsor	Samsung Bioepis Co., Ltd.
Drug/Biologic	Adalimumab
Indications for Use	HADLIMA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients from 4 to 17 years of age and ≥ 30 kg (66 lbs). HADLIMA can be used alone or in combination with methotrexate.
Device Constituent	**Autoinjector:** 40 mg/0.8 mL of HADLIMA is provided by a single autoinjector **(HADLIMA PushTouch)** containing a 1 mL pre-filled glass syringe with a fixed ½ inch needle. **Pre-filled Syringe:** 40 mg/0.8 mL of HADLIMA is provided by a single dose, 1 mL pre-filled glass syringe with a fixed ½ inch needle.
Related Files	ICCR2018-03350; ICC1600692; ICC1600685

Table 2. Review Team				
CDER/CBER Lead Review Division	DPARP			
Submission RPM	DPARP- Brandi Wheeler; OPQ/OPRO- Oumou Barry			
Lead Device Reviewer	Sarah Mollo			
The CDRH review is being managed under ICC #: ICC1800665				
Below is a list of the Discipline Specific ICCR#, ICC# and CON#. The CON# are under ICC1800665 in CTS.				
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**ICCR #**	**ICC #**	**CON #**
Engineering	Rumi Young	ICCR2018-03348	ICC1800665	CON1828709; CON190867
Compliance	Leslie Caster	ICCR2018-03350	ICC1800665	CON1819770; CON1820846

Table 3. Important Dates		
Interactive Review Goal Dates	2/25/2019	
Final Lead Device Review Memo Due	03/22/2019	
Interim Due Dates	**Meeting Date**	**Due Date**
Filing	October 12, 2019	
74-Day Letter		
Mid-Cycle	January 8, 2019	
Primary Review		

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2. PURPOSE/BACKGROUND

2.1. Scope

The following request details were provided in the sharepoint ICCR:

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Samsung resubmitted biologic license application (BLA) 761059 on July 23, 2018. This is a 351(k) BLA for approval as a biosimilar to Humira (adalimumab). OPQ is requesting a consult review of the single-dose auto-injector and the pre-filled syringe to determine if the information provided is adequate to support approval of the BLA.

This review covers the following areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Sterility of Primary Container Closure Pre-filled syringe
- Human Factors

The presentations being evaluated are below:

- **Autoinjector:** 40 mg/0.8 mL of HADLIMA is provided by a single autoinjector **(HADLIMA PushTouch)** containing a 1 mL pre-filled glass syringe with a fixed ½ inch needle.
- **Pre-filled Syringe:** 40 mg/0.8 mL of HADLIMA is provided by a single dose, 1 mL pre-filled glass syringe with a fixed ½ inch needle.

The following information is located in SN0015, 3.2.P.7 Container Closure:

The pre-filled syringe (PFS) without safety feature (safe-shield body) and autoinjector (AI) were initially developed and used up to SB5 clinical studies. To apply safety feature to the PFS and to improve the functionality of the autoinjector (AI), the design of SB5 PFS and AI was modified after clinical studies. The modifications were implemented to the extent which did not have any impact on the function of delivering drug product solution to the patients. All studies presented from Section 4 to Section 7 were performed with the modified Safety PFS and AI.

<u>PFS syringe</u>
After clinical study, the safe-shield body was added on the PFS, for prevention of needlestick injuries, by covering the needle after completion of the injection (refer to CTD Section 3.2.P.7.1.2.1.1 for details on the safe-shield body). Along with the addition of the safe-shield body, the design of the finger flange and the plunger rod was modified, as presented in Table 1, to support the safety function of the safe-shield body. The plunger rod was designed to support the activation of the safe-shield body upon completion of the injection. The finger flange was designed to enhance the patients' convenience for injection.

These modifications are considered to have no adverse impact on the patient's use as the primary packaging (glass syringe staked with needle) of current Safety PFS is identical with that of the PFS used for clinical study.

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(b) (4)

[redacted]

2.2. Prior Interactions

2.2.1. Related Files

ICCR2018-03350; ICC1600692; ICC1600685

2.3. Indications for Use

Combination Product	Indications for Use
HADLIMA (adalimumab-xxxx)	HADLIMA (adalimumab-xxxx) is biosimilar* to HUMIRA (adalimumab) for the indications listed • **Rheumatoid Arthritis (RA) (1.1):** Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. • **Juvenile Idiopathic Arthritis (JIA) (1.2):** Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients from 4 to 17 years of age and ≥30 kg (66 lbs). • **Psoriatic Arthritis (PsA) (1.3**): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. • **Ankylosing Spondylitis (AS) (1.4):** Reducing signs and symptoms in adult patients with active AS. • **Adult Crohn's Disease (CD) (1.5):** Reducing signs and

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	symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. • **Ulcerative Colitis (UC) (1.6):** Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers. • **Plaque Psoriasis (Ps) (1.7):** The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
Safety Pre-filley syringe and HADLIMA PushTouch Autoinjector	Subcutaneous administration of HADLIMA (adalimumab)

3. ADMINISTRATIVE

3.1. Documents Reviewed

Sequence	Section	Title
001	2.3 Introduction	Introduction
0015	3.2.P.7. Container Closure System	Container Closure System (SB5, Solution for Injection, ALL)
0015	3.2.P.2. Pharmaceutical Development	Container Closure System (SB5, Solution for Injection, All)
0015	3.2.P.2. Pharmaceutical Development	Design Verification Summary
0015	3.2.P.2. Pharmaceutical Development	Autoinjector Sharps Injury Prevention Feature Study Report
0015	3.2.P.2. Pharmaceutical Development	Safety PFS Sharps Injury Prevention Feature Study report

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0028	1.11.1 Quality Information Request	Quality Information Amendment (SN0028: 2019Jan07; Response to Information Request)
0028	3.2.P.8.1 Stability Summary and Conclusions	Stability Summary and Conclusions (SB5, Solution for Injection, All)
0028	3.2.P.8.3 Stability Data	Stability Data (SB5, Solution for injection, All)
0033	1.11.1 Quality Information Amendment	Quality Information Amendment (SN0033; 2019Jan29; Response to Information Request)
0036	1.11.1 Quality Information Amendment	Quality Information Amendment (SN0036; 2019Feb12; Response to Information Request)
0036	3.2.P.5.1 Specification(s)	Specifications

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The following information is located under SN0015; 3.2.P.7 Container Closure System (SB5, Single-Dose PFS/AI)

A. Device Description

Safety Pre-filled Syringe

The SB5 Safety PFS is a single, fixed dose, disposable injector for use in subcutaneous (SC) administration of SB5 drugs by healthcare providers, caregivers, and patients, including those with moderate to severe hand impairment.

To provide additional support for injecting drugs and prevent needlestick injuries, a Safety PFS was developed by adding the secondary packaging components (safe-shield body, finger flange, and plunger rod) to the PFS ((b) (4) glass barrel with staked needle and plunger stopper). The Safety PFS is considered device, a constituent part of a combination product within the meaning of the QS regulation [21 CFR 3.2(e)] where the drug provides the primary mode of action of the combination product.

A schematic overview of the Safety PFS is shown in Figure 1.

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(b) (4)

8. RISK ANALYSIS

8.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A

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Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities			

8.2. Summary of Risk Analysis

The following IR was sent to the sponsor regarding the risk analysis;

> *You have included a copy of the standard ISO 14971, Medical devices - Application of risk management to medical devices; however, the reviewer is unable to locate the risk analysis associated with the final finished combination product. Please provide the location of the risk analysis, which should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.)*

The following information was provided in the response:

1. DESIGN RISK ASSESSMENT

For SB5 Safety PFS, a system FMEA (sFMEA, Attachment 5-1) was conducted as a design risk assessment to evaluate and identify the design risks associated with Safety PFS. Then the risk control measures were determined to mitigate identified risks, and the residual risks were evaluated using the criteria defined in the sFMEA according to ISO 14971.

For the SB5 AI, a design FMEA (dFMEA, Attachment 5-2) for the device constituent components was conducted as design risk assessment by the device designer, (b) (4) The purpose of the dFMEA was to evaluate and identify the design risks associated with AI. Then the risk control measures were determined to mitigate identified risks, and the residual risks were evaluated using the criteria defined in the dFMEA according to ISO 14971.

Patient medical harm severity information from the Hazard Assessment for SB5 AI and PFS (Attachment 5-3) was incorporated in the generation of FMEA for Safety PFS and AI. For each failure mode, occurrence, severity, and detection were rated using a scale of 1 to 5. The Risk Priority Number (RPN) was then calculated (product of occurrence, severity, and detection) and the threshold for pursuing failures was an RPN (b) (4). The FMEA for Safety PFS and AI did not have any failure modes with an RPN (b) (4).

The summary of the design risks associated with SB5 Safety PFS and AI is presented in Table 1 and Table 2, respectively. The results demonstrate that all residual risks are mitigated to acceptable level and the residual risks do not outweigh the benefit.

Table 1: Summary of Design Related Potential Failure Modes Associated with SB5 Safety PFS

Failure Modes Identified by sFMEA	Failure Modes with RPN (b) (4) Before Mitigation	Failure Modes with RPN (b) (4) After Mitigation
113	0	0

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Table 2: Summary of Design Related Potential Failure Modes Associated with SB5 AI

Failure Modes Identified by dFMEA	Failure Modes with RPN Before Mitigation (b) (4)	Failure Modes with RPN After Mitigation (b) (4)
156	0	0

2. ATTACHMENTS

Attachment 5-1. SB5 Safety PFS System FMEA

Attachment 5-2. SB5 AI Design FMEA

Attachment 5-3. Hazard Assessment for SB5 AI and PFS

After the sponsor provided a response to the IR, Rumi Young evaluated the risk assessment. Her comments are provided below, for additional information, please see her review in Appendix A:

The sponsor provided a system and design fmea (b) (4) to address the design related risks and stated that the risk does not outweigh the benefit. However, a review of the provided risk assessments raised the following concerns/questions:

- The risk assessments include severity, occurrence and detection scores. Based on the detection score acceptance criteria if something is detected by design control it has a score of 1. However, that is the definition of prevention, not detection, because the risk is prevented by design. As a result, prevention mitigations (controlled by design) are counted twice and all risks are artificially lowered. This is evident in the marked-up risk table above showing with a detection score of 1 there is no chance of high/red risks.
- For risks where the score is not 1 it is unclear from the stated mitigation (actions) what the detection controls all (e.g. risk 1.1 only refers to design verification as an "action")
- The severity score assigned to needle sticks is only 3 – moderate, resulting in injury or impairment. At the very least it should be 4 because needle sticks could lead to bloodborne pathogens.

Therefore, the response is not adequate.

IRs were send requesting evidence that the sponsor:

-Identified design risks associated with the device
-Mitigated identified risks
-Determined that the residual risks do not outweigh the benefit

Addional information based on the sponsor's response below:

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According to the Agency's comment, the system FMEA (sFMEA) has been updated and attached to this response (Attachment 10-1).

- The definition of the detection score from 1 to 5 was updated.
- Detection scores were updated for each failure mode according to the revised definition.
- Severity scores related to needle stick injury were updated to 4 to account for the risk of bloodborne pathogens.
- Risk control measures were re-addressed following the score revision.
- Results after the risk control measures were updated and acceptability of the residual risks to ensure the residual risks do not overweigh the benefit was re-evaluated according to the risk acceptability criteria.

The summary of the design risks associated with SB5 Safety PFS is presented in Table 1. The results demonstrate that all residual risks are mitigated to acceptable level and the residual risks do not outweigh the benefit.

Table 1: Summary of Design Related Potential Failure Modes Associated with SB5 Safety PFS

Failure Modes Identified by sFMEA	Failure Modes with RPN (b) (4) Before Mitigation	Failure Modes with RPN (b) (4) After Mitigation
111	(b) (4)[a]	0

[a] The number of "failure modes with RPN (b) (4) before mitigation" was formerly 0. The number increased to (b) (4) after the score revision following the Agency's comment.

Reviewer Comment
The sponsor's updated their DFMEA and adequately rescored and mitigated the risks. They also added rationale for each score reduction to demonstrate how the risk was mitigated by inspection (detectability). Therefore, the response was adequate. **The deficiency is resolved.**

9. LABELING

The below information is from SN0012; 1.14.1.3. Draft Labeling Text:

(b) (4)

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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(b) (4)

Insert description of instructions for use

Insert relevant Warnings / Precautions from User Manual or Package Insert

10.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5:

PFS

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The release and shelf life specification for the SB5 drug product (DP) is provided in Table 1.

Table 1: SB5 DP Release and Shelf-life Specifications

Test Item			Release Acceptance Criteria	Shelf-life Acceptance Criteria
General test	Appearance	Clarity	(b) (4)	
		Colour		
		Visible particles		
	pH			
	Osmolality			
Identity	icIEF			
	Competitive inhibition binding assay to TNF-α by FRET			
Quantity	Protein concentration (A_{280})			
	Extractable volume			
Biological activity	Competitive inhibition binding assay to TNF-α by FRET			
	TNF-α neutralisation assay by NF-κB reporter gene			
Purity and impurity	CE-SDS (non-reducing)	%Total purity		
		%2H1L		
	SE-HPLC			
	icIEF	%Acidic		
		%Main		
		%Basic		
Safety	Container closure integrity			
	Sterility			
	Endotoxin			

Test Item			Release Acceptance Criteria	Shelf-life Acceptance Criteria
	Particulate matter	≥ 10 µm	(b) (4)	
		≥ 25 µm		

[a] N/P: Not performed

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Table 2: SB5 Saftey PFS Release and Shelf-life Specifications

Test Item for Functionality	Release Acceptance Criteria	Shelf-life Acceptance Criteria
Break loose force	(b) (4)	N/P[a]
Glide force		N/P
Safety shield activation		N/P
Confirmation of the locking after safety shield activation	Pass	N/P

[a] N/P: Not performed.

AI

Table 3: SB5 AI Release and Shelf-life Specifications

Test Item for Functionality	Release Acceptance Criteria	Shelf-life Acceptance Criteria
Deliverable volume	(b) (4)	
Needle extension		
Injection time		
Activation force	(b) (4)	N/P[a]

[a] N/P: Not performed.

11. Quality Systems and Facilities Inspection Review

Leslie Dorsey peformed a review of QS and inspection history:

PFS
CDRH does not need to conduct a compliance evaluation of the prefilled syringe form of Adalimumab, BLA 761059_Resubmision, based on our risk assessment. That includes:

- Desk review of 21 CFR 820 call-outs, and
- Evaluation of manufacturing facilities to determine the need for inspections associated with.

AI
The following information was sent by the sponsor is reponse to IRs regarding QS call outs sent my Leslie. Complete response to IRs 1-6 is SN 0018:

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Inspection History

The following information is located in Leslie's review memo:

> The following facilities were identified as being involved in the manufacturing and/or development of the Adalimumab-xxxx in BLA761059.
>
> Assessment from Viviana Matta of CDER/OPQ/OPF/DIA/IABI are provided below (see boxed comments) for each of Leslie's recommendations.

1. (b) (4)

   Responsibility – Secondary packaging, release test for functionality of autoinjector, and functional stability testing of autoinjector (all tests except container closure integrity test)

   Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that it has not been inspected.

   Inspection Recommendation:
   An inspection is required because:
   - The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
   - A recent medical device inspection of the firm has not been performed.

   OPQ Feedback:
   The two year rule is not applicable for inspections. The firm appears to be in compliance and adequate for the responsible operations. The (b) (4) PAI provided coverage for product (b) (4) which is a medical device (Class II) and drug combination product. Medical device areas covered during this inspection were the following: Management Controls, CAPA, MDR, Purchasing Controls, and Production and Process controls. At the close of the inspection an FDA 483 was issued for the following deficiency: (b) (4) Inspection was classified as VAI and approval was recommended for the medical device and drug combination product. The site has an acceptable profile (PRF) for kit assembler.

2. (b) (4)

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Responsibility – Secondary packaging

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4). The inspection covered drug GMPs and was classified VAI.

Inspection Recommendation:
An inspection is not required because:

- A recent medical device inspection of the firm was acceptable.

OPQ Feedback:
Concur with no PAI.

3. **Samsung Bioepis Co., Ltd.**

107, Cheomdan-daero, Yeonsu-gu
Incheon, Republic of Korea 21987
FEI #3012967727

Responsibility – Sponsor/Applicant
Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

Inspection Recommendation:
An inspection is required because:

- A recent medical device inspection of the firm has not been performed.

OPQ Feedback:
I am submitting the following IR (prior to a PAI request) as no responsibilities are clearly stated in the submission for the referenced site: Please identify the responsibilities for Samsung Bioepis Co., Ltd. FEI: 3012967727 related to the manufacturing and/or development of the device constituent part. This site is listed as not operational in FACTS and I would like to verify their responsibilities with the applicant.

I consulted with Nik Thakur, who is our division expert in compliance reviews:

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BOTTOM LINE, UP FRONT: Regarding CDRH's original request to have the Prefilled syringe manufacturing site inspected because it has not been inspected since 2015, we should, in this case, ask for a post-marketing scheduling of this inspection rather than requesting a PAI.

DETAILS:
To get everyone else up to speed, CDRH requested that the AI ~~PFS~~ manufacturer be inspected as part of bi-annual inspection paradigm. But, CDER facility reviewer has suggested that the PFS manufacturing site might not need a PAI.

I discussed this BLA briefly with Nazia Rahman. Based on that discussion, I agree with Leslie that, technically, the device constituent site should be inspected because it has been 4 years since the last site inspection. However, I believe that we should defer the inspection to Post-BLA action based on the following rationale:
1) current limited inspectional resources due to shut down
2) the last inspection was a comprehensive inspection that covered the medical device PAC Code, and it was NAI.

I want to stress that deferring the inspection means that CDRH still expects that the inspection be conducted.

I'm happy to discuss this approach further if it is necessary.

12.INTERACTIVE REVIEW

Agency Information Request #1 (sent on 12/20/2018)
Sponsor Response (received on 01/07/2019):

Please refer to lead review memo as well as Rumi Young's memo in Appendix A for additional information regarding sponsor's response and reviewer analysis:

1. You did not provide verification protocols or reports for the SB5 PFS or SB5 Autoinjector. We need the protocols and reports to determine if you have adequately tested your device constituents per the referenced ISOs with respect to test method, acceptance criteria and data analysis. Provide the design verification protocols and reports for SB5 PFS and SB5 Autoinjector.

Reviewer Comment: The requested reports were provided as attachments to the Information request letter response. **The response is adequate.**

2. You leveraged ISO 11608-1 and ISO 11608-5 test methods, sample size (n=60) and acceptance criteria for design verification deliverable volume and functional testing that required pre-conditioning(free fall, vibration, environment/temperature). However, you did not provide the statistical rationale for the sample size used nor the acceptance criteria (confidence/reliability, k-value or pass/fail) for the functional performance attributes that did not undergo preconditioning . Please clarify the sample size justification and acceptance criteria for the following design verification functional performance testing: Needle Shield Remover Force, Activation Force, Injection time, Needle Cover Override Force (after locking), Needle extension, and Separation Force (without label).

Reviewer Comment
- The sponsor clarified that the n=60 was used for attribute testing of the functional requirements listed (Table 1). This approach would not yield an adequately reliability level.
- The sponsor reanalyzed the existing data using k-value associated with 95% confidence 97.5% reliability.

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This confidence and reliability level is adequate given the indications for use. All data passed.

- The sponsor did not repeat testing and performed analysis on existing data. **Therefore, the response is adequate.**

3. You have provided a summary of the stability studies including device performance in 3.2.P.8. The stability testing for the autoinjector did not include activation force. The essential performance requirements should be included in the stability studies, including activation force. Please provide data to support the maintence of the activation force specification up to the labeled shelf-life of the combination product. Additionally, please include verification of the activation force specification in your upcoming real-time stability studies for the AI.

Reviewer Comment

- A review of the sections shows that the sponsor did include activation force to the stability program for the autoinjector.
- A review of the data (Tables 57-64, not pictured) shows activation force was tested and passed the acceptance criteria.

The response was adequate.

4. You have included release specifications under 3.2.P.3.1 for the DP release and shelf-life (Table 1) and the SB5 autoinjector.

   a. You have not provided release specifications for the safety pre-filled syringe. The release specification should include the essential performance requirements, which for a pre-filled syringe with needle safety device, should at least include: dose accuracy (e.g. deliverable volume), breakloose force, glide force, and activation of needle safety component. Please update the release specifications to include the essential performance requirements of the pre-filled syringe.

   b. You have inlcuded deliverable volume, needle extension, and injection time in the release specifications for the SB5 AI. You have not included activation force. Please update your release specifications to include activation force of the autoinjector.

Reviewer Comment

- A follow-on IR was sent on January 24, 2019 to address the following issues with the response:
  - The sponsor included dose accuracy, breakloose and glide force to the nude (not fully assembled) PFS release testing. In addition, they claim that the needle safety components have no impact on the injection.
  - This response is not adequate because the activation of the needle safety device is part of the injection force curve (glide force). If the force is too high, the needle safety will not activate. The force may be too high due to the DP fill and/or frictional forces of the plunger rod against the needle safety. Therefore, the response is not adequate and the request will be repeated for part a.
  - It is noted that the sponsor refers to the 510k, however, the 510k would not have tested their syringe filled with drug and would not have been assembled by the sponsor. Both may impact the needle safety activation. **The response is <u>not</u> adequate.**
- The sponsor adequately responded to part b of the IR by adding activation force to the release specification.

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5. You have made modifications to the PFS and AI, after completion of the clinical studies. You have provided verification testing on the to-be-marketed combination products as well as a *Design Change Risk Assessment* in Seq 005; Quality Informantion Amendment 1.11.1; however, it is unclear if there are differences between the clinically validated and commercial (to-be-marketed) products. Provide a comparison of the essential performance requirements acceptance criteria (specification, k-value) and a summary of the performance data (mean, min, max, standard deviation, and graphical summary) to adequately compare the clinical and commercial versions of the combination product.

    a. Additionally, the reviewer was unable to locate the information regarding device failures, leakage, local injection site reactions, etc. Please provide the location where any device failures were captured during the clinical studies.

Reviewer Comment
The sponsor provided verification testing demonstrating that the difference between clinical AI and Commercial AI does not affect the essential performance requirements. Additionally, the sponsor provided an adequate summary of the device failures and related device harms. They table (Table1) also described the location of the information. **The response is adequate.**

6. The cap removal force specification for both the PFS and AI is (b) (4) N is high for a cap removal force specification upper limit based on the indication of Rhematoid Arthritis. Provide a justification for upper limit as (b) (4) N that includes a discussion of the intended user population.

Reviewer Comment
The provided rationale is not adequate because the data provided, maximum pull strength of the knob, to support the (b) (4) N AI upper limit specification is not representative of the hand posture used to remove and AI cap, intended use or indication (Rhematoid arthritis). The response is not adequate. A follow on

7. You have included a copy of the standard ISO 14971, Medical devices - Application of risk management to medical devices; however, the reviewer is unable to locate the risk analysis associated with the final finished combination product. Please provide the location of the risk analysis, which should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.)

Reviewer Comment
The sponsor provided a system and design fmea (b) (4) to address the design related risks and stated that the risk does not outweigh the benefit. However, a review of the provided risk assessments raised the following concerns/questions:

- The risk assessments include severity, occurrence and detection scores. Based on the detection score acceptance criteria if something is detected by design control it has a score of 1. However, that is the definition of prevention, not detection, because the risk is prevented by design. As a result, prevention mitigations (controlled by design) are counted twice and all risks are artificially lowered. This is evident in

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the marked-up risk table above showing with a detection score of 1 there is no chance of high/red risks.

- For risks where the score is not 1 it is unclear from the stated mitigation (actions) what the detection controls all (e.g. risk 1.1 only refers to design verification as an "action")
- The severity score assigned to needle sticks is only 3 – moderate, resulting in injury or impairment. At the very least it should be 4 because needle sticks could lead to bloodborne pathogens.

Therefore, **the response is not adequate**; therefore a follow-up IR was sent on January 24, 2019.

8. You did not provide a letter of authorization to refer to 510(k) (b) (4). Provide a letter of authorization and location of the biocompatibility data you intend to leverage in the 510(k). In addition, provide a justification why the differences, if any, between your device constituent and the test article in the 510(k) do not hinder your ability to leverage the biocompatibility data.

Reviewer Comment
The sponsor provided a letter of authorization (LoA) to refer to 510(k) (b) (4) is provided in Section 1.4.1. **The response is adequate.**

9. You did not provide biocompatibility protocols or reports for the Sb5 Autoinjector. We need the protocols and reports to determine if you have adequately tested your device constituents per ISO 10993. Provide the biocompatibility protocols and reports.

Reviewer Comment
The sponsor has provided the requested information. **The response is adequate.**

10. You did not provide evidence that your SB5 PFS is compliant with recognized standard ISO 11040-4:2015 Prefilled syringe – Part 4: Glass barrels for injectables. Provide data and/or justification stating how SB5 PFS is compliant with ISO 11040-4:2015.

Reviewer Comment
The sponsor provided a statement of Compliance to ISO 11040-4:2015 Prefilled syringe – Part 4: Glass barrels for injectables. **The response is adequate.**

Follow on Agency Information Request # 2 (sent on 01/24/2019)
Sponsor Response (received on 01/27/2019)

Please refer to Rumi Young's memo in Appendix A for additional information regarding sponsor's response and reviewer analysis:

1. In response to Information Request 4a you proposed release testing on the nude PFS instead of the final finished combination product (i.e. prefilled syringe with needle safety device/PFSNSD). The proposed approach is adequate for EPRs deliverable volume and breakloose force. However, this proposal is not adequate for glide force. The NSD would impact the glide force through the needle safety activation force peak, which is caused by the plunger rod interfacing with the NSD trigger fingers. Testing the PFS alone would not capture this force that would be perceived by the end-user. Therefore, please update your control

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strategy approach to test for EPRs on the final finished product (PFS-NSD) not the intermediate component (nude PFS).

Reviewer Comments
The sponsor updated their control strategy to test EPRs on the final finished product. See IR#3 1/22/2019 in Rumi's memo for discussion regarding test rate (50mm/min). **The response is adequate.**

2. The response to Information Request 4a, you proposed testing on the nude PFS which would not include EPR needle safety activation as part of release testing. Therefore, you may not adequately control needle safety activation. Below are specific concerns:

    a. The needle safety activation may potentially be impacted by the injection forces (e.g. too high/no activation) and device assembly/processing (e.g. accidental activation). Therefore, the referenced 510(k) testing, evidence of design reliability, is not representative of your final finished combination product.

    b. The study SB5 Safety PFS sharps Injury Prevention Feature Study report only verifies the needle safety device performance at one instance. It does not ensure needle safety activation lot-to-lot. The needle safety component should be included in your control strategy of the combination product.

    Please include the needle safety activation in your release testing. Alternatively, please provide the upstream controls that contribute to the EPRs performance. If implementing upstream controls, demonstrate how they trace and control needle safety activation force.

Reviewer Comments
Needle safety activation was added to the release testing of the final finished device. **The response is adequate.**

3. In response to Information Request 5 you provided a comparison of the clinical and commercial PFS/PFS-NSD and AI performance. It was noted that PFS breakloose and glide force testing was conducted at a rate of 50mm/min, which appears low. A lower test rate would lower the breakloose and glide forces measured. Therefore, provide justification for the 50mm/min test rate.

    a. To better understand your injection force test method, we also recommend that you provide a representative PFS-NSD injection force curve showing the features (e.g. breakloose force, glide force, activation force) measured during the test method, including ranges of data capture (e.g. glide force measured over x mm to y mm).

Reviewer Comments
The sponsor's interpretation of ISO 11608-3 is incorrect (see below) and since they do not provide rationale based on intended use the **response in inadequate.** A follow-on IR was sent 2/4/2019 based on the following:

- The sponsor is using a test rate intended for empty cartridges: Test rate is from section 5.4 Plunger Force which specifically states, "Measurements shall be made at a test speed of 50 mm/min with test cartridges that are open to the atmosphere (i.e. no septum present, fluid to be removed immediately prior to testing), so that only the plunger friction is measured." The sponsor uses this test rate to test

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filled/assembled devices. A lower test rate is suitable to detecting inconsistent lubrication on the barrel due to (b) (4) migration on empty cartridges. However, it may not be representative of intended use and would artificially produce lower forces measured.

- The sponsor acceptance criteria is much higher than what is recommended by the ISO for the given test rate: Section 4.3.2 Cartridges of the ISO states, "The initiating force for cartridges shall not exceed 15 N, when tested in accordance with the method given in 5.4. The sustaining force for cartridges shall not exceed 10 N, when tested in accordance with the method given in 5.4." The sponsor recommends (b) (4)

The ISO 11608-3 is primarily for cartridges, not syringes. However, the ISO does mention some design considerations may be leverage so issues regarding applicability of the ISO will not be mentioned.

4. In response to Information Request 6 you provided a justification for the cap removal force for the AI and PFS. However, the provided rationale is not adequate because the data provided, maximum pull strength – convex knob, is not representative of the hand posture used to remove and AI cap and indication (rheumatoid arthritis). Below are specific concerns:

   a. The hand posture used for the maximum pull strength (Strength Data for design safety- Phase 1) is not the same as described in Figure 15 (i.e. thumb and forefinger pulls cap) provided in your response. In the maximum pull strength test, the test subject can use all their fingers and potentially hand to grasp the knob. However, the same referenced paper has pinch pull data that appears representative since it shows the user pulling on the fixture with their thumb and forefinger. A change in hand posture would change the users capability, which is demonstrated by the difference in forces measured between maximum pull strength (convex knob) and pinch pull strength (20mm or 40mm).

   b. Per your Attachment 7-1 and 7-2 you define an RA user as, "People with joint pain in their hands and fingers. Their manual dexterity and strength may be compromised by pain and/or swollen and disfigured hands and fingers". However, you did not adequate describe how anthropometric data from a static test fixture with unimpaired user groups translates to your indicated user population.

Therefore, address considerations a and b to support your (b) (4) N AI cap removal force specification Alternatively, adjust your upper limit specification based on a and b.

Reviewer Comments
The sponsor lowered the specification to account for grip and RA indication from (b) (4). In addition, the sponsor provided a summary showing that their device still meets that specification by reanalysis of the design verification results. The data shows cap removal force performance ranges between 11 and 26N. Rumi sent the following email to the RPM to send to DMEPA on 2/4/2019:

The sponsors provided rationale to support a new lower cap removal upper limit specification (b) (4) to account for the hand posture and indication (RA). While the sponsor used data that was more representative of the intended use with respect to hand posture it is uncertain that they adequately translated the capable user data to RA user data. Specific questions include if the referenced paper is adequate, the selection of "weakest user group", and how it compares to cap removal forces of other marketed products. Note: The sponsor provided a cap removal performance summary where the forces ranged from 11N-26N. Therefore, the HF or clinical study would not have demonstrated users removing caps at forces anywhere

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near (b) (4) N.

On 3/5/2019, DMEPA reached out to Rumi to discuss the cap removal force issue stating that there were no issues in the HF study. Rumi talked with Matthew Barlow and clarified that the product tested in the HF study had cap removal forces that were much lower than the proposed specification of (b) (4) and that what we needed help on was review of the literature with anthromomophic data that the sponsor was using to support the (b) (4) specification. DMEPA determined that review of the literature data to support the cap removal force specification for the indicated patient population is outside of their scope. Therefore, we consulted a HF subject matter expert in CDRH to help review the literature data. It was determined that the literature did not adequately support a (b) (4) cap removal force for RA patients; therefore, **the response was not adequate.** A follow-on IR was sent on 03/14/2019.

5. In response to Information Request 7 you provided PFS and AI Task Analysis and User Error Analysis to demonstrate that you have assessed the user risks associated with your devices per ISO 14971. However, you did not provide evidence that you:
   - Identified design risks associated with your device
   - Mitigated identified risks
   - Determined that the residual risks do not outweigh the benefit

   Therefore, provide a design risk assessment showing that design related risks are identified, mitigated and that the residual risks do not outweigh the benefit.

Reviewer Comments
The sponsor provided a system and design fmea (b) (4) to address the design related risks and stated that the risk does not outweigh the benefit. However, a review of the provided risk assessments raised the following concerns/questions:

- The risk assessments include severity, occurrence and detection scores. Based on the detection score acceptance criteria if something is detected by design control it has a score of 1. However, that is the definition of prevention, not detection, because the risk is prevented by design. As a result, prevention mitigations (controlled by design) are counted twice and all risks are artificially lowered. This is evident in the marked-up risk table above showing with a detection score of 1 there is no chance of high/red risks.
- For risks where the score is not 1 it is unclear from the stated mitigation (actions) what the detection controls all (e.g. risk 1.1 only refers to design verification as an "action")
- The severity score assigned to needle sticks is only 3 – moderate, resulting in injury or impairment. At the very least it should be 4 because needle sticks could lead to bloodborne pathogens.

Therefore, the response is not adequate.

<u>Follow on Agency Information Request # 3 (sent on 02/04/2019)</u>
Sponsor Response (received on 02/14/2019)

1. In your response to Information Request 3 you refer to ISO 11608-3 Part 5.4 as justification for the 50mm/min test rate for testing the injection forces (breakloose force, glide force, safety shield activation force) of your final finished combination product (SB5 pre-filled syringe). There are the following issues regarding your reference:

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a. ISO 11608-3 Part 5.4 test rate of 50mm/min is specific to empty cartridges and intended to only measure the friction of the plunger. However, your test article would be a filled prefilled syringe assembled into a needle safety device and you intend to measure the plunger friction force, force required to dispense drug and force to activate the needle safety device. Therefore, this test method rate is not applicable to your configuration.

b. ISO 11608-3 Part 4.3.2 states that the test rate of 50mm/min is associated with specific acceptance criteria of 15N and 10N for breakloose force (initiating force) and glide force (sustaining force), respectively. However, your proposed acceptance criteria for this test rate is in Table 1 (Information Request 1 response) is (b) (4) for breakloose force and activation force and (b) (4) for glide force. Therefore, your acceptance criteria are much higher than what IS 11608-3 recommends for a test rate of 50 mm/min

An injection force test rate that is lower than intended use would give artificially lower injection forces and result in ineffective design verification and release testing. Therefore, increase the test method rate to 100 mm/min while maintaining your proposed acceptance criteria (Information Request 1, Table 1). Alternatively, provide justification why the test rate of 50mm/min is representative of intended use.

Reviewer Comments
The linear regression is poor considering the R^2 values for breakloose force. It is adequate for glide force. The model was only based on three data points (test speeds), which is not sufficient to establish a trend. However, based on the data points presented at 2.7 mm/s (~160mm/min) and 5mm/s (300mm/min) the values (3.5N or 6.5N) are well below the specification of (b) (4). Therefore, there is a low risk that they would not meet their specification for breakloose or glide force.

We disagree that needle safety activation force would not be impacted by the test speed and the sponsor did not provide any data or scientific rationale to support that claim. However, the risk of proceeding without design verification testing at 100mm/min for needle safety activation is low because they intend to test this attribute at release and the sponsor provided needle safety activation testing per FDA guidance on sharps injury prevention. Together the risk of the user not being able to activation the needle safety device is low.

The written response was not adequate; however, the response included data and based the data the product performance is expected to be safe and acceptable for use; therefore, **no additional information is needed for approval.**

2. In your response to Information Request 5 you provided a system FMEA to address the design related risks and stated that the risk does not outweigh the benefit. A review of the provided risk assessments raised the following concerns:

a. The RPN for a given risk is based on the product of the severity, occurrence and detection scores. Based on the detection score definitions, if a risk is 'detected' by design control, it has a score of 1. However, that is the definition of prevention of a design risk, not detection, because the risk is prevented by occurring at all due to the design. As a result, prevention mitigations (controlled by

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design) are counted twice in your sFMEA making risks artificially lower. This is evident in the marked-up risk table below showing with a detection score of 1 there is no chance of high/red risks. Out of the 114 risks identified, 86 were assigned a detection score of 1 prior to implementation of mitigations. Therefore, this detection scoring approach significantly impacts the overall calculated risk of your sFMEA. Based on the provided definitions, if there is no detection of the identified design risk (e.g. controlled by design only), the appropriate detection score should be 5.

b. For risks where the detection score was 2 or 3, it is unclear from the stated mitigation ("actions") what the detection controls are pre and post mitigation. For example, risk 1.1 only refers to design verification as an "action". As stated in part a, this is not considered a detection mitigation and instead is a prevention mitigation that would drive the occurrence score.

c. The severity score assigned to needle sticks is only 3 – moderate, resulting in injury or impairment. At the very least it should be 4 because needle sticks could lead to bloodborne pathogens. A lower severity score would artificially lower your RPN value for the risk.

Your risk assessment should have accurate detection and severity scores because they are inputs to your decision if the benefit outweighs the risk and if your product is safe to market. Therefore, please update your sFMEA detection scores to reflect the effectiveness of true detection mitigations (e.g. release testing) while keeping in mind that risks mitigated by design are not detection mitigations. To address a and b, update your sFMEA detection scores to reflect the effectiveness of true detection mitigations (e.g. release testing) and clearly state the mitigations driving the detection and occurrence scores for each risk, respectively. To address c, update your severity score for needle sticks to at least 4 to account for the risk of bloodborne pathogens due to needle sticks.

Reviewer Comment
The sponsor's updated their DFMEA and adequately rescored and mitigated the risks. They also added rationale for each score reduction to demonstrate how the risk was mitigated by inspection (detectability). **Therefore, the response was adequate.**

Follow on Agency Information Request # 4 (sent on 03/14/2019)
Sponsor Response (received on 03/18/2019)

1. You have provided retroactive analysis based on the Sferra da Silva G et al. study data and Pinch-pull Strength Data (DTI, 2002) to support the design of AI with (b) (4). The analysis is not acceptable to support the design of AI of (b) (4) for Rheumatoid Arthritis patients.

   i. Bridging postures: By bridging postures key/lateral to chuck/3-point you increase the force capability by 113%. However, the key/lateral and chuck/3-point postures as illustrated in figure 3 are both representative of potential cap removal postures. Therefore, the translation from key/lateral to chuck/3-point is unnecessary and results in higher forces that may not be suitable for the intended user. The change in posture also results in a change of RAG to CG ratio from 32% to 21%, which would calculate a higher force

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specification.

ii. RAG to CG: Your paper shows that there are different ratios for pinch strength depending on the posture. Therefore, the ratio of CG vs. RAG may differ as well from pinch to pull strength. Your calculation uses the pinch strength ratio, which can lead to an inaccurate estimate of capability of pull strength for RA patients.

iii. Patient Population: Factors such as finger size, posture and proportion vary greatly between populations of U.S and Central America.

Please provide literature supporting your specification of (b) (4) using the appropriate posture and patient population (RA). Please identify the representative gender, associated finger size, posture with Anthropometric Data based on the US population and statistical analysis using 5% percentile estimate. You may use Strength Data (DTI, 2002) as Anthropometric Data. We recommend that you use values from the chuck/3-point posture to take into account the less capable patient population. Alternatively, please modify your specification to (b) (4).

Reviewer Comments
The sponsor provided the following response:

In accordance with the Agency's comments, the upper limit of AI cap removal force will be modified from (b) (4) as described in Table 1.

Test	Acceptance Criteria	
	Current	Proposed
Cap removal force	(b) (4)	

All historical data generated so far has been reviewed and evaluated against the new acceptance criteria. As a result, the cap removal forces of all samples met the revised acceptance criteria of (b) (4).

The sponsor has updated the specification to (b) (4) as recommended. **The response is adeqauate.**

Follow on Agency Information Request # 4 (sent on 03/29/2019)
Sponsor Response (received on 04/012019)

1. In response to the IR sent on March 14, 2019, your response stated that you would be updating the cap removal force for the AI to (b) (4) from (b) (4) Please confirm that you also plan to update the specification for the PFS as the intended user population is the same for both.

Reviewer Comments
The sponsor provided the following response:

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In accordance with the Agency's comments, the upper limit of Safety PFS cap (needle shield) removal force will be modified from (b) (4) to (b) (4) as described in Table 1.

Table 1: Cap (Needle Shield) Removal Force Adjustment for the SB5 Safety PFS

Test	Acceptance Criteria	
	Current	Proposed
Cap (needle shield) removal force		(b) (4)

All historical data generated so far has been reviewed and evaluated against the new acceptance criteria. As a result, the cap (needle shield) removal forces of all samples met the revised acceptance criteria of (b) (4)

The sponsor has updated the specification to (b) (4) as recommended. **The response is adeqauate.**

13. OUTSTANDING DEFICIENCIES

n/a

14. RECOMMENDATION

Recommending approval based on review of device constituent with a post-approval inspection of (b) (4)

This recommendation is based on the firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and a recent medical device inspection of the firm has not been performed, i.e. it has been 4 years since the last site inspection.

CDRH is recommending that the inspection is deferred to a Post-BLA action based on the following rationale:
1) current limited inspectional resources due to shut down
2) the last inspection was a comprehensive inspection that covered the medical device PAC Code, and it was NAI.

14.1. Recommended Post-market commitments/post-market requirements

n/a

15. APPENDIX

Reference ID: 4466647

Appendix A

Memorandum: Engineering Consult

To: Sarah Mollo, Lead Reviewer, CDRH/ODE/DAGRID/GHDB

From: Rumi Young, Biomedical Engineer, CDRH/ODE/DAGRID/GHDB

Date: January 30, 2019

Subject: BLA 761059/ ICC1800665 / CON1828709/CON190867

Device: Autoinjector and prefilled syringe

Associated Drug: Adalimumab, SB5

Sponsor: Samsung Bioepis Co., Ltd.

Documents Reviewed:

Sequence	Section	Title
001	2.3 Introduction	Introduction
0015	3.2.P.7. Container Closure System	Container Closure System (SB5, Solution for Injection, ALL)
0015	3.2.P.2. Pharmaceutical Development	Container Closure System (SB5, Solution for Injection, All)
0015	3.2.P.2. Pharmaceutical Development	Design Verification Summary
0015	3.2.P.2. Pharmaceutical Development	Autoinjector Sharps Injury Prevention Feature Study Report
0015	3.2.P.2. Pharmaceutical Development	Safety P S Sharps Injury Prevention eature Study report
0028	1.11.1 Quality Information Request	Quality Information Amendment (SN0028: 2019Jan07; Response to Information Request)
0028	3.2.P.8.1 Stability Summary and Conclusions	Stability Summary and Conclusions (SB5, Solution for Injection, All)
0028	3.2.P.8.3 Stability Data	Stability Data (SB5, Solution for injection, All)
0033	1.11.1 Quality Information Amendment	Quality Information Amendment (SN0033; 2019Jan29; Response to Information Request)
0036	1.11.1 Quality Information Amendment	Quality Information Amendment (SN0036; 2019Feb12; Response to Information Request0

1. RECOMMENDATION:

The responses to all IRs were adequate except for Information Request 1 sent on 2/4/2019(Section 6.6.1.1). However, a review of the data provided and commitment to test the EPRs at release is sufficient to mitigate the risk of high injection forces. **Therefore, the device constituent of the combination product is safe and acceptable for market.**

Note: Although IR 4 sent 1/22/2019 (Section 6.7.1) appears adequate from a CDRH device specification perspective, I recommend that the justification is reviewed by CDER/DMEPA. See comment to CDER/DMEPA

Comment to CDER Sent 1/31/2019

1. The sponsors provided rationale to support a new lower cap removal upper limit specification ([redacted] (b) (4) N) to account for the hand posture and indication (RA). While the sponsor used data that was more representative of the intended use with respect to hand posture it is uncertain that they adequately translated the capable user data to RA user data. Specific questions include if the referenced paper is adequate, the selection of "weakest user group", and how it compares to cap removal forces of other marketed products. Note: The sponsor provided a cap removal performance summary where the forces ranged from 11N-26N. Therefore, the HF or clinical study would not have demonstrated users removing caps at forces anywhere near [redacted] (b) (4).

2. SUMMARY:

This is a focused engineering consult for BLA761059-resubmission. Specifically, the purpose of this memo is toG review the response to IRs #1-7 and #10 issued. IR#8 and #9 associated with the biocompatibility are deferred toG the lead reviewer, Sarah Mollo, for adequacy.G

Of note: quotes from the Sponsor are written in *italics*. References are noted as '(REF: XXXX)'.G

Reference ID: 4466647

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3. Proposed Indications for Use:

Rhematoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Adult Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis.

4. Device Description:

The Sponsor provided two device constituent formats for the delivery of SB5 to the subcutaneous space. The Sponsor provided the following device description (REF: 3.2.P.7 Container Closure System (SB5, Solution for Injection, ALL)).

(b) (4)

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(b) (4)

Consultant Comment:

- They did not identify any EPRs for the Safety P S, but they did include all relevant EPRs for the AI. I defer [redacted] However, I would recommend breakloose/glide force, delivered volume and needle safety for the Safety P s EPRs.
- The EPRs will be evaluated as part of the design verification review.

5. Design Verification Review

The Sponsor provide the following design verification program overview for the P s and AI. See Section 5.1 and 5.2 for detailed analysis of DV data for each device constituent format.

5.1. Safety P S Design Verification

The Sponsor tested the following attributes per the conditions described in Table 38 (REF: Table 38,3.2.P.2 Pharmaceutical Development, *Container Closure System (SB5, Solution for Injection, All))*.

- Cap (needle shield) removal force
- Breakloose
- lideability
- Safety shield activation
- Safety shield activation lockingG
- Deliverable volume testingG

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Table 38: Summary of the Results for SB5 Safety PFS DVT

Number	Test Name	Test Type	Sample Size (pc)	Results Summary
1	Operating environment test for warm atmosphere	Functional and visual inspection	60	Pass
2	Operating environment test for cool atmosphere	Functional and visual inspection	60	Pass
3	Operating environment test for standard atmosphere	Functional and visual inspection	60	Pass
4	Leakage test	Visual inspection	60	Pass
5	Free-fall test (drop test)	Functional and visual inspection	60	Pass
6	Vibration test	Functional and visual inspection	60	Pass

In addition, they provide data tha their device meets the 'applicable' sections ISO 11608-2 since they did not believe it is applicable to a prefilled staked in needle syringe(REF: 3.2.P.2 Pharmaceutical Development, *Container Closure System (SB5, Solution for Injection, All))* .

Table 1: Summary of the Test Results in Accordance with ISO 11608-2

Test Item	Result
Needle pull-out test	Pass
Needle points	Pass
Freedom from defects	Pass
Lubrication	Pass
Elasticity	Pass
Flexural Strength	Pass

They also refer (b) (4) 510k (b) (4) demonstrate that their device constituent components (needle shield body, plunger rod, and finger flange) met the following biocompatibility endpoints as described in ISO 10993-1 assuming a surface device, limited contact (less than 24 hours).

- Cytotoxicity per ISO 10993-5
- Sensitization per ISO 10993-10
- Irritation and Intracutaneous reactivity per ISO 10993-10

They also tested needle safety performance in a separate needle safety study (REF: 3.2.P.2. Pharmaceutical Development, *SB5 Safety PFS sharps Injury Prevention Feature Study report*) per FDA guidance "Medical Devices with Sharps Injury prevention features, Section 10. Simulated Clinical Use Testing". Below is an overview of the study parameters:

Table 41: Summary of Sharps Injury Prevention Feature Assessment for SB5 Safety PFS

Sample Size	Successful Needle Shield Extending and Locking	Failed Needle Shield Extending and Locking	Success Rate of Safety Feature Activation
555	555	0	100%

For details on the results, refer to the attachment, SB5 Safety PFS Sharps Injury Prevention Feature Study Report.

The report was reviewed, and additional study arameters are below:

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Parameter	Description
Sample	(b) (4)
Environment	Usability testing facility. Gloves and injection pads provided
Training	All participants trained to proficiency
Participant demographics	16 nurses • left and right handed • Age 20-59 • Yrs of exp 0-31 • Male/female • Different hand sizes
Sample size	N=55, Each participant used 30-49 devices each

Reviewer Comment:

- The selected EPRs tested as part of design verification were adequate.
- They did not provide evidence for conformance to ISO 11040-4:2015. However, their DV package appears complete in terms of what was tested. I will provide deficiency wording if the lead reviewer would like to ask for evidence of compliance to this recognized standard. See Minor Deficiency 1.
- They did not provide the design verification protocols or reports. We need the data to determine if their testing approach was adequate. See Deficiency 1.
- The needle safety performance testing report was thorough, and they met the FDA guidance requirements (97.5/99%). Note: If the sponsor does not address deficiency 1, this would be adequate for the needle safety performance attributes only because their separate needle safety report adequately addresses the agency's guidance recommendations thoroughly.
- The Sponsor did not provide DVT data over stability to support the shelf-life. However, it appears that they provided non-dv functional stability testing in 3.2.P.8.1.2 and 3.3.P.8.3.3. This approach is adequate if the non-dv functional stability testing tests the final finished device. the shelf life of the final finished product to the lead reviewer.
- The Sponsor did not provide a letter of authorization for (b) (4) in order to leverage biocompatibility data. eficiency 2. .

5.2. AI Design Verification

The Sponsor states that design verification testing was conducted in accordance with ISO 11608-1 and ISO 11608-5. They provide specific testing details in a separate Design verification summary (REF: 3.2.P.2 Pharmaceutical Development, *Design Verification Summary*).

They preface their testing summary by first providing an assessment of the ISO 11608-1 and ISO 11608-5 sections which are and are not applicable to their AI (REF: Table 1 and 2, REF: 3.2.P.2 Pharmaceutical Development, *Design Verification Summary).* We agree with their assessment since the applicability assessment was based on system designation (D1), and design (single use, staked in needle, no needle retraction feature, no electronics).

They tested the following attributes:

- Deliverable volume

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- Sharps Injury Testing → See (REF: 3.2.P.2. Pharmaceutical Development, *SB5 Autoinjector Sharps Injury Prevention Feature Study Report*)
- unctional Testing
    - Needle shield remover force
    - Activation force
    - Injection time
    - ree fall test on activated device
    - Needle cover override force (after locking)
    - Needle extension
    - Separation orce (without label)

The Sponsor tested deliverable volume per ISO 1108-1 conditions (pre-conditioning and sample size). They provide the following summary below (REF:3.2.P.2 Pharmaceutical Development, Design Verification Summary)

Table 8: Results of Deliverable Volume Testing According ISO 11608-1 and ISO 11608-5

Test Condition	Specification	Sample Size	Calculation	Result
	(b) (4)		(b) (4)	
Warm Atmosphere (40 ± 2°C and 50 ± 10%RH) for at least 4 hours		60		Pass
Cool Atmosphere (5 ± 3°C) for at least 4 hours		60		Pass
Standard Atmosphere (23 ± 5°C and 50 ± 25% RH) for at least 4 hours		60		Pass
Pre-condition Cold Storage Environment Test (-40 ± 3°C) for 96 hours[a]	≥ 0.8 mL	60		Pass

Test Condition	Specification	Sample Size	Calculation	Result
			(b) (4)	
	(b) (4)			
Pre-condition Dry Heat Storage Environment Test (60 ± 2°C and 50 ± 10% RH) for 96 hours[a]		60		Pass
Free Fall Test (Drop Test) – Horizontal		10		Pass
Free Fall Test (Drop Test) – Vertical A		10		Pass

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Test Condition	Specification	Sample Size	Calculation	Result
			(b) (4)	
Free Fall Test (Drop Test) – Vertical B	(b) (4)	10		Pass
Vibration Test		20		Pass
Transportation		60		Pass
Test Condition	**Specification**	**Sample Size**	**Calculation**	**Result**
			(b) (4)	

*Subassembly pre-conditioning was performed in alignment with recommended ISO 11608-1 test conditions

Table 10: Results of Functional Testing at Standard Atmosphere Conditions According to ISO 11608-1 and ISO 11608-5

Test Condition	Specification	50mg/mL Presentation			
		Sample Size	Mean	Standard Deviation	Result
Needle Shield Remover Force	(b) (4)	60	19	1.4	Pass
Activation Force		60	12	0.5	Pass
Needle extension		60	6.6	0.12	Pass
Injection Time		60	5	0.5	Pass
Needle Cover Override Force (after locking)		60	0.7	0.03	Pass
Free Fall Test (Drop Test) –Horizontal Needle Shield Override Force on Activated Device		10	0.7	0.05	Pass
Free Fall Test (Drop Test) –Vertical A Needle Shield Override Force on Activated Device		10	0.7	0.06	Pass
Free Fall Test (Drop Test) –Vertical B Needle Shield Override Force on Activated Device		10	0.6	0.03	Pass
Separation force (without label)		60	80	0.13	Pass

Table 12: Results of Function Test After Pre-conditioning According to ASTM D4169

Function Test Description	Specification	Sample Size	Mean	Standard Deviation	Result
Needle Shield Remover Force	(b) (4)	60	15	1.6	PASS
Activation Force		60	12	0.5	PASS
Needle Extension		60	6.6	0.1	PASS
Deliverable Volume		60	0.8	0.005	PASS
Injection Time		60	6	0.5	PASS
Needle Shield Override Force (after locking)		60	0.6	0.03	PASS
Separation Force (without label)		60	80	0.2	PASS

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They demonstrate that their device constituent components (rear shell, rear shell cap, front shell, needle cover, needle cover extension, cap, shield remover, and syringe carrier) met the following biocompatibility endpoints as described in ISO 10993-1 assuming a surface device, limited contact (less than 24 hours).

- Cytotoxicity per ISO 10993-5
- Sensitization per ISO 10993-10
- Irritation and Intracutaneous reactivity per ISO 10993-10

Table 44: Biocompatibility Test Results

Test Item	Reference	Acceptance Criteria	Result
Cytotoxicity	ISO 10993-5	(b) (4)	Pass
Irritation	ISO 10993-10		Pass
Skin Sensitization	ISO 10993-10		Pass

They also tested needle safety erformance in a separate needle safety study (REF: 3.2.P.2. Pharmaceutical Development, *SB5 Autoinjector Sharps Injury Prevention Feature Study Report*) per FDA guidance "Medical Devices with Sharps Injury prevention features, Section 10. Simulated Clinical Use Testing". Below is an overview of the study parameters:

Table 41: Summary of Sharps Injury Prevention Feature Assessment for SB5 Safety PFS

Sample Size	Successful Needle Shield Extending and Locking	Failed Needle Shield Extending and Locking	Success Rate of Safety Feature Activation
555	555	0	100%

For details on the results, refer to the attachment, SB5 Safety PFS Sharps Injury Prevention Feature Study Report.

The report was reviewed, and additional study arameters are below:

Parameter	Description
Sample	(b) (4)
Environment	Usability testing facility. Gloves and injection pads provided
Training	All participants trained to proficiency
Participant demographics	17 nurses • Male/female • Left/right handed • Age 22-59

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	• Experience 0-20+ yrs • Different hand sizes
Sample size	N=55, Each participant used 30-49 devices each

Reviewer Comment:

- This reviewer agrees with the ISO 11608-1 and ISO 11608-5 applicability assessment.
- The sponsor tested the essential performance requirements identified in the device description. However, they did not provide the design verification protocols and reports to assess if they adequately tested their device (correct methods, analysis of data). See Deficiency 1.
- Although the contact classification and biocompatibility endpoints appear adequate for the device constituent of the AI, they did not provide biocompatibility protocols or reports. We need this information to determine if they have tested the AI adequate. See Deficiency 3. I defer adequacy of the biocompatibility protocols/reports to the lead reviewer.
- The Sponsor uses a n=60 sample size for their functional performance testing. Although it is adequate to use the ISO recommended sample sizes for ISO tests(free fall, vibration, etc.), there isn't a recommended sample size for the functional testing alone (e.g. injection time). This is also of concern since it appears that the testing was attribute (pass/fail) instead of variable which would mean a very low confidence/reliability for those tested attributes. Therefore, the Sponsor should provide statistical rationale for the selected sample size and clarify the acceptance criteria (confidence/reliability, k-value, or pass/fail) for the following attributes that did not undergo ISO pre-conditioning: needle shield remover force, activation force, injection time, needle cover override force, needle extension, separation force. See Deficiency 4.
- The needle safety performance testing report was thorough, and they met the FDA guidance requirements (97.5/99%). Note: If the Sponsor does not address Deficiencies 1 and/or 4, this would be adequate for the needle safety performance attributes only because their separate needle safety report adequately addresses the agency's guidance recommendations thoroughly.
- The Sponsor did not provide DVT data over stability. However, it appears they provided separate non-DV stability testing (REF: pg. 76-Table 48, 3.2.P.2 Pharmaceutical Development, Container Closure System) to support the shelf life of the device constituents.

6. Review of Information Request Responses

(b) (4)

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Rumi Young, M.S. RAC Biomedical Engineer Reviewer

Digital Signature Concurrence Table	
Consultant Reviewer	

Reference ID: 4466647

U.S. FOOD & DRUG ADMINISTRATION

BLA 761059 Quality Assessment
Product: SB5
Proposed Trade Name: Hadlima
Manufacturer: Samsung Bioepis Co, Ltd

João Pedras-Vasconcelos:
Drug Substance, Analytical Similarity and Immunogenicity
Merry Christie: Validation of Analytical methods

Division of Biotechnology Review and Research III

Reference ID: 4466647

U.S. FOOD & DRUG ADMINISTRATION

OBP CMC Assessment Data Sheet

1. BLA#: 761059

2. Assessment Date: March 22, 2019

3. Primary Assessment Team:

Clinical	DPARP – Raj Nair / Nikolay Nikolov DDDP –Roselyn Epps / David Kettl DGIEP –Anil Rajpal
Clin/Pharm	Lei He / Anshu Marathe
Clin Stats	Becky Rothwell / Nie Lei
Pharm/Tox	David Klein / Tim Robison
TBBS	Cristina Ausín-Moreno /Stacey Ricci
Product Quality & Immunogenicity	João Pedras-Vasconcelos (AS, DS Imm)/Merry Christie (VAM)/ Tracy Denison (DP) / Maria Cecilia Tami
CMC Stats	Yu-Ting Weng / Meiyu Shen
Process and Facilities	DIA-– Viviana Matta / Peter Qui DMA – Bo Chi (DS)/ Jessica Hankins (DP) /Maria Candauchacon
CDRH	OC/ODE- Sarah Mollo/Stevens Alan / Carolyn Dorgan

4. Major GRMP Deadlines:

Milestone	Target Date for Completion
Filing Action Date (60 Day Letter)	September 21, 2018
74 Day Letter	October 5, 2018
Mid Cycle Communication	January 22, 2019
Primary Assessments	March 22, 2019
Secondary Assessments	March 30, 2019
Wrap Up Meeting	June 3, 2019
BsUFA Action Date (12 months)	July 23, 2019

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request (OBP I)	August 31, 2018

Reference ID: 4466647

74-day letter Information Request (OBP II)	October 5, 2018
Information Request (OBP III)	October 6, 2018
Information Request (OBP IV)	December 07, 2018
Midcycle Meeting	January 8, 2019
Midcycle Communication	January 22,2019
Information Request V	February 4, 2019
Information Request VI	February 27, 2019
Information Request VII	February 28, 2019
Information Request VIII	March 8, 2019
Information Request IX	March 14, 2019
Information Request X	March 22, 2019

6. Submission Assessed:

Submission:	Date Received:	Assessment Completed (yes or no)
761059/0012	July 23, 2018	Yes
761059/0015 (Response to IR I)	September 10, 2018	Yes
761059/0022 (D74 letter response 1)	November 5, 2018	Yes
761059/0023 (response to IR III)	November 6, 2018	Yes
761059/0027 (OBP IR IV)	December 31, 2018	Yes
761059/0031 (D74 letter Response) II)	January 15, 2019	Yes
761059/0035 Mid cycle minutes	February 5, 2019	Yes
761059/0036 OBP IR V	February 12, 2019	Yes
761059/0041 OBP IR VI	March 06, 2019	Yes
761059/0041 OBP IR VII	March 06, 2019	Yes
761059/0043 OBP IR VIII	March 13, 2019	Yes
761059/0044 OBP IR VI	March 14, 2019	Yes
OBP IR IX	March 18, 2019	Yes
OBP IR X	Pending	N/A

Assessor note: By the time this review memo was uploaded in Panorama, the responses to IRX (sent to the Sponsor on March 22, 2019) had not been received. The responses to this IR will be reviewed and discussed in an addendum to this memo

7. Drug Product Name/Code/Type:
   - a. Proprietary Name — SB5
   - b. Trade Name — Hadlima/Hadlima PushTouch (proposed)
   - c. Non-Proprietary Name/USAN/INN — adalimumab-xxxx
   - d. CAS Name — 331731-18-1
   - e. Common Name
   - f. Compendial Name — not applicable
   - g. OBP systematic name: — MAB HUMAN (IGG1) ANTI P01375

(TNFA_HUMAN) [SB5]

8. Pharmacological Category: Immunosuppressant, TNF-α inhibitor

9. Dosage Form: Injection in single-dose pre-filled autoinjector (Hadlima PushTouch)
Injection in a single-dose pre-filled syringe (Hadlima)

10. Strength/Potency:
(i): The concentration/strength of the Drug Product: 40 mg/0.8 mL
(ii): Type of potency assay(s): Reporter Gene bioassay, FRET binding assay

11. Route of Administration: subcutaneous injection

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	No review required. Sufficient information provided in the application
			Yes	
			Yes	
			Yes	
			Yes	
			Yes	
			Yes	Assessment by CDRH

(b) (4)	Yes (NF)	Assessment by CDRH. No LOA provided. No review of DMF required because sufficient information provided in the application

13. Inspectional Activities:

Three pre- approval inspections were performed for BLA 761059:

1- A PAI of the DS manufacturing site was conducted (b) (4). Information about the facility and FDA personnel involved is described below:

Firm:	(b) (4)	
Location:		
FEI:		
Dates of inspection:		
Days in the facility:	7	
FDA Participants:	Bo Chi, Ph.	DCDER/OPQ/OPF/DMA
	Tracy Denison, Ph.D.	CDER/OPQ/OBP/DBRRIII

A six-item 483 form was issue to (b) (4)) Manufacturing Aps at the end of the DS facility inspection on (b) (4)(Appendix II). The inspection was classified as VAI. The 483 observations included:

(b) (4)

2- A PAI of the DP manufacturing site was conducted from February (b) (4). Information about the facility and FDA personnel involved is described below:

Firm:	(b) (4)
Location:	
FEI:	
Dates of inspection:	

Days in the facility:	7	
Participants:	Viviana Matta, Ph.D.,	CDER/OPQ/OPF/DIA
	Jessica Hankins, Ph.D.	CDER/OPQ/OPF/DIA

A five-item 483 form was issue to [redacted] (b) (4) at the end of the DP facility inspection on [redacted] (b) (4) (Appendix III). The inspection was classified as VAI. The 483 observations included:

[redacted] (b) (4)

3- A PAI of the site where analytical similarity data were collected was conducted from November 12-15, 2018. Information about the facility and FDA personnel involved is described below:

Firm:	Samsung Bioepsis Co, Ltd	
Location:	107 Cheomdan-daero, Yeonsu-gu, Incheon, South Korea	
FEI:	3010031951	
Dates of inspection:	November 12-15, 2018	
Days in Facility:	3	
FDA Participants:	Viviana Matta, Ph.D.	CDER/OPQ/OPF/DIA
	Tracy Denison, Ph.D.	CDER/OPQ/OBP/DBRRIII
	Frances Namuswe, Ph.D.	CDER/OPQ/OBP/DBRRIII

This pre-license inspection of Samsung Bioepis was conducted on November 12-15, 2018 and covered the assessment of the analytical similarity data. This inspection was limited to SB5. Three verbal observations were made to the firm:

[redacted] (b) (4)

(b) (4)

14. Consults Requested by OBP:

Discipline/ Topic	Date Requested	Recommendation	Assessor
CDRH/OC	08/9/2018	Pending	Dorsey Leslie/Tegero Isabel

15. Quality by Design Elements:
The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: None

17. Administrative:

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation

We recommend approval of BLA 761059, pending review of an outstanding information request. The data submitted in this Biologics License Application support the conclusion that the manufacture of SB5 Drug substance is sufficiently controlled to be able to consistently deliver a product that is pure and potent. The DS manufacturing process is robust for inactivation or removal of viral adventitious agents and leads to a product free of endogenous and adventitious infectious agents. The conditions used in manufacturing have been validated, and a product of the expected quality has been manufactured from multiple production runs. The analytical similarity testing approach and results provided in the submission support a determination that SB5 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components. A robust analytical bridge among SB5, US-licensed Humira, and EU-approved Humira was established to support the safety data collected in clinical studies performed with EU-approved Humira as comparator. Clinical batches were evaluated in the analytical similarity study. The manufacturing process for the clinical material, process validation material, and the commercial process material are highly similar.
There are no issues identified so far in the reviewed sections that would preclude approval of this application.

II. List of Deficiencies to be Communicated

There are no CMC-Product Quality deficiencies identified at this time that may preclude approval of this BLA.

III. List of Post-Marketing Commitments/Requirements

There are 3 potential Product Quality-related Post-Marketing Commitments, which will include due dates negotiated with the sponsor. The final PMC list agreed with the Sponsor will be documented in the addendum to this report once outstanding information has been reviewed.

1. To implement rejection limits [redacted] (b) (4)
2. To implement in process action limits [redacted] (b) (4)
3. To provide additional data to further characterization the coverage of the anti-HCP antiserum

IV. Assessment of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

Samsung requests categorical exclusion from the preparation of an environmental assessment requirement under 21 CFR Part 25.31(g): "*Establishment of bioequivalence requirements for a human drug or a comparability determination for a biologic product subject to licensing*". Samsung developed SB5 as a proposed biosimilar to US-licensed Humira and considers that establishment of analytical similarity is conceptually similar to establishing comparability between pre- and post-change products. *Approval of this submission will not increase the overall use of the active moiety. Therefore, exclusion may be granted.*

V. Primary Container Labeling AssessmentAssessment

The primary container labeling was reviewed by Vicky Borders-Hemphill. Refer to Vicky Borders-Hemphill review in Panorama.

VI. Assessment of Common Technical Document- Quality Module 3.2

CTD Modules 3.2.S (except for sections 3.2.S.4.2 and 3.2.S.4.3), 3.2.R, and 3.2.A are reviewed by João Pedras-Vasconcelos. Modules 3.2.P (except for sections 3.2.P.5.2 and 3.2.P.5.3) were reviewed by Tracy Denison. Sections, 3.2.S.4.2 and 3.2.S.4.3 and 3.2.P.5.2 and 3.2.P.5.3 were reviewed by Merry Christie.

VII. Assessment of Immunogenicity Assays- Module 5.3.1.4

The immunogenicity assays were reviewed by Joao Pedras-Vasconcelos, Maria Cecilia Tami and Susan Kirshner. Refer to review by Joao Pedras-Vasconcelos in Panorama.

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Description of Drug Substance

3.2.S. Drug Substance

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

Information on the nomenclature of SB5, the proposed Samsung biosimilar to US- licensed Humira (adalimumab) is provided in Table 3.2.S.1.1-1.

Table 1. Nomenclature of SB5 Drug Substance

Name/code	Description
International Nonproprietary Name (INN) for Reference Product	adalimumab
International Nonproprietary Name (INN) for SB5	adalimumab
United States Adopted Name (USAN)	adalimumab
Chemical Name (IUPAC)	Not applicable
Internal Company or Laboratory Code (Samsung)	SB5 (Samsung) BIIB606 (CMO code)
CAS Registry Number for adalimumab	331731-18-1

3.2.S.1.2 Structure

SB5 is a recombinant fully human IgG1 monoclonal antibody (mAb) expressed in (b) (4) cells against human tumor necrosis factor alpha (TNF-α). SB5 has two identical heavy (H) chains with a molecular weight of approximately 51 kDa (glycosylated) and two identical kappa light (L) chains with a molecular weight of approximately 23 kDa, covalently linked with four inter-chain disulfide bonds.

Assessor notes: *The protein sequence of SB5 is experimentally verified and it is the same as the biosimilar reference product, US-licensed Humira.*

3.2.S.1.3 General Properties

SB5 DS is a clear to opalescent and colorless to pale brown solution of (b) (4) mg/mL adalimumab.
Molecular weight: 148 kDa
pH: (b) (4)
Calculated pI: 8.5
Coefficient of Extinction: 1.39 mL mg^{-1} cm^{-1}
Glycosylation: One N-linked glycosylation site located at Asn301 on each heavy chain. No O- linked glycosylation sites.
Biological Activity: Adalimumab binds specifically to TNF-a and neutralizes its biologic function by blocking its interaction with the p55 and p75 cell surface TNF-a receptor. Adalimumab also modulates

biological responses induced or regulated by TNF-a including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1 and ICAM-1).

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Table 1 lists the sites and their responsibilities in the manufacture of SB5 Drug Substance (DS).

Table 1 SB5 Manufacturing Sites

Name and Address	Responsibilities
(b) (4)	Manufacturing of master cell bank (MCB) and working cell bank (WCB) MCB and WCB storage
	MCB and WCB storage
	MCB and WCB storage[a]
	MCB and WCB storage[a]
	Manufacturing and packaging QC release testing (appearance, protein concentration, endotoxin, and microbial enumeration) In-process testing (b) (4)
	In-process testing (b) (4)
Samsung Bioepis Co., Ltd 107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Korea, Republic Of	In-process testing (b) (4)

(b) (4)	QC release testing (all tests except appearance, protein concentration, endotoxin, and microbial enumeration) Stability testing (all tests)
	QC release testing (all tests except appearance, protein concentration, endotoxin, and microbial enumeration) Stability testing (all tests except endotoxin and microbial enumeration)
	Stability testing (endotoxin and microbial enumeration)
	DS Storage
(b) (4)	

Assessor Comment: *BLA 761059's pre-approval inspection (PAI) of the DS manufacturing facility at* (b) (4) *was conducted by OBP inspector Tracy Denison and DMA inspector Bo Chi on* (b) (4)*. A six-item 483 form was issue to* (b) (4) *Manufacturing Aps at the end of the DS facility inspection on* (b) (4) *(Appendix III). The inspection was classified as voluntary action indicated (VAI).*

3.2.S.2.2, 3.2.S.2.4, 3.2.S.2.5 Description of Manufacturing Process, Control of Critical Steps and Intermediates, Process Validation and/or Evaluation

3.2.S.2.2 Description of Manufacturing Process and Process Controls

Overview of Manufacturing Process

(b) (4)

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U.S. FOOD & DRUG ADMINISTRATION

3.2.R Biosimilarity with Reference Product
ANALYTICAL SIMILARITY ASSESSMENT

Assessor comment:
The data from 3.2.R assessed below support the following conclusions:
• Samsung demonstrated that the proposed biosimilar, SB5, is highly similar to US- Humira.
• Samsung established an analytical bridge between US-licensed Humira and EU- Humira.
• For attributes where, minor differences between SB5 and US- Humira were observed, the totality of the analytical data supports the conclusion that there is no impact on function, activity, or stability in vitro. Specifically, the differences noted in charged or glycosylation variants did not result in differences functional assays, such as ADCC, CDC, and the corresponding CD16 and C1q binding assays. Therefore, these differences are not expected to affect the mechanism of action of the product and did not affect the demonstration that SB5 and US-Humira are highly similar.
• The method validation or qualification results support the suitability of the methods used in the analytical similarity assessment
• Samsung used an acceptable risk-based statistical approach to assess analytical similarity results using:

- for quantitative assays:
  - equivalence testing for highest risk attributes;
  - quality ranges calculated from 3-standard deviations of the mean for moderate risk attributes;
- for qualitative assays:
  - visual display comparisons.

• Samsung intends to license two different presentations of SB5, a pre-filled syringe (PFS) and an autoinjector. The analytical similarity assessment was performed with the PFS. According to the drug product assessment by Tracy Denison, the assembly into the secondary packaging component of the autoinjector does not negatively impact product quality attributes. Therefore, it is acceptable to analyze only PFS batches in the analytical similarity assessment.

3.2.R.1 Overall Strategy

The analytical similarity assessment consisted of three pairwise comparisons: SB5 drug product to US-licensed Humira, SB5 drug product to EU-approved Humira, and EU-approved Humira to US-licensed Humira. Hereafter, US-licensed Humira and EU-approved Humira are respectively referred to as US-Humira and EU-Humira. With this approach, the Sponsor can demonstrate that SB5 drug product is highly similar to US-Humira and establish an analytical bridge between SB5, US- and EU- Humira.

The comparative physicochemical and functional assessment includes:

• Comparative similarity characterization studies of the following quality attributes (QA):
  - Primary structure, post-translational modifications, and sequence variants
  - N-linked glycosylation
  - Charge heterogeneity
  - Product purity
  - Product related attribute

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- Higher order structure
- Biological activity

• Assessment of the similarity of the degradation profiles resulting from forced degradation studies.
• Assessment of the similarity of the long-term stability profile at accelerated storage conditions (25 ± 3 °C) for up to 12 months and stressed conditions (40 ± 3 °C) for up to 6 months.

The analytical similarity exercise was mostly performed at Samsung Bieopis (Inchon, Korea), with some tests being performed at (b) (4) . Samsung ranked quality attributes (QA) for the similarity assessment by their criticality assessed by the potential impact of each attribute on efficacy (potency), immunogenicity, pharmacokinetics (PK), pharmacodynamics (PD), safety, and uncertainty. The risk priority number (RPN) is determined by multiplying Impact and Uncertainty to the risk assessment for the quality attribute. QAs directly related to the mode of action and with a high-risk score (>59) were assessed using Equivalence Testing (ET) statistical assessment. Attributes having a moderate risk score (24-59) were evaluated using Quality Range (QR) statistical assessment, and the remaining attributes (risk score <24), including those without a quantitative readout, were assessed by Visual Display Comparison (VDC) of graphical data. When using the Quality Range approach, analytical similarity for the attribute was met if 90% or greater of all test values fell within the statistical quality range of 3 standard deviations of estimated mean of the comparator product. QAs evaluated by VDC were assessed using a descriptive evaluation of the raw data, and a simple dot plot is used for quantitative QAs.

Samsung generated the analytical similarity data in three separate analytical similarity (AS) studies (see Sponsor's Fig 1 from amendment 27) to include material from different manufacturing sites for SB5 DS and DP. The data from the three studies were pooled for the similarity assessment.

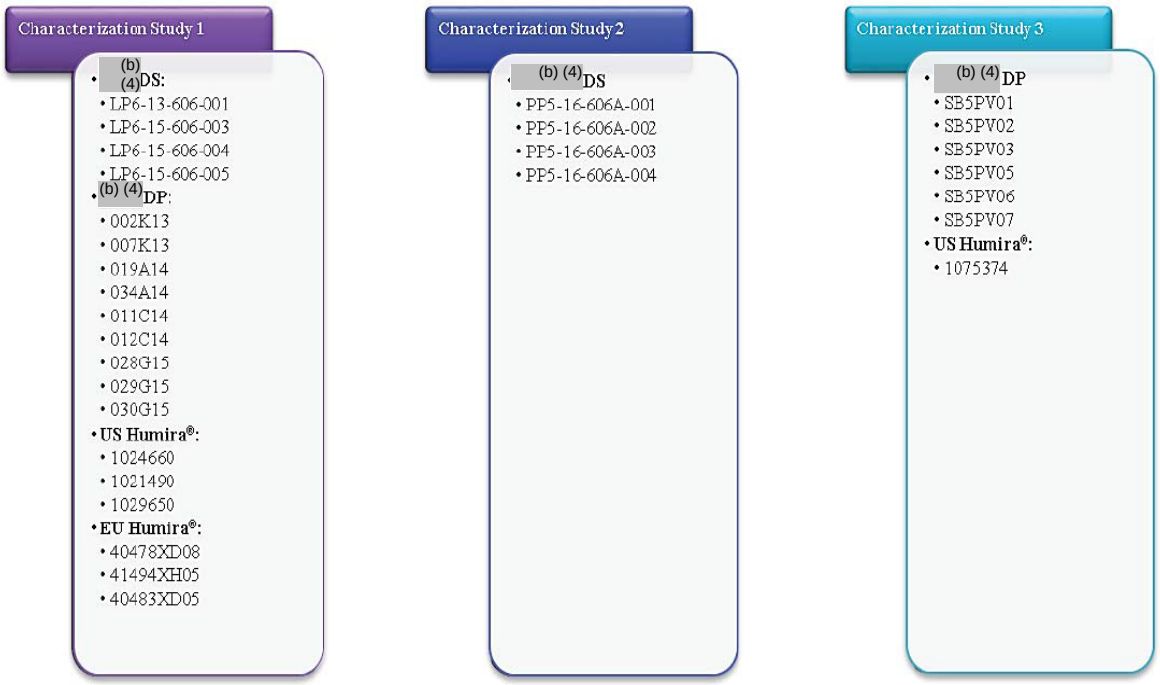

Figure 1: Overview of SB5 Characterization Study and the Characterized Batches in Each Study

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Assessor comment: *The Sponsor's risk ranking acceptably identified critical quality attributes to be included in the analytical similarity assessment. The choice of statistical approaches for assessing assay results is also appropriate because there is acceptable stringency around the acceptance criteria to establish analytical similarity.*

The Sponsor's choice of DS and DP lots to include in the analytical similarity exercises was appropriate because:

- *Lots used in clinical and non-clinical studies were included*
- *Lots manufactured using the proposed commercial process were included*
- *Comparability was established for SB5 lots manufactured at different sites or using different manufacturing processes.*

A total of 53 drug product (DP) batches of US- Humira, expiry dated from 06/2013 to 11/2018, and 53 DP batches of EU- Humira, expiry date from 03/2013 to 03/2017, were purchased and included as comparators in the similarity assessment. A total of 9 DP batches, each derived from a different DS batch, and one additional DS batch never used for SB5 DP production were included in the similarity assessment, see Table 1 below for details on the batches used.

Table 1: SB5 Analytical Similarity Batches.

Table adapted from submission by assessor

Type	Development Stage	Batch Number	Description	DS Batch used (manufacturing site)	DP Manufacturing Information		Used for Similarity		
					Date	Site	ET	QR	VDC
DS (50 mg/mL)	PVR batch	PP5-16-606A-001	· Process validation run · Stability studies	N/A	Jan 2017	(b) (4)	X	X	NP
DP (50 mg/mL)	Clinical batch	002K13	· Stability studies	LP6-13-606-001 (b) (4)	Nov 2013		X	X	X
		007K13	· Stability studies	LP6-13-606-004 (b) (4)	Jan 2014		X	X	X[a]
		019A14	· Stability studies	LP6-13-606-002 (b) (4),	Jan 2014		X	X	X[a]
	PVR batch	028G15	· Process validation run · Stability studies	LP6-15-606-003((b) (4)	Oct 2015		X	X	X
		029G15	· Process validation run · Stability studies	LP6-15-606-004((b) (4)	Nov 2015		X	X	X[a]
		030G15	· Process validation run · Stability studies	LP6-15-606-005((b) (4)	Nov 2015		X	X	X[a]
	PVR batch	SB5PV05	· Process validation run · Stability studies	PP5-16-606A-002 (b) (4)	Oct 2017		X	X	X

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		SB5PV06	Process validation run Stability studies	PP5-16-606A-003 (b) (4)	Oct 2017		X	X	X[a]
		SB5PV07	Process validation run Stability studies	PP5-16-606A-004 (b) (4)	Oct 2017		X	X	X[a]

N/A: Not applicable; NP: Not performed; ET Equivalence Testing; QR Quality Range; VDC Visual Display Comparison; PVR-Process Validation Run; (b) (4)

[a] Batch which was not included for all test items included in respective testing approach

Assessor comment:
To assess analytical similarity Samsung provided pooled data results from the three studies to the BLA. There are 10 batches of SB5 included in the analytical similarity exercise- 9 DP batches and 1 DS lot. The 9 batches of SB5 DP included in the exercise are from 9 different DS batches and are thus considered independent. The 10th lot of SB5 included in the assessment is a DS batch that was not used to produce DP and is also considered independent. Non-independent batches were excluded from the analytical similarity assessment. This is acceptable.
Samsung established quality ranges for US- and EU-Humira between 2012 and 2015 using up to 45 batches of each, prior to the first analytical similarity study (referred to as Characterization Study 1in Fig 1 above) in 2015. How early in the SB5 biosimilar program the analytical method qualification was performed impacted the number of US- and EU-Humira batches used to establish the analytical ranges, with the older established methods using more reference batches than more recent methods to establish the analytical ranges. Samsung states in amendment27 (Dec 31, 2019) that the US- and EU-Humira QRs were locked prior to starting analytical similarity studies. A list of the 53 US- and 53 EU-Humira batches, the testing approach to analytical similarity (ET, QR and VDC), and whether they were tested side-by-side with SB5 batches are detailed in Tables 7 and 8 of document 3.2.R.4. The choice of reference product batches tested side-by-side with SB5 was based on availability, quantity, and expiration date at the time of testing. The chosen US- or EU-Humira batches needed to be within expiry up to the completion of the AS studies, and to have enough quantities available. The batches were analyzed in order of purchase, with older batches tested first. The numbers of both US- and EU-Humira batches included in the analytical similarity assessment are acceptable.
In amendment 27 (Dec 31, 2018), Samsung provided information on eight additional US- and EU-Humira batches that were purchased following the completion of the analytical similarity studies. According to Table 2 of 2.3.R.4, most of the analytical similarity methods were qualified and performed at Samsung. Some of the methods used for assessing biophysical properties were performed at (b) (4) s. Qualification summaries were provided in amendment 27 (Dec 31, 2018) for the following test methods: TNF-α Binding Assay, TNF-α Neutralization Assay; Apoptosis Induction Assay; Binding Assays for FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa (V/V type and F/F type), FcγRIIIb, FcRn and C1q; ADCC and CDC bioassays; Protein Concentration by UV; CE-SDS (reducing and non-reducing); SE-HPLC; CEX-HPLC; icIEF; HILIC-UPLC. The information submitted indicates that the methods were suitably qualified.

Analytical Similarity Data:

Below is a summary table prepared by the assessor describing the data provided in the submission, including comparisons of SB5 vs. US-Humira, SB5 vs. EU-Humira, and US-Humira vs EU-Humira. In the Table below, "Similar/comparable" means that the pairwise comparison met the criteria for the analytical similarity testing approach, equivalence testing, quality ranges or visual comparison.

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"Comparable" refers to the comparison between US- Humira and EU- Humira. "Not similar" means the that the pairwise comparison did not meet the equivalence, quality ranges, or visual comparison criteria. The "not similar" results are discussed in detail in the following sections of the review. However, note that a "not similar" assessment for assay results does not necessarily mean a failure of the analytical similarity assessment as a determination of highly similar is made based on the evaluation of the totality of evidence.

Table 2: SB5 Analytical Similarity Assessment Summary Data (prepared by assessor).

Parameter	Quality Attribute	Test Method	Analytical Similarity Testing Approach	Number of Batches (SB5: US- licensed Humira: EU-approved Humira)	SB5 min – max Range	US-licensed Humira Quality Range or Visual Range	EU-approved Humira Quality Range or Visual Range	SB5 vs. US-licensed Humira /SB5 vs. EU- approved Humira / US-licensed Humira vs EU - approved Humira
Primary Structure, Amino acid modifications and sequence variants	Amino Acid Sequence	UPLC-ESI-MS/MS (trypsin, Asp-N, Lys-C)	VDC	1:1:1	Expected aa sequence and peptide masses	Identical aa sequence and peptide masses to US-licensed Humira	Identical aa sequence and peptide masses to US-licensed Humira	similar/similar/comparable
	N-terminal sequencing	UPLC-ESI-MS/MS (trypsin, Asp-N, Lys-C) N term pyro-Glu	VDC	9:4:3	HC N-term: (98.7-99.3%) HC-pyroGlu : (0.7-1.3%)	HC N-term: (98.4-99.1%) HC-pyroGlu (0.9-1.6%)	HC N-term: 98.3-98.5% HC-pyroGlu: (1.5-1.7%)	**N terminal pyroGlu** similar/**not similar (9 batches OOR)**/comparable
	C-terminal sequencing	UPLC-ESI-MS/MS (trypsin, Asp-N, Lys-C) C term lys	VDC	9:4:3	HC C-term (1.3-3.1%) HC Lys$^-$ C-term (96.7-98.7%)	HC C-term (5.7-9.6%) HC Lys$^-$ C-term (90.4-94.3%)	HC C-term (6.8-8.1%) HC Lys$^-$ C-term (91.9-93.2%)	**C term Lys content Not similar (9 batches OOR)/not similar (9 batches OOR)**/comparable
	Peptide Mapping	UPLC-ESI-MS/MS (trypsin, Asp-N, Lys-C)	VDC	3:1:1	Peak pattern of UV chromatograms is visually superimposable	Peak pattern of UV chromatograms is visually superimposable	Peak pattern of UV chromatograms is visually superimposable for US-licensed	similar/similar/comparable

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	Disulfide bonds	UPLC-ESI-MS/MS (Trypsin, DTT)	VDC	3:2:1	Correct MWs and numbers of disulfide linked peptides	Similar MWs and numbers of disulfide linked peptides to US-licensed Humira	Similar MWs and numbers of disulfide linked peptides to US-licensed Humira	similar/similar/comparable
	Free sulfhydryl groups µM (%)	FLR	VDC	9:4:3	1.1-62 µM (0.5-3.1%)	0.2-2.2 µM (0.1-1.1%)	0.1-0.3 µM (0.1-0.3%)	**Not-similar (3 batches OOR)/not-similar (9 batches OOR)**/comparable
	Methionine Oxidation Met 256 Met 34	UPLC-ESI-MS/MS	VDC	9:4:3	Met 256: 3.0-6.4% Met 34: 0.2-0.5%	Met 256: 2.3-3.9% Met 34: 0.1-0.7%	Met 256: 2.9-3.5% Met 34: 0.4-0.5%	**Met 256: Not Similar (3 batches OOR)/ not-similar (3 batches OOR)** /comparable *3 clinical batches > Met 256 than Humira.*
	Asparagine Deamidation (peptides LH27 and LH30)	UPLC-ESI-MS/MS	VDC	9:4:3	HC Asn 77/84: 0-1.1% HC Asn319: 0-1.7 LC Asn137/138: 0-0.9%	HC Asn 77/84: 0-1.0% HC Asn319: 0-1.1% LC Asn137/138: 0-0.9%	HC Asn 77/84: 0.7-0.8% HC Asn319: 0 5-0.7% LC Asn137/138: 0.4-0.6%	similar/similar/comparable
	Molecular Mass	UPLC-ESI-MS (NR) of intact protein (2H2L+ 2G0F)	VDC	9:4:7	Similar molecular mass and size (148.1 kDa)	Similar molecular mass and size to US-licensed Humira (148.1 kDa)	Similar molecular mass and size to US-licensed Humira (148.1 kDa)	similar/similar/comparable
		UPLC-ESI-MS –(R) of Heavy Chain Light Chain	VDC	9:4:7	Similar molecular mass and size HC+G0F:50.6 kDa LC:23.4 kDa	Similar molecular mass and size to US-licensed Humira HC+G0F:50.6 kDa LC:23.4 kDa	Similar molecular mass and size to US-licensed Humira HC+G0F:50.6 kDa LC:23.4 kDa	similar/similar/comparable
		UPLC-ESI-MS –(R/NR) of Deglycosylated mAb (2H2L), LC, HC	VDC	9:4:7	Similar molecular mass and size 2H2L: 145.2 kDa HC:49.2 kDa LC:23.4 kDa	Similar molecular mass and size to US-licensed Humira 2H2L: 145.2 kDa HC:49.2 kDa LC:23.4 kDa	Similar molecular mass and size to US-licensed Humira 2H2L: 145.2 kDa HC:49.2 kDa LC:23.4 kDa	similar/similar/comparable

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		SE-HPLC /MALLS of Monomer	VDC	4:2:2	Similar molecular mass and size (144.2-150.4 kDa)	Similar molecular mass and size to US-licensed Humira (143.8-154.1 kDa)	Similar molecular mass and size to US-licensed Humira (144.4-145.9 kDa)	similar/similar/comparable

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Parameter	Quality Attribute	Test Method	Analytical Similarity Testing Approach	Number of Batches (SB5: US- licensed Humira: EU-approved Humira)	SB5 min –max Range	US-licensed Humira Quality Range or Visual Range	EU-approved Humira Quality Range or Visual Range	SB5 vs. US-licensed Humira /SB5 vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Purity	% Main	SE-HPLC	QR	10:45:46	99.4-99.8%	99.2-99.6%	99.5-99.6%	similar/similar/comparable
	Monomer	SE-HPLC/MALLS	VDC	4:2:2	99.3-99.9%	99.5-99.8%	99.2-99.8%	similar/similar/comparable
		SV-AUC	VDC	4:2:2	98.6-99.1%	98.2-98.5%	96.2-97.6%	similar/similar/comparable
	HMW variants	SE-HPLC	QR	10:45:46	0.2-0.4%	0.3-0.5%	0.3-0.5%	similar/similar/comparable
		SV-AUC	VDC	4:2:2	0.94-1.37%	1.46-1.84%	1.72-2.44%	**Not-similar (4 batches OOR)/not-similar (4 batches OOR)**/comparable
	Dimers	SE-HPLC /MALLS	VDC	4:2:2	0.1-0.6%	0.1-0.3%	0.1-0.5%	similar/similar/comparable
	LMW Variants	SE-HPLC	QR	10:45:46	0-0.2%	0.1-0.5%	0.2-0.5%	similar/similar/comparable
	Antibody mAb fragments	CE-SDS (R)	QR	10:45:42	NGHC: 1.5-4.2%	NGHC: 1.0-1.4%	NGHC: 0.8-1.5%	**Not-similar (9 batches OOR)/ Not-similar (8 batches OOR)**/comparable
		CE-SDS (NR)	QR	10:45:42	2H1L: 1.4-2.2%	2H1L: 1.2-2.1%	2H1L: 1.1-2.2%	similar/similar/comparable
	Intact IgG	CE-SDS (NR)	QR	10:45:42	95.4-96.7%	95.7-97.1%	95.5-98%	similar/similar/comparable
Glycosylation	Site occupancy Fc N-glycan on D15 peptide	UPLC-ESI-MS/MS (± PNGase)	VDC	3:1:1	MW of glycosylated and deglycosylated D15 peptides (2663 vs 1999 Da)	MW for glycosylated and deglycosylated D15 peptides (2663 vs 1999 Da)	MW for glycosylated and deglycosylated D15 peptides (2663 vs 1999 Da)	similar/similar/comparable
	N-Glycan Identification	UPLC-ESI-MS/MS with procainamide	VDC	3:1:1	13/14 glycans detected	14/14 glycans detected	14/14 glycans detected	Similar: similar: comparable *Mannose 4 glycan peak not detected in SB5*

	N-glycan non-fucosylated + N-glycan high mannose	HILIC-UPLC	QR	10:45:45	8.4-11.9%	6.2-11.4%	5.8-12.0%	**Not Similar (3 batches OOR)**/ similar/comparable
	N-glycan non-fucosylated	HILIC-UPLC	QR	10:45:45	2.0-3.6%	1.6-2.3%	1.6-2.7%	**Not similar (9 batches OOR) /not similar (8 batches OOR) / comparable (6/45 batches OOR)**
	N-glycan high mannose	HILIC-UPLC	QR	10:45:45	5.2-9.9%	4.4-9.3%	4.1-9.4%	**Not similar (2 batches OOR)/not-similar (2 batches OOR)**/comparable
	N-glycan galactosylated	HILIC-UPLC	VDC QR	10:45:45	19.3-28.3%	18.3-21.4%	16.7-22.2%	**Not similar (8 batches OOR)/not similar (7 batches**
	Charged glycans (sialylated)	HILIC-UPLC	VDC QR	10:45:45	2.1-3.5%	0-0.6%	0-1.2%	**Not similar (10 batches OOR)/not Similar (10 batches OOR)**/comparable
	%G0F	HILIC-UPLC	QR	10:45:45	59.1-63.7%	65.8-71.2%	64.5-72.9%	**Not similar (10 batches OOR)/not Similar (10 batches OOR)**/comparable
	%G1F	HILIC-UPLC	QR	10:45:45	12.4-21.1%	12.8-16.4%	12.9-15.9%	**Not Similar (6 batches OOR)/Not Similar (7 batches OOR)**/comparable
	%G2F	HILIC-UPLC	QR	10:45:45	0.7-1.9%	0.9-1.5%	0.8-1.4%	**Not Similar (4 batches OOR)/ Not Similar (4 batches OOR)**/comparable

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Parameter	Quality Attribute	Test Method	Analytical Similarity Testing Approach	Number of Batches (SB5: US-licensed Humira: EU-approved Humira)	SB5 min –max Range	US-licensed Humira Quality Range or Visual Range	EU-approved Humira Quality Range or Visual Range	SB5 vs. US-licensed Humira /SB5 vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Charge	Acidic variants	CEX-UPLC	QR	10:38:46	22.6-25.6%,	11.9-18.7%	11.4-19.3%	**Not similar (10 batches OOR)/not Similar (10 batches OOR)**/comparable
		icIEF	QR	10:38:36	22.9-27.6%	10.8-20.5%	11.9-19.3%	**Not similar (10 batches OOR)/not Similar (10 batches OOR)**/comparable
	Basic variants	CEX-UPLC	QR	10:38:46	8.6-10.9%	17.5-30.2%	18.1-27.8%	**Not similar (10 batches OOR)/not Similar (10 batches OOR)**/comparable
		icIEF	QR	10:38:36	9.3-12.6%	18.5-30.1%	17.7-30.0%	**Not similar (10 batches OOR)/not Similar (10 batches OOR)**/comparable
	Main peak	CEX-UPLC	QR	10:38:46	65.0-66.9%	56.9-64.8%	56.5-66.9%	**Not similar (9 batches OOR)**/ similar/comparable
		icIEF	QR	10:38:36	61.1-64.6%	54.0-66.1%	53.3-67.8%	Similar/similar/comparable
Hydrophobicity		ANS Fluorescence spectroscopy	VDC	4:4:2	Similar profile	Similar profile to US-licensed Humira	Similar profile to US-licensed Humira	Similar/similar/comparable

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Parameter	Quality Attribute	Test Method	Analytical Similarity Testing Approach	Number of Batches (SB5: US-licensed Humira: EU-approved Humira)	SB5 min –max Range	US-licensed Humira Quality Range or Visual Range	EU-approved Humira Quality Range or Visual Display Range	SB5 vs. US-licensed Humira /SB5 vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Higher Order Structure	Secondary Structure	Far-UV CD	VDC	4:2:2	Similar secondary structure	Similar secondary structure to US-licensed Humira	Similar secondary structure to US-licensed Humira	Similar/similar/comparable
		FTIR		4:2:2				
	Tertiary Structure	Near-UV CD	VDC	4:2:2	Similar tertiary structure	Similar tertiary structure to US-licensed Humira	Similar tertiary structure to US-licensed Humira	Similar/similar/comparable
		H/D-exchange	VDC	1:1:1	3D structure	Similar 3D structure to US-licensed Humira	Similar 3D structure to US-licensed Humira	Similar/similar/comparable
		Antibody Conformation array ELISA	VDC	1:1:1	Conformational structure	Similar conformational structure to US-licensed Humira	Similar conformational structure to US-licensed Humira	Similar/similar/comparable
	Thermal Stability (°C)	DSC	VDC	4:2:2	Tm1: 63-64.9 Tm2: 71-71.5 Tm3: 79-81	Tm1: 63.1-64.9 Tm2: 71-71.5 Tm3: 79-81.1	Tm1: 63.1-64.7 Tm2: 71-71.4 Tm3: 79-81.2	Similar/similar/comparable
	Extinction Coefficient	Pico Tag	VDC	3 2:2	1.51-1.55	1.47-1.49	1.48-1.51	Similar/similar/comparable
		ACCQ Tag		2:1:0	1.37-1.39	1.38	ND	

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Parameter	Quality Attribute	Test Method	Analytical Similarity Testing Approach	Number of Batches (SB5: US-licensed Humira: EU-approved Humira)	SB5 min – max Range	US-licensed Humira Quality Range or Visual Range	EU- approved Humira Quality Range or Visual Range	SB5 vs. US-licensed Humira /SB5 vs. EU- approved Humira / US-licensed Humira vs EU-approved Humira
	Particulate Levels	Dynamic Light Scattering 3) Hydrodynamic diameter (nm)	VDC	4:2:2	1) 10.5, 12.6 nm 2) 0.034, 0.212	1) 10.6, 12.1 nm 1) 2) 0.036, 0.195	1) 10.6, 12.1 nm 2) 0.039, 0.190	Similar/similar/comparable
		Micro-flow imaging(Particles/mL)	VDC	4:2:1	≥10µm: 184-747 ≥25µm: 1-23	≥ 10µm: 338-828 ≥ 25µm: 4-16	≥ 10µm: 563 ≥ 25µm: 12	Similar/similar/comparable
	Concentration of active ingredient (mg/mL)	UV absorbance	QR	10:50:36	48.3-50.4	47.5-52.6	47.8-52.7	Similar/similar/comparable

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Parameter	Quality Attribute	Test Method	Analytical Similarity Testing Approach	Number of Batches (SB5: US- licensed Humira: EU-approved Humira)	SB5 min –max Range	US-licensed Humira Quality Range or Visual Range	EU- approved Humira Quality Range or Visual Range	SB5 vs. US-licensed Humira /SB5 vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Biological Activity—Proven MoA: Binding of Fab Domain to TNFα	Binding TNF	TNF-α neutralization by NF-kβ reporter gene assay	ET	10:35:40	93-106%	91-117%	90-117%	Equivalent/equivalent/ comparable
		Binding to TNFα Target Antigen by FRET	ET	10:40:41	90-108%	91-110%	92-112%	Equivalent/equivalent/ comparable
		Stimulation of mTNF-α induced Jurkat cell apoptosis	QR	10:36:39	98-112%	87-117%	87-114%	Similar/similar/comparable
		Binding to mTNF by flowcytometry	VDC	10:7:6	87-99%	66-116%	73-118%	Similar/similar/comparable
		Inhibition of sTNF-α ¡nduced HCT-116 cell apoptosis in in vitro IBD model	VDC	10:7:6	92-101%	82-113%	93-105%	Similar/similar/comparable
		Inhibition of sTNF-α induced IL-8 Cytokine Release by HCT-116 cells in in vitro IBD model	VDC	9:7:6	95-108%	88-120%	84-116%	Similar/similar/comparable
		Inhibition of sVCAM-1 adhesion molecule expression	VDC	9:7:6	95-120%	76-139%	81-139%	Similar/similar/comparable
		Binding to TNF-β by FRET	VDC	3:2:1	Not detected	Not detected	Not Detected	Similar/similar/comparable
Biological Activity- Functional	ADCC Activity	NK Cell ADCC Assay	QR	10:40:40	81%-114%	71-145%	80-141%	Similar/similar/comparable

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Parameter	Quality Attribute	Test Method	Analytical Similarity Testing Approach	Number of Batches (SB5: US-licensed Humira: EU-approved Humira)	SB5 min – max Range	US-licensed Humira Quality Range or Visual Range	EU-approved Humira Quality Range or Visual Range	SB5 vs. US-licensed Humira / SB5 vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Characterization of Fc Domain	CDC Effector Function	CDC Assay	QR	10:37:40	89-99%	86-112%	87-110%	Similar/similar/comparable
		C1q Binding ELISA	QR	10:40:41	70-111%	78-113%	75-116%	**Not Similar (2 batches OOR)/Similar (1 lot OOR)/ Not Comparable (3 batches OOR)**
	Regulatory Cell Induction (reverse signaling)	MLR Assay EdU incorporation by flowcytometry	VDC	9:7:6	17-52%	0-70%	9-41%	Similar/**Not Similar (3 batches OOR)/Not Comparable (2 batches OOR)**
		Regulatory Macrophages (CD206 expression) by flowcytometry	VDC	10:7:6	87-114%	69-120%	81-112%	Similar/Similar /comparable
	Fcγ Receptor Binding by Alpha Assay	FcγRIIa	QR	10:34:35	76-103%	61-156%	71-136%	Similar/similar/comparable
		FcγRIIb	QR	10:28:34	91-102%	76-151%	72-146%	Similar/similar/comparable
		FcγRIIIa High Affinity (158V/V)	QR	10:40:42	90-116%	82-126%	95-118%	Similar/similar/comparable
	Additional Fcγ Receptor Binding assays	FcγRIa by FRET	QR	10:37:36	89-110%	87-113%	87-113%	Similar/similar/comparable
		FcγRIIIa Low Affinity (158F/F) (M) by SPR	VC	6:4:3	1.65E-06 to 1.86E-06 M	1.26E-06 to 2.01E-06 M	1.31E-06 to 1.92E-06 M	Similar/similar/comparable
		Binding to FcγRIIIb (M) by SPR	QR	10:5:6	9.74E-06 to 1.24E-05M	9.47E-06 to 1.17E-05M	7.93E-06 to 1.14E-05M	**Not Similar (4 batches OOR) /Not Similar (4 batches OOR)**/ Comparable

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Biological Activity—half-life	Neonatal Fc receptor binding	Binding to FcRn by AlphaScreen	QR	10:39:40	85-111%	81-115%	80-120%	Similar/similar/Comparable

3.2.R.2 Analytical Similarity Assessment Results

3.2.R.2.1 Comparative Assessment for Assays evaluated by Equivalence Test

The equivalence test (ET) is the most stringent statistical approach of the three approaches typically used to assess analytical similarity, the other two being quality range comparisons (QR) and visual display comparisons (VDC). Samsung chose which approach they used to evaluate a QA using a risk assessment of the potential clinical impact of the attribute on activity, PK, PD, safety, and immunogenicity. The primary MOA of adalimumab entails binding of the Fab domain to soluble TNF-α. Samsung assessed two activities relevant to the MOA of the product 1) TNF-α activity neutralization measured using an NF-κb Reporter Gene Assay (NRGA) and 2) TNF-α binding measured by FRET and analyzed the results using an equivalence test.

TNF-α Neutralization Assay by NF-κb Reporter Gene

When soluble TNF-α binds to TNFR1, a series of intracellular signaling pathways are activated that lead to the production of proinflammatory cytokines, and other effector molecules, that lead to apoptosis or cell death (see Sponsor's Figure 5 from amendment 22 below.) A crucial step in this inflammatory cascade is the induction of NF-κb nuclear factor. Samsung chose a cell-based assay using a HEK 293NF-κB-Luc cell line, which has an NF-κB binding sequence upstream of the luciferase reporter gene. The binding of TNF-α to cell surface TNFR1 of this cell line leads to a signal cascade that results in the activation of NF-κB, which in turn activates the expression of the luciferase reporter gene. This cell line does not express TNF-α, so the levels of autologous luciferase expression are negligible. The luciferase assists oxidation of luciferin which then emits light. By measuring the decrease in luciferase activity (luminescence) in the presence or absence of SB5 or US- or EU-Humira, the potency of the drug can be assessed.
The similarity assessment included the comparison of 10 independent batches of SB5 DS and DP to 35 US- and 40 EU- Humira drug product batches. The Sponsor's Table 9 and Figure 2 below from section 3.2.R.4 summarize the data provided.

Assessor comment:
The use of DS batches in the assessment of TNF-α neutralization activity is acceptable because the biological activity of adalimumab is not impacted by the DP manufacturing process.

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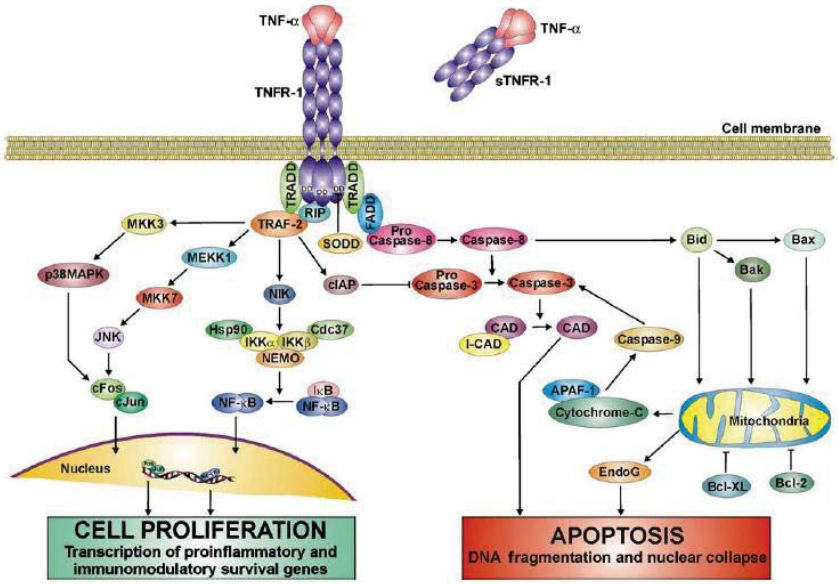

Figure 5: TNF-α Receptor 1 Signalling Pathway

Table 9: Descriptive Statistics for TNF-α Neutralization Assay Results

Product	Number of Batches	%Relative Potency			SD	%CV
		Min	Max	Mean		
SB5	10	93	106	100	5	5
US Humira®	35	91	117	101	6	6
EU Humira®	40	90	117	101	6	6

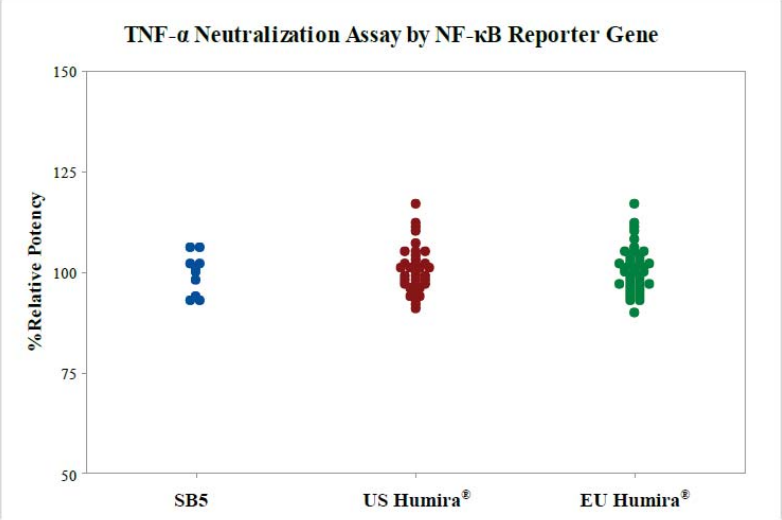

Figure 2: Result of TNF-α Neutralization Activity of SB5 and Humira®

An equivalence test was performed for these assay results and is summarized in Table 3 adapted by the assessor with concurrence from CMC Stats.

Table 3: Equivalence Testing Results for TNF-α Neutralization Assay by NF-κb Reporter Gene (%relative inhibition)

Mean difference	-EAC	Lower bound CI	Upper bound CI	+EAC	assessment

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SB5 (n=10) vs. US-licensed Humira (n=35)	-8.86	-5.14	2.26	8.86	equivalent
SB5 (n=10) vs. EU-approved Humira (n=40)	-8.56	-4.94	2.34	8.56	equivalent
US-licensed (n=35) vs. EU-approved Humira (n=40)	-8.86	-2.39	2.10	8.86	equivalent

Table adapted by assessor based on submitted information. EAC Equivalence acceptance criteria; CI 90% Confidence interval of the mean.

Assessor Comment:
Because the 95% confidence intervals fall within the corresponding equivalence acceptance limits, the Sponsor concluded that SB5 is similar to US- and EU- Humira in the neutralization of TNF-α induced NF-kb induction. The results also demonstrate that EU- Humira is similar to US- Humira with respect to neutralization of TNF-α induced NF-κb activation. We defer to CMC Stats Assessment by Dr. Yu-Ting Weng as to the validity of the analysis. He concurred with the data presented.

Reference Standards:
Five reference standards were used for generating TNF-α NRGA data for analytical similarity. (b) (4)

Assessor comment:
Potency assignment of the five different RSs used to determine relative potency by TNF-α NRGA was made sequentially rather than against a primary RS. However, the data provided show that the five reference standards have equivalent relative potency in the TNF-α NRGA. Therefore, potency data generated using the different RSs can be pooled for similarity assessment.

Analytical similarity assay qualification: The TNF-α NRGA was developed and qualified at Samsung Bioepis for determination of relative potency of SB5 and US- and EU-Humira for analytical similarity. According to the method qualification summary submitted in amendment 27 (Dec 31, 2018) data were analyzed using parallel line analysis software and the relative biological potency was calculated. The results are presented as %relative potency (RP) compared to the reference standard, and its linear range is 50-150% (RP). The original qualified assay had an accuracy of 88-98% at target and a precision of 3-6% geometric relative standard deviation.

Assessor comment:
The Sponsor developed a TNF-α NRGA as the primary method to measure adalimumab mediated inhibition of TNF-α activity. The equivalence test results show shows equivalent TNF-neutralization activity for SB5, US-Humira and EU-Humira in the three-way pairwise comparison.

The NF-κB reporter gene assay evaluates only early steps in the TNFα signaling cascade. To support the use of the NF-κB reporter gene assay rather than a cell-based inhibition of apoptosis bioassay in the analytical similarity assessment, the Sponsor provided data in amendment 22 (11/6/2018), comparing the NF-κB reporter gene assay and the cell-based inhibition of apoptosis bioassay. Apoptosis is a downstream event to NF-kβ

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induction, and it involves activation of caspases such as Casp 3 and Casp 7. Apoptosis occurs primarily when inflammation reaches excessive levels and the NF-kB pathway is overwhelmed leading to caspase activation and DNA fragmentation and nuclear collapse (Sponsor's Fig 5 above). Summary comparison is provided in the Sponsor's Table 17 below from amendment 22.

Table 17: Comparison of Assay Conditions for Reporter Gene-based Assay and Apoptosis-based Assay

Material/Condition	Reporter Gene System using 293-NF-κB (NF-κB Reporter Gene-based Assay)	Cytotoxicity using L929 (Apoptosis-based Assay)
Core Analysis	Neutralization	Neutralization
TNF-α	WHO international standard (200 IU/mL)	WHO international standard (20 IU/mL)
Adalimumab Concentration Range	0.98-125 ng/mL (8 points, 1:2 dilution)	0.98-125 ng/mL (8 points, 1:2 dilution)
Cell Line	293-NF-κB	L929
Assay Readout	Reporter gene (luminescence)	Viable cell (fluorescence)
Readout Reagent	Steady-Glo®	Cell Titer-Blue®
Software for Potency Calculation	Parallel Line Analysis	Parallel Line Analysis
Assay Period	27 hours	30 hours

Samsung also provide performance comparison data for precision, accuracy, and linearity (see Sponsor's Table 18 amendment 22), and sensitivity and stability indicating potential (Sponsor's Table 19 in amendment 22).

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Table 18: Comparison of Assay Performance

Assay Parameter		Concentration Level	Reporter Gene System using 293-NF-κB (NF-κB Reporter Gene-based Assay)	Cytotoxicity using L929 (Apoptosis-based Assay)
Precision	Repeatability	100%	%RSD: 5% (n=6)	%RSD: 2% (n=3)
	Intermediate Precision	75%	%RSD: 6% (n=6)	%RSD: 4% (n=6)
		100%	%RSD: 4% (n=6)	%RSD: 1% (n=6)
		125%	%RSD: 3% (n=6)	%RSD: 12% (n=6)
Accuracy		75%	91% (n=6)	96% (n=6)
		100%	98% (n=9)	100% (n=6)
		125%	91% (n=6)	103% (n=6)
Linearity[a]		Set 1	0.96	1.00
		Set 2	0.96	1.00
		Set 3	0.97	N/A[b]

[a] Linearity was evaluated for concentration range of 50-150% for reporter gene-based assay.
[b] Not applicable

Table 19: Results of Supplementary Study for Sensitivity Comparison

Assay Setting				Reporter Gene System using 293-NF-κB (NF-κB Reporter Gene-based Assay)		Cytotoxicity using L929 (Apoptosis-based Assay)	
Reference Standard	Sample	Expected Relative Potency	Replicate	Mean	SD	Mean	SD
PRS	Stressed SB5	Lower than 100%	3	69	2	91	2
PRS	PRS	100%	4	97	4	103	3
Stressed SB5	PRS	Higher than 100%	3	141	3	112	7

The assays show comparable performance with regards to precision, accuracy, and linearity over a concentration range of 75-125% of PRS. However, when sensitivity was tested using a heat stressed (40°C for 9months) SB5 (b) (4) *lot SB5PV06, the TNF-α NRGA appears to more sensitively detect loss of potency in the stressed sample, highlighted in yellow, than the L929-apoptosis assay (69% activity versus 91% activity, respectively). When the stressed sample is used as the RS, PRS correspondingly shows higher activity by the NRGA assay than by the apoptosis assay (141% versus 112%, respectively). These data support Samsung's claim that the TNF NRGA may be better suited for testing the TNFα neutralization activity of adalimumab than the inhibition of apoptosis assay. In an IR response provided 12/31/2018, Samsung provided study details along with comparative data from two additional heat-stressed* (b) (4) *batches (SB5PV05 and SB5PV 07), including primary response curves for TNF NRGA (Sponsor's Figure 1 in amendment 22) and Apoptosis inhibition assay (Sponsor's Figure 4 in amendment 22), performed side-by-side.*

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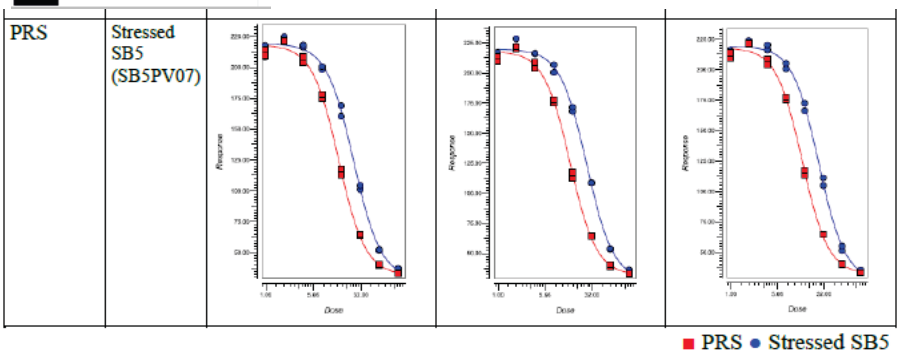

Figure 1: **Dose Response Curves for Stressed SB5 Relative to PRS (NF-κB Reporter Gene-Based Assay)**

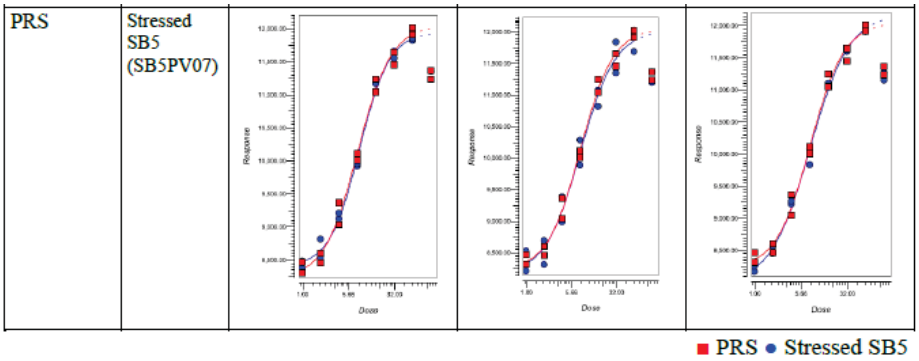

Figure 4: **Dose Response Curves for Stressed SB5 Relative to PRS (Cytotoxicity-Based Assay)**

Table 3: **Results of Sensitivity Comparison (SB5)**

Assay Setting				Reporter Gene System using 293-NF-κB (NF-κB Reporter Gene-based Assay)		Cytotoxicity using L929 (Apoptosis-based Assay)	
Expected Relative Potency	**Reference Standard**	**Sample**	**Replicate**	**Mean**	**SD**	**Mean**	**SD**
Lower than 100%	PRS	Stressed SB5 (SB5PV05)	1	60	N/A	92	N/A
	PRS	Stressed SB5 (SB5PV06)	3[a]	69	2	91	2
	PRS	Stressed SB5 (SB5PV07)	1	57	N/A	96	N/A
	Mean			**62**		**93**	
	SD			**6**		**3**	
100%	PRS	PRS	7 (4[a], 3)	95	8	105	5
	Mean			**95**		**105**	
	SD			**4**		**3**	
Higher than 100%	Stressed SB5 (SB5PV05)	PRS	1	138	N/A	118	N/A
	Stressed SB5 (SB5PV06)	PRS	3[a]	141	3	112	7
	Stressed SB5 (SB5PV07)	PRS	1	149	N/A	123	N/A
	Mean			**143**		**118**	
	SD			**6**		**6**	

[a] Data were submitted in the Response to Q5 of Amendment 0022.

The data submitted, including the activity curves provided for both assays, further support that TNF NRGA is more sensitive to potency changes than the Apoptosis inhibition assay. Therefore, the TNF NRGA potency

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assay is an acceptable alternative to the cell-based inhibition of apoptosis assay for the analytical similarity exercise.

TNF-α Binding Assay by FRET

The relative binding of SB5, US-, and EU-Humira to TNF-α was evaluated using a fluorescent resonance transfer (FRET) based competitive inhibition assay. The assay uses Europium-labelled adalimumab and Cy5 fluorophore-labelled TNF-α, which result in a detectable fluorescent signal from Cy5 if the Europium-adalimumab is bound to Cy5-TNF-α and excites Cy5 via the emission wavelength of Europium. This binding is competed by unlabeled SB5 or US- or EU-Humira, with the measured fluorescence being inversely proportional to the binding of unlabeled drug. The analytical similarity assessment included 10 independent SB5 DS or DP batches, 40 US- and 41 EU-Humira DP batches. The Sponsor's Table 12 and Figure 3 from 3.2.R.4 below summarize the data provided.

Table 12: Descriptive Statistics for TNF-α Binding Assay Results

Product	Number of Batches	%Relative Binding Activity			SD	%CV
		Min	Max	Mean		
SB5	10	90	108	100	6	6
US Humira®	40	91	110	98	4	4
EU Humira®	41	92	112	99	5	5

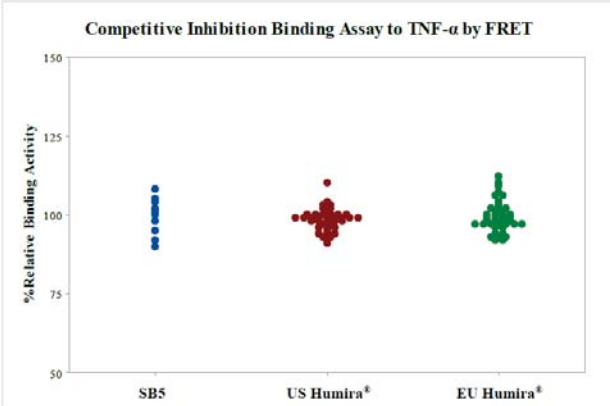

Figure 3: Result of TNF-α Binding Activity of SB5 and Humira®

The data were analyzed by equivalence testing. The results are summarized in Table 4 adapted by assessor with concurrence from CMC Stats.

Table 4: Equivalence Testing Results for TNF-α Binding by FRET (% Relative Potency)

Mean difference	-EAC	Lower bound CI	Upper bound CI	+EAC	assessment
SB5 (n=10) vs. US-licensed Humira (n=40)	-5.40	-2.46	4.76	5.40	equivalent
SB5 (n=10) vs. EU-approved Humira (n=41)	-7.31	-3.80	3.88	7.31	equivalent
US-licensed (n=40) vs. EU-approved Humira (n=41)	-5.40	-0.47	2.70	5.40	equivalent

Table adapted by assessor based on submitted information. EAC Equivalence acceptance criteria; CI 90% Confidence interval of the mean.

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Assessor Comment:
Because the 95% confidence intervals fall within the corresponding equivalence acceptance limits, the Sponsor concluded that SB5 is similar to US- and EU- Humira for TNF-α binding by FRET. The results also demonstrate that EU- Humira is similar to US- Humira with respect to binding to TNF-α. We defer to CMC Stats Assessment by Dr. Yu-Ting Weng as to the validity of the analysis. He concurred with the data presented and subsequent conclusions.

Reference Standards: The same five reference standards [redacted] (b) (4) used to collect TNF-α N RGA data were used for generating TNF-α FRET binding data for analytical similarity (see earlier discussion). The Sponsor performed reference standard bridging for TNF-α binding FRET assay *(see 3.2.S.5 Reference Standards or Materials).*

Assessor comment:
Potency assignment of the five different RSs used to determine relative potency by TNF-α FRET was performed sequentially rather than against a primary RS. However, based on the data provided, no shift was observed in the relative potency results for the TNF-α FRET assay for adalimumab product batches tested against different reference standards (see section 3.2.S.5, Reference Standards or Materials). Therefore, potency data generated with the different RS can be pooled for similarity assessment.

TNF-α FRET Assay Qualification: The TNF-α FRET method was developed and qualified at Samsung Bioepis for determination of relative potency of SB5 and US- and EU-Humira. According to the method qualification summary submitted in amendment 27 (Dec 31, 2018) data were analyzed using parallel line analysis software and the relative biological potency was calculated. The results are presented as %Relative potency compared to the reference standard, and its linear range is 50-150% relative potency. The original qualified assay had an accuracy of 95-98% at target and a precision of 3-4% RSD.

Assessor comment:
The TNF-α binding FRET assay was developed as an orthogonal method to the TNF-α NRGA for measuring the TNF-α binding activity of adalimumab. The Sponsor's choice of this second method aligns with OBP expectation for assessing analytical similarity of biological activity for adalimumab biosimilars. Based on the analysis performed, the binding of SB5, US-, and EU-Humira to soluble TNF-α is statistically equivalent and all binding results for both EU-Humira and SB5 are within the US-Humira similarity acceptance criteria.

[redacted] (b) (4) *Overall, the data provided for the TNF-α binding and neutralizing assay indicate no shift in relative potency with use of any RS. All US- and EU-Humira batches were tested with both potency methods (35-41 batches) to establish statistically valid equivalence CI and quality ranges. The selection of US- Humira batches included in the assessment was random over the 6-year development period based on expiry date, available quantities, and order of acquisition. From a product quality perspective, it is acceptable to use a subset of batches of US-Humira in the similarity assessment, given both the number of batches and time-period covered. The batches selected are representative of all batches acquired, had expiry dates between March*

2013 and April 2018, and do not appear to have been chosen in a manner that would bias the results. All the reference standards were equivalent in potency measured using the TNF-α NRGA (see earlier discussion) and the TNF-α binding FRET assay and the data show no shift in relative potency when different RS were used in the assessment of biological activity and binding.

3.2.R.2.1 Similarity Assessment Using Quality Range Approach

A quality range (QR) approach is the second most stringent statistical approach to test for analytical similarity. Samsung calculated the QR as the estimated mean of US- Humira ± 3 standard deviations (SD). Samsung considered analytical similarity or comparability established for the quality attribute if at least 90% of the batches of SB5 or EU- Humira, respectively, are within the quality range of US- Humira. Quality attributes evaluated using QR approach are those of moderate to high risk for impact on quality for which quantitative data can be obtained. Samsung evaluated both physicochemical tests as well as biological activity tests using this approach. Depending on the test, up to 45 batches of US- Humira, and 46 batches of EU-Humira were used to establish the quality ranges. The tables in the section below provide a summary of similarity assessment results for quality attributes analyzed using this approach. In grey are comparisons in which minor differences were observed.

Assessor Note: Discussion in subsequent sections will focus on quality attributes where similarity was NOT met.

A) Analytical Similarity Assessment using Quality Range Approach for Physicochemical Properties

Samsung examined the following physicochemical properties by the QR approach: sum of afucosylated and high mannose glycans in N- glycan profile, levels of high molecular weight (%HMW) variants in SE-HPLC, purity by reducing and non-reducing CE-SDS (R/NR), level of charge variants in both CEX-HPLC and icIEF, and protein concentration (quantity) by UV A260nm. Samsung reported several differences in quality attributes between SB5, US- and EU- and Humira: the sum of levels of afucosylated and high mannosylated glycans (%Afucose + %HM) in N-glycan profile, %Main (%HC + %LC) and %Non-glycosylated heavy chain (%NGHC) in CE-SDS (reducing) and the level of charge variants in both CEX-HPLC and icIEF for the physicochemical characteristics. These are discussed in more detail in the sections below. Table 5 below was prepared by the assessor to summarize differences in physicochemical properties observed for the quality range analytical similarity methods.

Assessor note: For the purposes of the table below, 0 batches OOR are classified as "Similar"; 1 batch OOR classified as "Similar?"; 2-10 batches OOR, classified as "Not-Similar".

Table 5: Similarity Summary for Physicochemical Quality Range Methods

Parameter	Quality Attribute	Test Method	Analytical Similarity Testing Approach	SB5 vs. US-licensed Humira	SB5 vs. EU-approved Humira	EU-approved Humira vs US-licensed Humira
Glycosylation	N-glycan non-fucosylated +	HILIC-UPLC	QR	**Not- similar 3/10 batches OOR**	Similar	Comparable

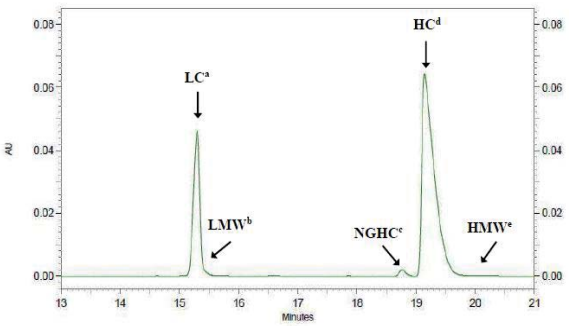
	N-glycan high mannose					
	N-glycan non-fucosylated		QR	**Not Similar 9/10 batches OOR**	**Not Similar 8/10 batches OOR**	Comparable
	N-glycan high mannose		QR	**Not-similar 2/10 batches OOR**	**Not-Similar 2/10 batches OOR**	Comparable
	N-glycan galactosylated		VDC QR	**Not Similar 8/10 batches OOR**	**Not Similar 7/10 batches OOR**	Comparable
	Charged glycans (sialylated)		VDC QR	**Not-Similar 10/10 batches OOR**	**Not-Similar 10/10 batches OOR**	Comparable
Purity	%HMW	SE-HPLC	QR	Similar	Similar	Comparable
	%Main		QR	Similar	Similar	Comparable
	%LMW		QR	Similar	Similar	Comparable
	%Main (LC+HC)	CE-SDS (R)	QR	**Not-Similar 6/10 batches OOR**	**Not-Similar 6/10 batches OOR**	Comparable
	%NGHC		QR	**Not-Similar 10/10 batches OOR**	**Not-Similar 9/10 batches OOR**	Comparable
	%IgG	CE-SDS (NR)	QR	Similar? 1/10 batches OOR	Similar? 1/10 batches OOR	Comparable
	%2H1L		QR	Similar? 1/10 batches OOR	Similar? 1/10 batches OOR	Comparable
Charge	Acidic variants	CEX-UPLC	QR	**Not-Similar 10/10 batches OOR**	**Not-Similar 10/10 batches OOR**	Comparable
		iCIEF	QR	**Not-Similar 10/10 batches OOR**	**Not-Similar 10/10 batches OOR**	Comparable
	Basic variants	CEX-UPLC	QR	**Not-Similar 10/10 batches OOR**	**Not-Similar 10/10 batches OOR**	Comparable
		iCIEF	QR	**Not-Similar 10/10 batches OOR**	**Not-Similar 10/10 batches OOR**	Comparable
	Main peak	CEX-UPLC	QR	**Not-Similar 10/10 batches OOR**	Similar	Comparable

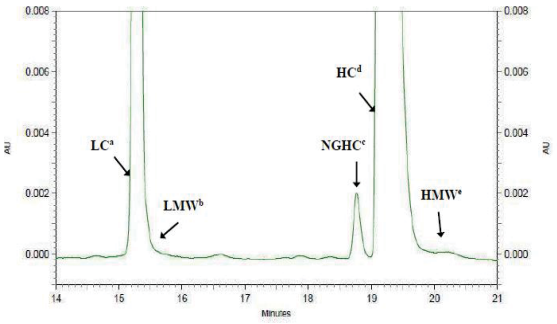
		iCIEF	QR	Similar	Similar	Comparable

Size Exclusion- High Performance Liquid Chromatography (SE-HPLC)
Samsung uses SE-HPLC to monitor purity of adalimumab, particularly high molecular weight (HMW) impurities. The data provided in the analytical similarity assessment were initially limited to %HMW, with SB5 ranges (0.2-0.4%, n=10) falling within US (0.3-0.5%, n=45) and EU-Humira ranges (0.3-0.5%, n=46), with both reference products being comparable. In amendment 27 (Dec 31, 2018) data on %Main peak content was provided for SB5, 99.4- 99.8%, US- Humira, 99.2-99.6%, and EU-Humira, 99.5-99.6%. The %LMW content was 0.0-0.2% for SB5, 0.1-0.5% for US- Humira, and 0.2-0.5% for EU- Humira.

Assessor comment:
Samsung updated the analytical similarity assessment with the requested SE-HPLC %Main and %LMW data for SB5 and US - and EU- Humira. The data showed that, as for HMW, the %Main peak and % LMW for SB5 are within the quality ranges for US- and EU- Humira.
During the analytical similarity inspection of Samsung Bioepis in Korea (Nov 11-14, 2018), OBP inspectors noticed that different peak integration criteria had been used to analyze SE-HPLC %HMW similarity data. In amendment 27 (Dec 31, 2018), Samsung explained that there had been five different integration criteria from 2012 to 2018 and provided information for the integration values used for each of the five criteria. Criteria I (2012-Nov2013) and II (Nov2013-Dec 2015) were used to establish the analytical ranges for US- and EU-Humira. Criteria III (Dec 2015-March 2017) and IV (March 2017-Aug 2018) were used in analytical similarity studies 1-3. The current integration is criterion V that has been used since Aug 2018 to present. Samsung stated that all batches that were tested side-by-side used same integration criteria and the results obtained using the different integration criteria were similar. Samsung provided data for %HMW from 9 SB5 batches and 4 US-Humira and 3 EU-Humira batches analyzed initially using criteria III (AS Study 1) and IV (AS Study 3) and subsequently reanalyzed using current criterion (V) showing that the 3 criteria gave analogous results. This is acceptable.

Capillary Electrophoresis-Sodium Dodecyl Sulfate (CE-SDS): Reducing (R)
Samsung used Reducing CE-SDS as a purity assay to examine the molecular heterogeneity of SB5, US-Humira, and EU- Humira, by analyzing %Main and % non-glycosylated heavy chain (%NGHC) contents. Samples were treated with the reducing agent, 2-mercaptoethanol to separate the HCs and LCs. To calculate % Main the Sponsor added %HC+%LC together. Representative low-resolution and high-resolution electropherograms of SB5 are provided in the figures below.





Results showed that the content of %Main was 95.0-98.0% for SB5. The data provided of batches tested side-by-side are summarized in the graphs below: 6/10 SB5 batches were out of the US- (%Main

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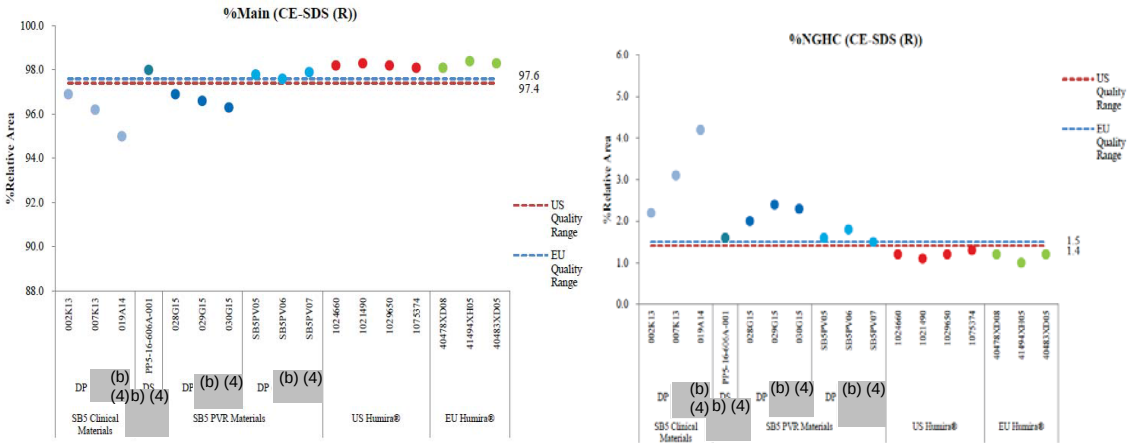
97.4%-98.6, n=45 batches) and EU-Humira quality ranges (%Main 97.6%-98.6, n=42), while all 42 batches of EU-Humira (97.9%-98.7%) were within the quality range for US-Humira. The difference of SB5 %Main was attributed to the higher %NGHC level (1.5-4.2%). All SB5 batches were outside the US-Humira quality range (%NGHC1.0-1.4%), and all SB5 batches except one were outside the EU-Humira quality range (%NGHC0.8-1.5%) for %NGHC.



The N-glycosylation in the Fc region of antibodies is known to be associated with Fc-related functional activities such as FcRN binding, TNF-α binding, antibody-dependent cellular cytotoxicity (ADCC), and to a lesser extent complement dependent cytotoxicity (CDC). To determine the potential impact on Fc effector functions of the levels of %NGHC observed in SB5 (1.5-4.2%), Samsung performed a structure-activity relationship (SAR) study using %NGHC-enriched samples from individual batches of DP of SB5 (PVR (b) (4) 030G15), US-Humira (1021490), and EU-Humira (40483XD05), functionally tested with FcRN binding assay, TNF-α binding assay, and ADCC assay (Sponsor's Table 18 in 3.2.R.4).

Table 18: SAR Study Results of %NGHC Enriched Samples

Starting Material	Enriched Level of %NGHC	FcRn Binding (%Rel. Binding Activity)	TNF-α Binding (%Rel. Binding Activity)	ADCC (%Rel. Activity)
SB5 PVR DP (030G15)	2.3	100	100	100
	5.8	N/T	N/T	86 [SD: 7]
	9.2	N/T	N/T	80 [SD: 5]
	15.9	N/T	N/T	66 [SD: 1]
	22.6	90 [SD: 8]	99 [SD: 1]	62 [SD: 3]
US Humira® (1021490)	1.1	100	100	100
	4.7	N/T	N/T	88 [SD: 1]
	8.1	N/T	N/T	80 [SD: 5]
	14.4	N/T	N/T	74 [SD: 5]
	21.0	98 [SD: 16]	97 [SD: 2]	65 [SD: 6]
EU Humira® (40483XD05)	1.1	100	100	100
	4.6	N/T	N/T	86 [SD: 3]
	7.8	N/T	N/T	79 [SD: 4]
	15.2	N/T	N/T	69 [SD: 9]
	20.9	99 [SD: 11]	99 [SD: 5]	56 [SD: 5]

N/T: Not tested

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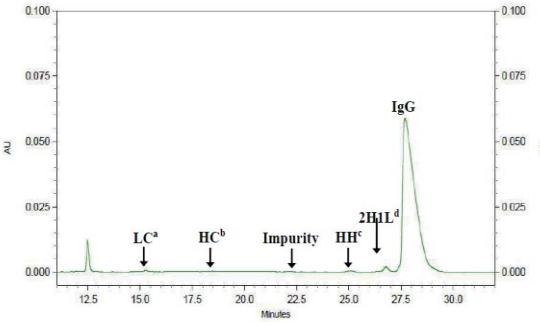
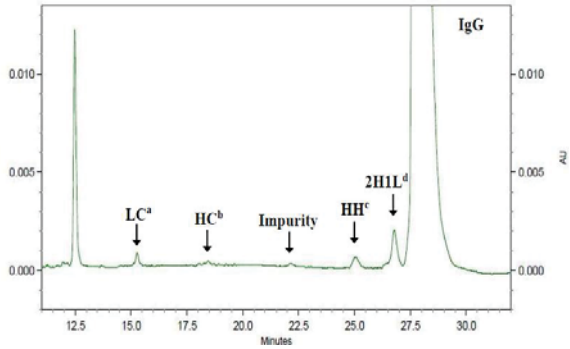
Assessor comment:

All the 10 SB5 batches fell outside the %NGHC quality ranges of both US- and EU-Humira and thus failed to meet the acceptance criteria of 90% or more results falling within the US and EU Humira quality range. SAR study data show that %NGHC increase of ~3.5% may result in ~10% decreased ADCC activity. However, no differences were observed when ADCC activity was compared between SB5 and US-Humira (see assessor's summary Table 2: SB5 Analytical Similarity Assessment Summary Data). In addition, differences in %NGNH did not impact binding to TNF-α or FcRn and differences in %Main and %NGHC did not impact biological activity measured by the NF-kb Reporter Gene and TNF-α Binding Assay measured by FRET. Furthermore, the %NGHC levels were below 2% in the DP batches manufactured at the proposed commercial sites. Therefore, the observed differences in %NGHC do not preclude a determination of highly similar.

Capillary Electrophoresis-Sodium Dodecyl Sulfate (CE-SDS): Non-reducing (NR)

Purity of SB5, US- and EU- Humira were also compared using CE-SDS (NR), allowing for the monitoring of intact IgG (%2H2L), and impurities such as free LC (%LC), free HC (%HC), ½ IgG (%HL), and incomplete IgG impurity (%2H1L). The experimental procedure was similar to that of CE-SDS(R), but without the use of 2-mercaptoethanol. Samsung provided data on %IgG and %2H1L contents of SB5 and US- and EU-Humira by CE-SDS (NR). The levels other LMW species (LC, HC, HH) were not provided because individual levels of each species fell below LOQ of assay. Representative low-resolution and high-resolution electropherograms are provided in the figures below.





The data for batches tested side-by-side is summarized in the graphs below: %IgG was 95.4-96.7% for SB5. Excluding one SB5 batch ([redacted] (b) (4) DP SB5PV06; 95.4%), which was slightly out of range, the content of %IgG for the remaining SB5 batches (96.1-96.7%) was within the US- (%IgG 96.0%-97.8%; n=45) and EU-Humira quality ranges (%IgG 95.5%-98; n=42) and all 42 batches of EU-Humira (Min: 95.5%, Max: 98.0%) were within the US-Humira quality range based on 45 tested batches. The content of 2H1L for SB5, 1.4-2.2%, was within the EU quality range (%2H1L≤ 2.2%). One PPQ batch ([redacted] (b) (4) DP 0SB5PV06) was outside the US-Humira quality range (≤ 2.1%). The 2H1L content of all 42 batches of EU-Humira (1.1%-2.2%) was within the quality range of US-Humira except for one lot which was 0.1% higher than the US-Humira quality range.

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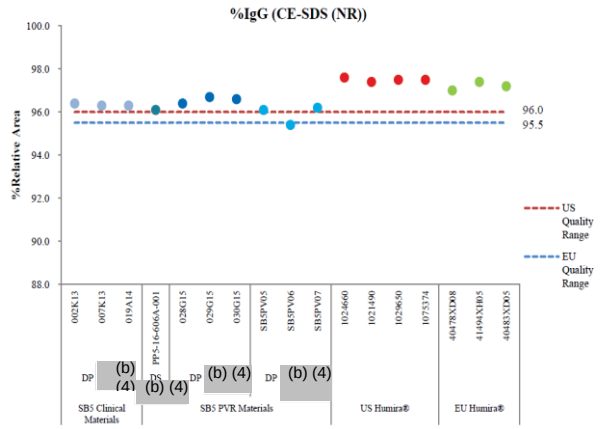

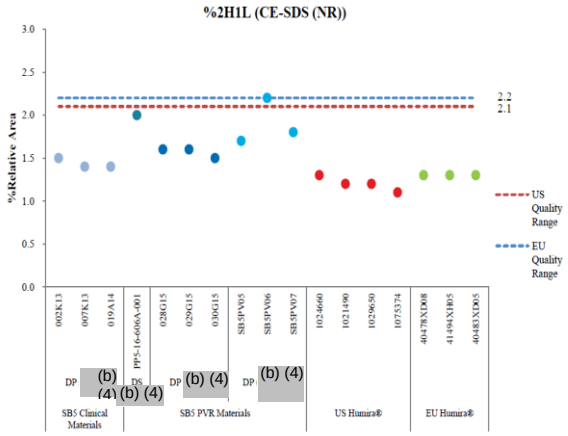

Assessor comment:

The %IgG and %2H1L of DP (b) (4) SB5PV06 batch were outside both US- and EU-Humira quality ranges, however, the difference was very small, %IgG: 0.1-0.6%, and %2H1L: 0.1% with US-Humira. The data support that 90% of the data are within the US- and EU-Humira QR. Therefore, I conclude that SB5, US- and EU-Humira are similar in terms of purity by CE-SDS (R).

N-Glycan Profile Analysis Using 2-AB Labeling and HILIC-UPLC

The levels of N-linked glycans are important for therapeutic antibodies because of their impact on effector function activity. Humira has moderate Fc domain effector function, antibody-dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC). Adalimumab is a highly glycosylated mAb whose sugar content impacts its activity. The level of afucosylated glycans can impact ADCC function and the level of terminal neutral galactosylated glycans can impact CDC function. High-mannose glycans can impact PK due to scavenging by CD206/mannose receptor and subsequent removal of the mAb from circulation.

Samsung analyzed N-glycan profile of 10 batches of SB5 and 45 batches each of US and EU-Humira by hydrophilic interaction ultra- performance liquid chromatography (HILIC-UPLC). The N-glycans are released by PNGase F, labeled with 2-aminobenzamide (2-AB), separated by HILIC-UPLC and identified via mass spectrometry or quantified via fluorescence spectroscopy (excitation 330 nm, emission 420 nm). Samsung categorized N-glycan species into four different groups according to structural compositions: Afucose (%Afucose), high mannose glycans (%HM), neutral galactosylated glycans (%Gal) and charged sialylated glycans (%Charged). The Sponsor analyzed %Afucose + %HM combined and %Gal and %Charged glycans individually using quality ranges. %Gal and %Charged glycans were analyzed initially using VDC statistical approach and thus the data are presented in the last section of the analytical similarity study.

1) Sum of Afucosylated and High Mannose Glycans

Results for batches tested side-by-side are summarized in the graph below: %Afucose + %HM was 8.4-11.9% for SB5, with 3/10 SB5 batches (2 clinical and 1 (b) (4) PPQ batch) showing slightly higher levels than the US quality range (6.2-11.4%), while the %Afucose + %HM content of all SB5 batches was within the EU quality ranges (5.8-12.0%). Per cent Afucose + %HM of all 45 batches of EU-Humira (6.9%-10.7%) was within quality range of the 45 US batches.

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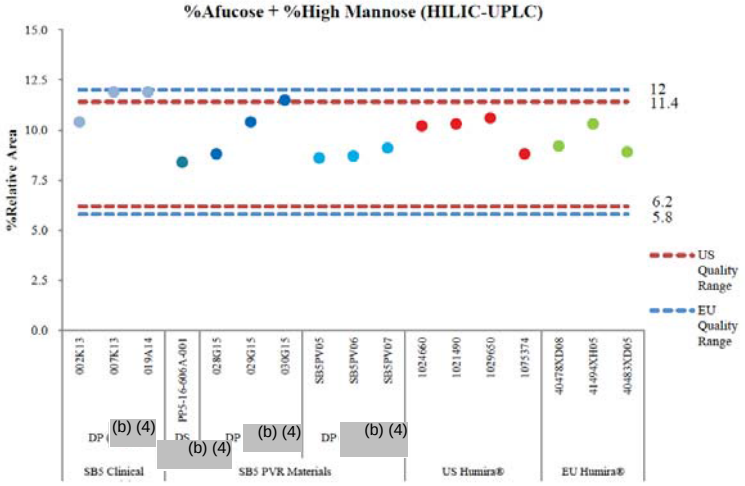

Assessor comment:

Samsung combined %Afucose+%HM levels to perform the analytical similarity assessment using quality ranges. Higher levels of afucosylated glycans and high mannose glycans increase ADCC activity. Each of these glycan types impact Fc mediated functions differently: afucosylated glycans impact FcγRIIIa binding and ADCC function, while high mannose glycans impact PK, primarily, although they can also have a minor impact on ADCC.

The combined %Afucose + %HM for SB5 ranged from 8.4 to 11.9% and 3/10 SB5 batches fell outside the US quality range of 6.2 to 11.4%. These results do not meet the acceptance criteria of 90% or more results falling within the quality range. The batches outside the US-Humira quality range include two clinical batches and one lot manufactured at (b) (4), the original proposed commercial DP manufacturing site. These batches have slightly higher %Afucose + %HM that US-Humira (0.1- 0.5%). As discussed below, under biological activities, FcγRIIIa binding and ADCC activity for the 10 SB5 batches, which correlate with afucosylated +high mannose glycans content, were similar between SB5 (81%-114%) and US- (71-145%; n=40) and EU- Humira (80-141%; n=40). Therefore, the slight difference observed in the content of %Afucose + %HM is unlikely to affect biological activity and do not preclude a determination that SB5 and US-Humira are highly similar.

2) Individual Levels of Afucosylated and High Mannose Glycans

Under amendment 22 (Nov 5, 2018) Samsung provided an assessment of similarity of individual levels of %Afucose and %HM glycans, as well as their respective correlations with FcγRIIIa binding and ADCC activity. Results for batches tested side-by-side are summarized in the graphs below.

For SB5, 9/10 batches had higher levels of %Afucose glycans (2.0-3.6%) than US-Humira (1.6-2.3%) and 8/10 batches had higher levels than EU-Humira (1.6-2.7%). Higher levels of %Afucose glycans were detected in 6/45 batches of EU-Humira when compared to US-Humira (0.1-0.2%).

For %HM, SB5 results ranged 5.2-9.9% and only 2/10 batches were outside US and EU quality ranges (4.4-9.3% and 4.1-9.4%, respectively). All 45 batches of EU-Humira were within the quality range for the 45 batches of US-Humira that were tested.

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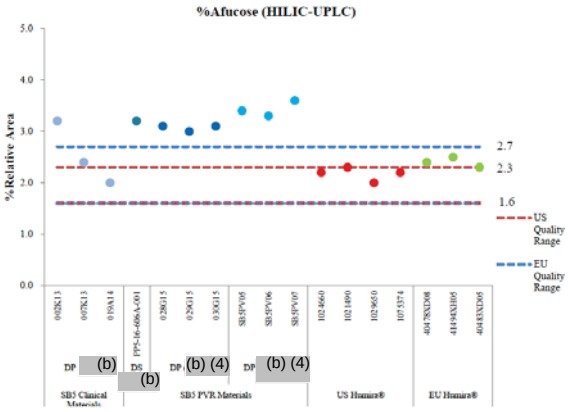

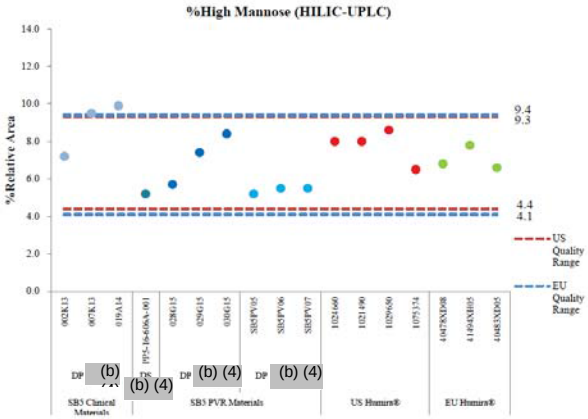

Assessor comment:

The %Afucose are consistently higher in SB5 than in US- or EU-Humira. Analysis of the %Afucose and %High Mannose individually indicated that the differences observed in the %(Afucose + High Mannose) combined assessment were mostly due to increased afucosylation in the SB5 batches. Except for one or two of the clinical batches, the %Afucose is consistently higher in SB5 batches than in US- or EU-Humira, respectively. The differences are <2%, sufficiently small not to impact FcγRIIIa binding and ADCC biological activity assays, as discussed later in the memo. High %Afucose variability was observed in the batches of SB5 used in the clinical studies which could be due to limited process control in early product development. US- and EU-Humira results show higher variability in the %High Mannose than in the %%Afucose, resulting in wider quality ranges for this attribute. Two of the 10 SB5 batches fell slightly outside the US- and EU- Humira quality ranges. High Mannose content is known to impact PK of antibodies because of uptake in the liver by the mannose receptor. However, the high %High Mannose content was only in early batches and %High Mannose content of later batches all fell within the US-Humira Q4. In addition, as discussed later in this memo, the differences in HM did not impact ADCC or CDC activity. Therefore, the differences in %Afucose + %High Mannose content do not preclude a determination that SB5 and US-Humira are highly similar.

The figures below summarize the data provided regarding the correlations between individual % Afucose and %High Mannose in historical SB5 batches with FcγRIIIa binding and ADCC activity. Correlations of individual glycans with FcγRIIIa binding and ADCC activity were substantially weaker than those obtained when %Afucose+%High Mannose were assessed together: % Afucose: FcγRIIIa binding r^2=0.41, ADCC activity r^2=0.43; % High Mannose: FcγRIIIa binding r^2=0.78, ADCC activity r^2=0.56; compared to %Afucose + %HM: FcγRIIIa binding r^2=0.90, ADCC activity r^2=0.80.

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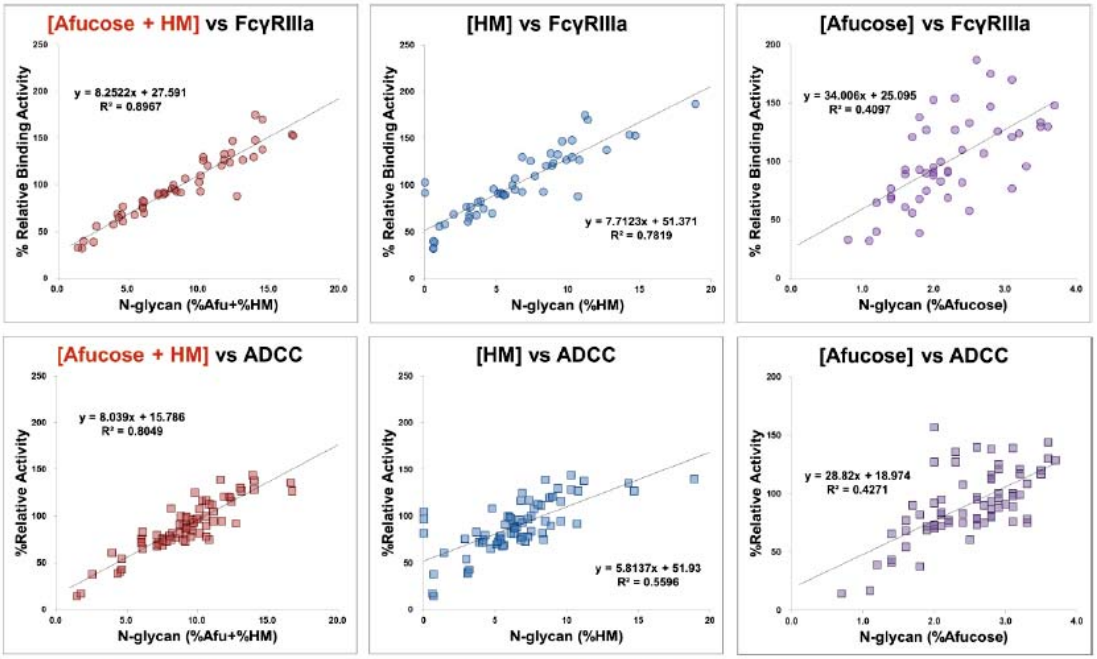


Figure 2. Correlation between N-glycan Species and Biological Activities of SB5

Assessor comments:

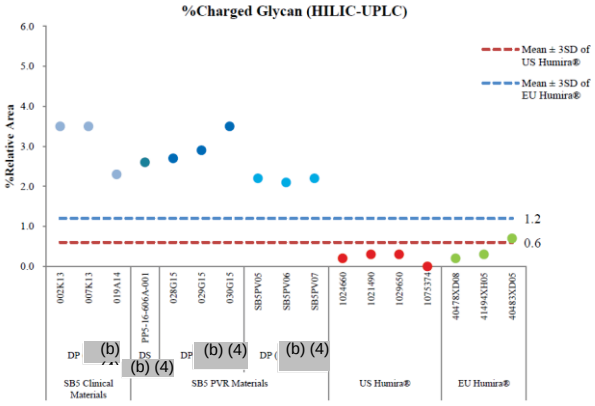
The correlation data provided in amendment 22 dated November 5, 2018 show strong correlation of %Afucose + %HM with FcγRIIIa binding and ADCC and support the Sponsor's classification of %Afucose + %HM as a critical quality attribute over individual levels of Afucose and HM glycans.

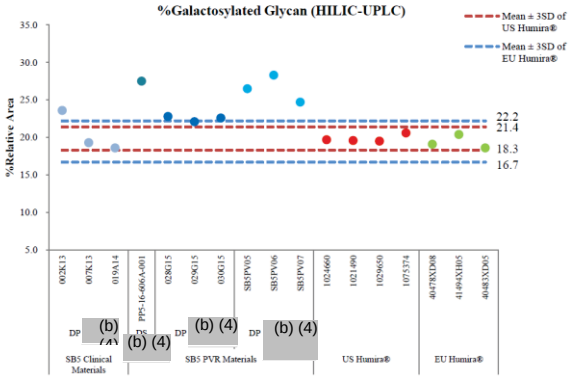
Individual Levels of Charged (Sialylated) Glycans and Galactosylated Glycans

Samsung originally assessed galactosylated (neutral) and charged glycans using visual display comparisons and then reevaluated these attributes using the quality range approach upon realizing these glycans levels also differed between SB5, US-, and EU-Humira. Results for batches tested side-by-side are summarized in the graphs below.

For %Charged glycans, all batches of SB5 were higher, 2.1-3.5%, than the %Charged glycans in US- and EU-Humira and therefore, outside the quality ranges (0.0- 0.6% and 0.0-1.2%, respectively).

For %Gal, 8/10 batches of SB5 had %Gal content (18.6-28.3%) outside US-Humira QR (18.3-21.4%) and 7/10 SB5 batches were outside QR for EU-Humira (16.7-22.2%). The % charged and gal glycans was comparable between US- and EU-Humira.





The Sponsor identified that the increase in % charged glycans in SB5 were due to higher terminal sialylated glycan levels based on CEX-HPLC peak fractionation and MS/MS structure-activity relationship studies. Higher sialic acid may increase serum half-life and impact Fc effector function. However, no differences were observed between SB5 and US and EU-Humira for ADCC, as discussed later in this memo. In addition, Samsung performed an SAR study with individual batches of DP of SB5 (PVR (b) (4) 030G15), US-Humira 1021490, and EU Humira (40483XD05), with or without sialidase treatment and tested for FcRN binding, TNF-α binding, and ADCC activity. The SAR data (table below) showed that removal of sialic acid, which is the principal charged glycan, from SB5, US- and EU- Humira did not result in measurable differences in biological activity by any of the assays tested.

Sample				TNF-α Binding (%Rel. Binding Activity)	FcRn Binding (%Rel. Binding Activity)	ADCC (%Rel. Activity)
SB5 PVR	DP (b) (4)	030G15	Intact	103 [SD: 5]	93 [SD: 12]	97 [SD: 3]
			w/ sialidase	97 [SD: 7]	108 [SD: 3]	96 [SD: 5]
Humira®	US	1021490	Intact	104 [SD: 5]	91 [SD: 4]	107 [SD: 4]
			w/ sialidase	98 [SD: 5]	103 [SD: 0]	93 [SD: 6]
	EU	40483XD05	Intact	102 [SD: 8]	107 [SD: 3]	108 [SD: 4]
			w/ sialidase	100 [SD: 7]	97 [SD: 4]	110 [SD: 3]

The Sponsor also identified that the differences in %Gal content were due to lower G0F species in SB5 (data not shown). Lower galactose content can lead to decreased binding to C1q and reduced CDC activity. As discussed later in the biological activity section, while data for C1q binding (76-124%) showed 1/10 batches of SB5 with lower C1q binding than the US (78-113%; n=40) or EU Humira (75-116%; n=41) quality ranges, the data provided for CDC activity showed that SB5 quality range (89-99%) was within the US (86-112%; n=37) and EU quality range (87-110%; n=40) respectively.

Assessor comment:
There are differences in % charged glycans between SB5 and US- and EU-Humira with SB5 showing consistently higher levels of sialic acid. These differences do not translate in differences in Fc related function as measured by several functional assays. A trend towards higher levels of %gal in SB5 was also observed, which does not translate in differences in CDC activity or C1q binding. Therefore, the differences in % charged glycans do not preclude a determination that SB5 and US-Humira are highly similar.

Individual Levels of G0F, G1F, and G2 Glycans

In 3.2.S.3.1 Elucidation of Structure and Other Characteristics, Samsung provided data on G0F, G1F, and G2 glycans for three SB5 DS batches produced at RTP and three DP batches produced at (b) (4) from the same DS batches. In amendment 27 (Dec 31, 2019) the Sponsor provided data on G0F, G1F, and G2 glycan content, which is summarized in the table below prepared by reviewer.

Table 6: G0F, G1F and G2 N-Glycan ranges in SB5, US and EU-Humira

N-Glycan	Number of Batches (SB5: US- licensed Humira: EU-approved Humira)	SB5 min –max Range	US-licensed Humira Quality Range	EU-approved Humira Quality Range	SB5 vs. US-licensed Humira /SB5 vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
%G0F	10:45:45	59.1-63.7%	65.8-71.2%	64.5-72.9%	**Not-similar (10 batches OOR)/not similar (10 batches OOR)**/comparable

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%G1F	10:45:45	12.4-21.1%	12.8-16.4%	12.9-15.9%	**Not-Similar (6 batches OOR)/Not-Similar (7 batches OOR)**/comparable
%G2F	10:45:45	0.7-1.9%	0.9-1.5%	0.8-1.4%	**Not -Similar (4 batches OOR)/Not-Similar (4 batches OOR)**/comparable

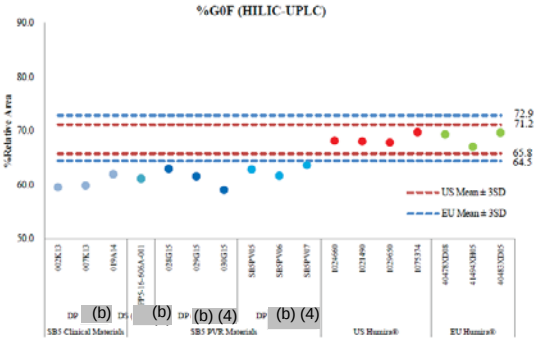


Figure 1: Similarity of %G0F between SB5 and Humira® by HILIC-UPLC

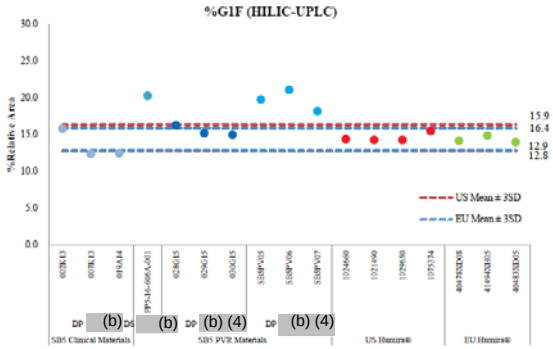


Figure 2: Similarity of %G1F between SB5 and Humira® by HILIC-UPLC

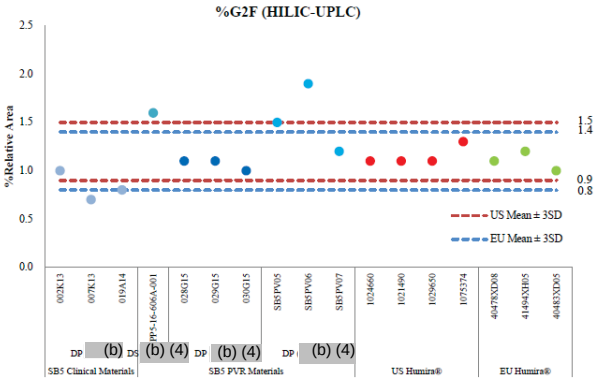


Figure 3: Similarity of %G2F between SB5 and Humira® by HILIC-UPLC

Assessor comment

Consistent with glycan data provided in the original application, differences are seen between SB5, US- and EU-Humira for G0F, with all 10 batches of SB5 (59.1-63.7%) showing lower levels outside the quality ranges of US-Humira: 65.8-71.2% and EU-Humira: 64.5-72.9%. For G1F, 6 batches of SB5 fall outside the US-Humira quality ranges, 4 above and 2 below, and 7 batches fall outside EU-Humira quality ranges,5 above and 2 below. For G2F, 4 batches of SB5 are outside the US-Humira quality ranges, 2 above and 2 below, and 4 batches fall outside EU-Humira quality ranges, 3 above and 1 below. The data indicate that the differences in % galactose observed between SB5, US-, and EU-Humira were mostly due to the lower content of G0F in SB5. Low levels of galactosylation are not expected to influence ADCC but are known to impact CDC activity. However, no differences in CDC or C1q binding were observed, as discussed later in this memo.

Conclusion regarding analytical similarity of N-Glycan profiles:

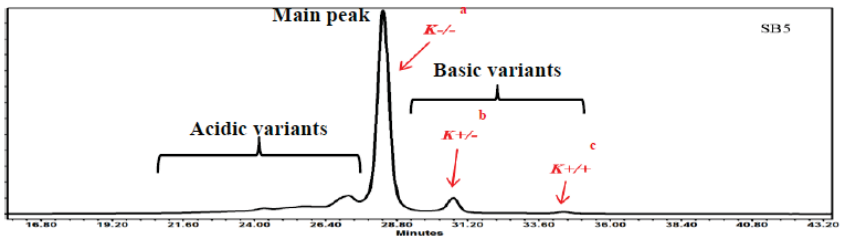
The analytical similarity results for % Afucose, %HM, %charged glycans, and %gal indicate differences in the glycan profiles of SB5, US-, and EU-Humira. However, these differences do not seem to impact Fc receptor functions as measured by the functional assays included in the analytical similarity exercise. Considering the totality of the data and the fact that Fc effector function is not the main mechanism of action of SB5 and that SB5 is similar to US and EU-Humira in all the Fc function assays, the differences noted in the glycan profile by HILIC between SB5 and US-and EU-Humira do not preclude a determination that SB5 and US- Humira are highly similar.

Charge Variant Assessment

Adalimumab charge variants may result from deamidation, oxidation, C-terminal Lys variations, formation of N-terminal pyroglutamate, aggregation, isomerization, sialylated glycans, antibody fragmentation, glycation at Lys residues, and succinimide formation. Samsung utilized two main assays to examine charge variants in SB5, US-, and EU-Humira: 1) Cation Exchange-High Performance Liquid Chromatography (CEX-HPLC), and 2) Imaged Capillary Isoelectric Focusing (icIEF). Data from both assays were analyzed using quality ranges to determine analytical similarity.

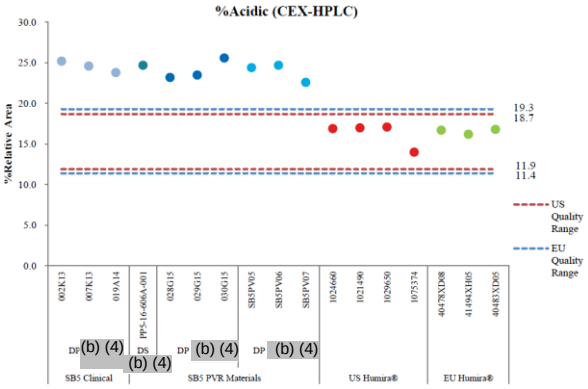
Cation Exchange-High Performance Liquid Chromatography (CEX-HPLC)

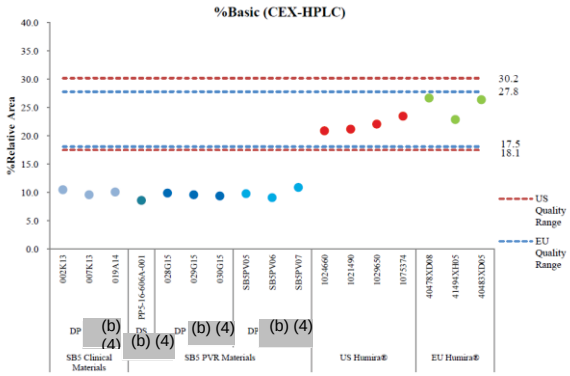
Samsung developed and qualified CEX- HPLC as the initial method to determine the relative contents of acidic variants (%Acidic), main peak (%Main), and basic variants (%Basic). The method used a MAbPac SCX-10 column (Thermo Scientific) and UV detection, and the relative peak area of charge variants is calculated to evaluate charge heterogeneity. An example chromatogram is shown below.



[a] *K-/-: Main peak without C-terminal lysine variant*
[b] *K+/-: Basic peak with one C-terminal lysine variant*
[c] *K+/+: Basic peak with two C-terminal lysine variants*

Summary data of batches tested side-by-side are provided in the graphs below: for SB5, %Acidic, %Main, %Basic were 22.6-25.6%, 65.0-66.9%, and 8.6-10.9%, respectively. For %Acidic, all 10 SB5 batches showed higher level than US- (11.9-18.7%; n=38) and EU-Humira (11.4-19.3%; n=46) and fell outside the quality ranges. For %Main, 9/10 SB5 batches showed slightly higher levels than the US-Humira quality range (56.9- 64.8%), but all 10 SB5 batches met the EU-Humira quality range (56.5-66.9%). For %Basic, all 10 SB5 batches showed lower levels than the US- (17.5-30.2%) and EU-Humira (18.1-27.8%), and all SB5 batches fell outside the quality ranges. The %Acidic, %Main, and %Basic of all 46 batches of EU-Humira (13.2%-18.7% %Acidic; 58.0%-64.8% %Main; 19.3%-25.8% %Basic) were within the corresponding US-Humira quality ranges (Appendix 1 tables 115 and 117).





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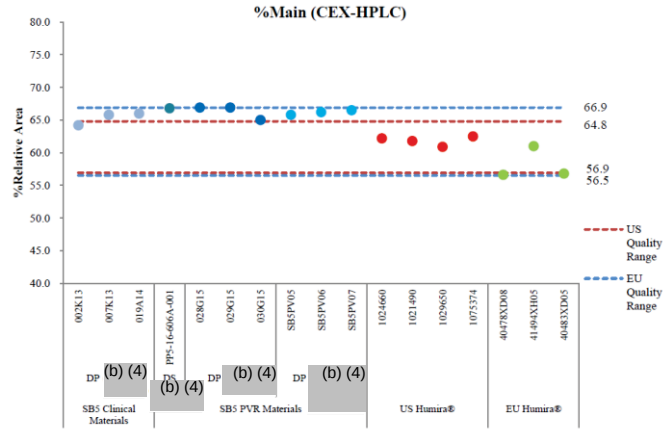

To assess the potential impact of the differences observed in charge variants on biological activity, Samsung performed SAR studies to elucidate the nature of the charge variants in CEX acidic, main, and basic regions. This study involved extended characterization of charge variants using one lot of SB5 (b) (4) PVR DP #030G15; US-Humira #102490, and EU-Humira #40483XD05. Three acidic (A1, A2, A3), two basic (B1 and B2), and main peak CEX fractions were collected from each sample and subjected to N- glycan profiling (%Afuco+%HM; %Charged/ Sialylated) and peptide mapping analysis by Trypsin digestion and UPLC-ESI-MS/MS for post translation modifications (PTMs; see example chromatograms below from Sponsor's Figure 26, in 3.2R.4).

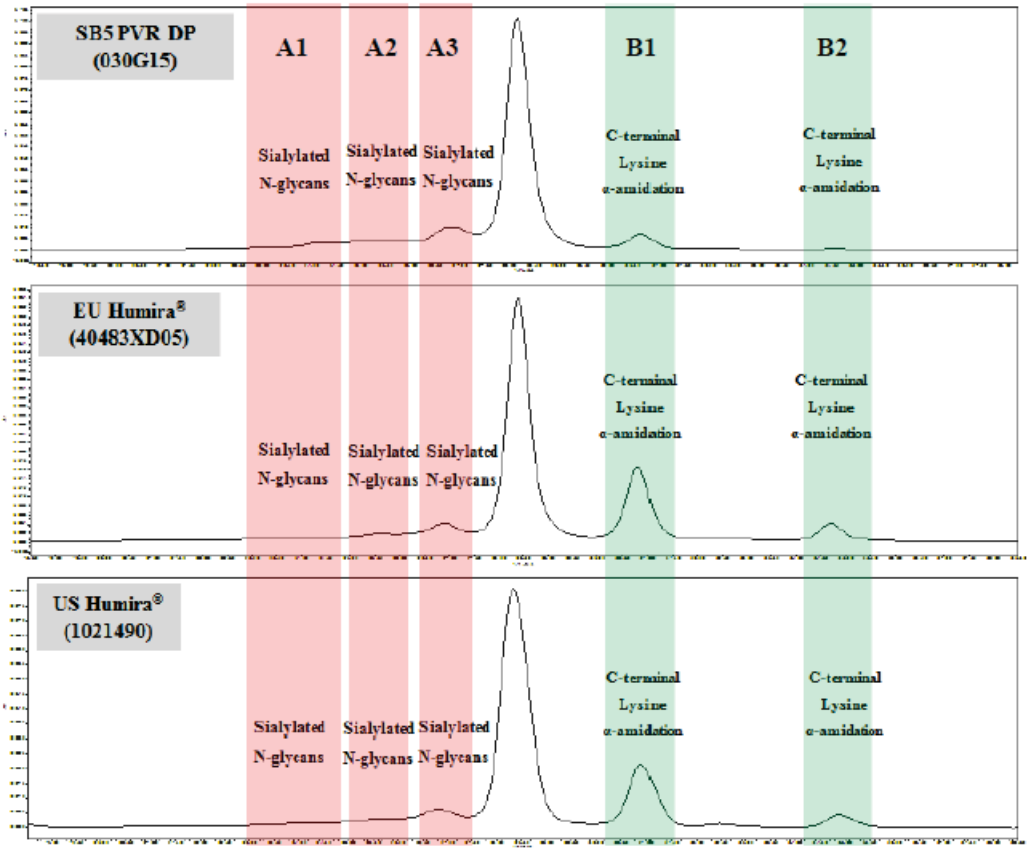

Figure 26: Identified PTMs at Each Variants of SB5 and Humira® without Carboxypeptidase B Treatment

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PTMS characterized included N- terminal pyroglutamate; oxidation at Met 34, Met 83, and Met 256; deamidation at Asn 77 or Asn 84; glycosylation at Asn 301 (%NGHC), C-terminal Lys and α-amidation. Data provided showed that acid peaks A1-A3 were enriched in sialylated N-glycans (see Table 23 of 3.2R.4); basic peaks B1 and B2, had high levels of C terminal Lys and α-amidation of the heavy chain C terminal proline residues (see Table 24 of 3.2R.4). The higher levels of basic peaks B1 and B2 observed in US- and EU-Humira decreased to levels similar to SB5 when C terminal Lys were removed using Carboxypeptidase B treatment (Fig 27 of 3.2R.4). Levels of other PTMS were spread across various acidic and basic peaks in the three batches tested, as were %Afuco+%High Mannose glycans without predominance in any peak.

Assessor comment:
Scientific literature indicates that C-terminal lysine is enzymatically cleaved in serum, and consequently the differences in the levels of C terminal lysine are not considered a CQA. In addition, literature also indicates that proline amidation of the C-terminus of monoclonal antibody does not exert effect on the Fc region mediated effector function, which is confirmed by the SAR study data below, and is also not considered a CQA.

Subsequently as part of the SAR study, the various charged variant peaks were tested for functional activity using the TNF-α binding FRET assay and the ADCC assay. The SAR data summarized in the table below indicate that both acidic and basic fractions had similar activities to the main peak in both activity assays. The Sponsor concluded that the slight differences observed in the contents of charge variants determined by CEX were not expected to have a significant impact on bioactivity and therefore should not preclude a conclusion that SB5 is similar to US and EU-Humira.

Sample	Fraction No.	TNF-α Binding (%Rel. Binding Activity)		ADCC (%Rel. Activity)	
		Mean	SD	Mean	SD
SB5 (030G15) DP (b) (4)	F1 (A1)	77	4	76	3
	F2 (A2)	94	4	71	6
	F3 (A3)	96	4	113	4
	F4 (Main)	103	6	114	5
	F5 (B1)	95	6	83	5
	F6 (B2)	89	4	105	4
US Humira® (1021490)	F1 (A1)	83	2	91	6
	F2 (A2)	93	2	74	2
	F3 (A3)	92	4	92	2
	F4 (Main)	93	4	111	11
	F5 (B1)	98	5	122	3
	F6 (B2)	93	6	132	10
EU Humira® (40483XD05)	F1 (A1)	95	5	93	4
	F2 (A2)	96	2	71	5
	F3 (A3)	94	1	109	6
	F4 (Main)	99	4	98	6
	F5 (B1)	98	6	114	11
	F6 (B2)	99	2	119	9

Assessor comment:
There are differences %acidic and %basic peaks between SB5 and both US- and EU-Humira. All SB5 batches show decreased basic peaks and increased acidic peaks when compared with US- and EU-Humira The Sponsor provided characterization and biological activity data demonstrating that these differences are unlikely to impact biological activity given that basic and acid variants retain similar %relative activity compared to main peak in the TNFa binding assay and the ADCC assay. In addition, the differences in acidic and basic peak area are largely driven by C-terminal lysine and a-amidation of C-terminal proline content, neither of which is a critical quality attribute. Therefore, the differences see in CEX-HPLC profiles between

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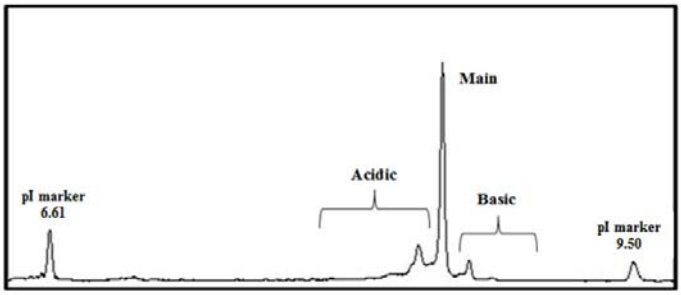
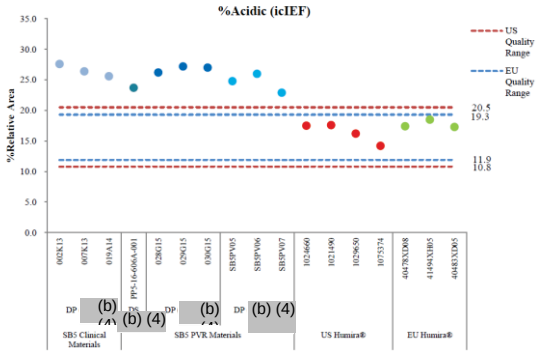
SB5 and US-Humira do not preclude a determination of highly similar.

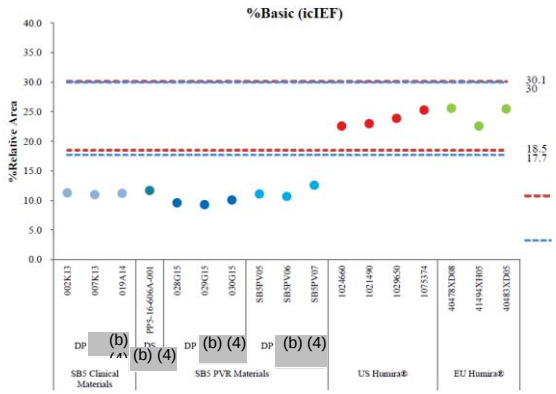
Imaged Capillary Isoelectric Focusing (icIEF)

Imaged capillary isoelectric focusing (icIEF) is an analytical method that separates species primarily on the basis of a molecule's isoelectric point (pI) intrinsic net charge. Variants are separated in an ampholytic pH gradient through an applied electric field. Samsung performed icIEF as an orthogonal method to CEX-HPLC to determine the %Acidic, %Main, and %Basic contents of SB5, US-, and EU-Humira. In addition, an isoelectric point (pI) was measured. An example icIEF electropherogram is provided below.



Summary data of batches tested side-by-side are shown in the graphs below. The contents of %Acidic, %Main, %Basic were 22.9-27.6%, 61.1-64.6%, and 9.3-12.6%, respectively, for SB5. For %Acidic, all 10 SB5 batches showed slightly higher level than both US- (10.8-20.5%; n= 38) and EU-Humira (11.9-19.3%, n=36) and fell outside the respective quality ranges. For %Basic, all SB5 batches showed slightly lower levels than US-, and EU-Humira and fell outside the quality ranges (18.5-30.1% and 17.7-30.0%, respectively). For %Main (provided in 3.2R Biosimilarity), all SB5 batches fell within both the US (54.0-66.1%) and EU (53.6-67.8%), quality ranges, respectively. The %Acidic (12.5%-17.4%), %Main (57.2%-64.7%), and %Basic (19.5% -26.9%) of all 36 batches of EU-Humira (Appendix 1, Table 118) were within the corresponding US-Humira quality ranges of the 38 batches tested. For pI, data showed SB5, US-, and EU-Humira were similar, ranging from 8.4 to 8.6 (data provided in 3.2R.4 Biosimilarity, section 2.36).





Assessor comment:

icIEF data orthogonally confirm that there are differences in the levels acidic and basic charged variants between SB5 and US- and EU-Humira. The two methods agree within 5% in the levels of %Acidic, %Basic and %Main Peak (summary table below). icIEF was validated as a release and stability assay while CEX-HPLC was not. Samsung provided characterization data on the identification of acidic and basic species present in each peak of the CEX-HPLC chromatogram. However, Samsung did not characterize the charge

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species that are present in each peak of the icIEF chromatogram
In amendment 27 (Dec 31, 2018), Samsung explained that icIEF provides better resolution and quantitative assessment compared to the CEX, but identification of the resolved variants is challenging because it is difficult to fractionate the peaks of icIEF electropherograms and biological assays cannot be performed even if the peaks are obtained because the fractions are denatured when collected and analyzed. Therefore, Samsung provided SAR study data for SB5 and US- Humira treated with sialidase, to remove sialic acid, and carboxypeptidase B, to remove C-terminal lysine, and ran in CEX and icIEF. The charge profiles of untreated samples are similar with both methods (Fig 1 of amendment 22). Following carboxypeptidase B treatment, there is a significant loss in basic peaks (see below Sponsor's Figure 3, amendment 22) detected by both methods compared to the SB5 and US-Humira untreated controls (see below, Sponsor's Figure 1 amendment 22,) These results indicate that the C-terminal lysine is the dominant factor in the basic peaks for both methods. For sialidase treatment, there is a comparable loss detected in the acidic peaks by both methods (not shown), indicating that sialic acid residues are the dominant factor in acidic peak formation.

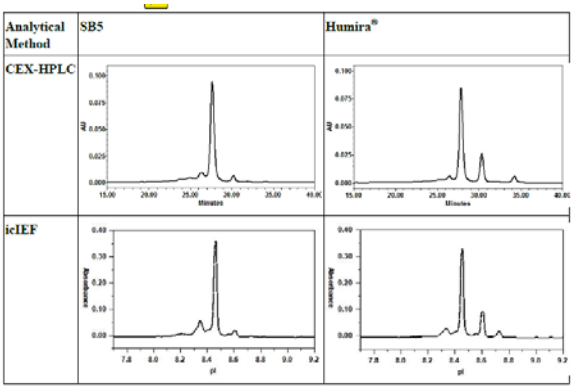

Figure 1: Charge Profile for SB5 and Humira® by CEX-HPLC and icIEF

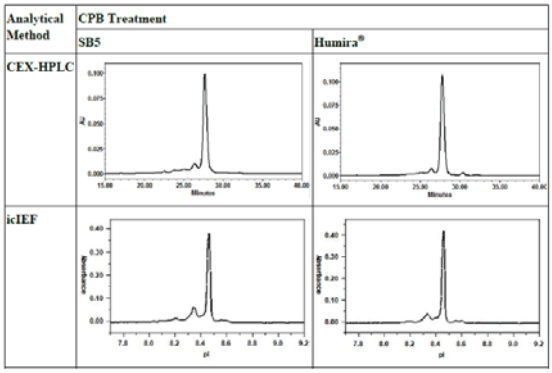

Figure 3: Charge Profile for SB5 and Humira® by CEX-HPLC and icIEF after CPB Treatment

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In addition, Samsung took the acidic, main, and basic fractions separated by CEX and analyzed them by icIEF. The data show that acidic, main, and basic CEX fractions are also separated into acidic, main, and basic fractions by icIEF, although they may run as different peaks (see below Sponsor's Fig. 4 from amendment 27).

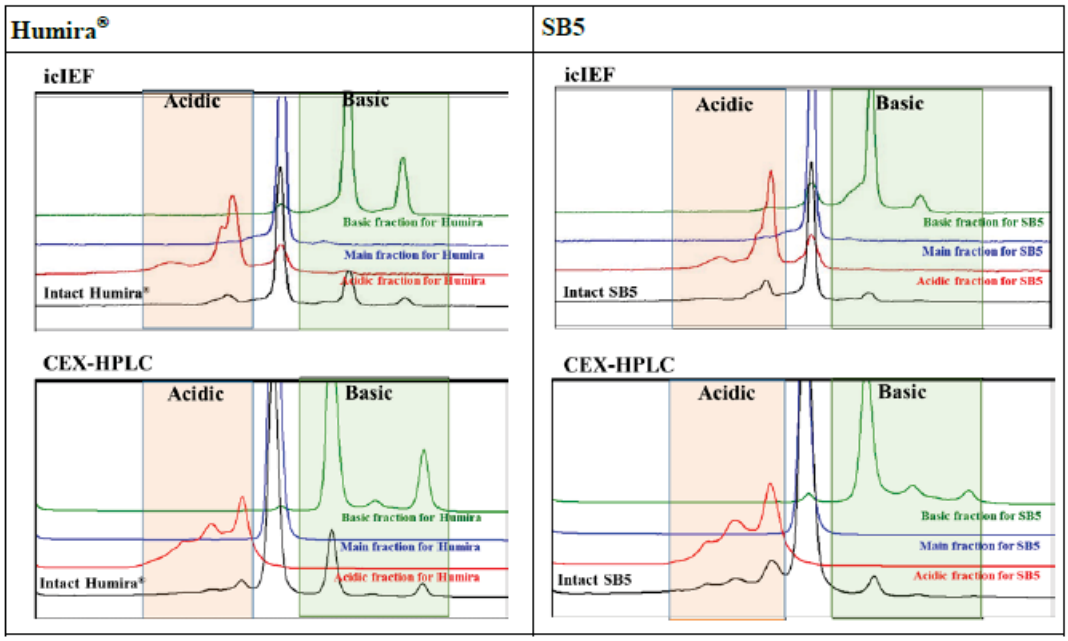

Figure 4: icIEF and CEX Profiles of CEX Fractions for SB5 and Humira®

(Top: icIEF Profiles, Bottom: CEX-HPLC Profiles)

The Agency concurs that the above data support the assertion by Samsung that the content of the basic and acidic peaks in CEX and icIEF is broadly the same.

Table 7: Analytical Similarity Summary Data for Charge Variants by CEX-UPLC and icIEF

Table prepared by assessor; Not Similar;10/10 batches OOR of US-licensed or EU-approved Humira.

Quality Attribute	Test Method	SB5 min –max Range	US-licensed Humira Quality Range or Visual Range	EU-approved Humira Quality Range or Visual Range	SB5 vs. US-licensed Humira /SB5 vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Acidic variants	CEX-UPLC	22.6-25.6%,	11.9-18.7%	11.4-19.3%	**Not similar/not similar**/comparable
	icIEF	22.9-27.6%	10.8-20.5%	11.9-19.3%	**Not similar/not similar**/comparable
Basic variants	CEX-UPLC	8.6-10.9%	17.5-30.2%	18.1-27.8%	**Not similar/not similar**/comparable
	icIEF	9.3-12.6%	18.5-30.1%	17.7-30.0%	**Not similar/not similar**/comparable
Main peak	CEX-UPLC	65.0-66.9%	56.9-64.8%	56.5-66.9%	**Not similar/** similar/comparable
	icIEF	61.1-64.6%	54.0-66.1%	53.3-67.8%	Similar/similar/comparable

Protein Concentration

Protein concentration is a critical quality attribute which is directly associated with dosing and strength. The protein concentration of SB5 and US-, and EU-Humira was determined by UV method using UV/VIS

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spectrophotometer at 280nm. The Sponsor used the reported Humira extinction coefficient 1.39 mL/mg.cm to calculate the SB5 concentration. Results showed that the protein concentration was 48.3-50.4 mg/mL for 10 batches of SB5. The concentration of SB5 was within both the US (47.5-52.6; n=36 batches) and EU-Humira quality ranges (47.8- 52.7mg/mL, n=36). 35/36 batches of EU Humira were within US quality ranges, with 1 lot being 0.1mg/ml higher.
In addition to using the published extinction coefficient of Humira, Samsung also experimentally determined extinction coefficients using AccQ Tag method: SB5 (n=2) were 1.37 and 139 mL/mg.cm, while for US-Humira(n=1) it was 1.38 mL/mg.cm.

Assessor comment:
SB5, US- Humira and EU-Humira have similar protein concentrations, and experimental extinction coefficients.

B) Analytical Similarity Assessment using Quality Range Approach for Biological Activities

Humira has moderate Fc domain effector function including ADCC and CDC. As mentioned before in this memo, the glycosylation pattern in the Fc region of SB5 and US and EU-Humira may influence Fc effector functions: increase in terminal galactosylation may increase CDC activity by increasing C1q binding. Decreases in fucose levels are expected to increase ADCC activity by increasing the affinity of IgG1 to FcγRIIIa receptors on immune cells. Samsung examined Fc effector function using the following in vitro biological activity assays and results were evaluated by the quality range approach: Fc binding to human IgG receptors FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, and FcRn, and complement activation by C1q binding as well as multi-attribute activity assays including mTNF-α induced apoptosis, ADCC assay, and CDC assay. For most of the biological activity assays the data support similarity between SB5 and US- and EU-Humira. except for the results obtained in FcγRIIIb binding and C1q binding Assays. Comparability between US- and EU-Humira was met in all assays except C1q binding and FcRn binding. Below is a summary table of the similarity assessment data for biological activities assays that were tested using quality range. Only those quality attributes that failed similarity assessment will be discussed in this section.

Assessor comment: *Biological assay quality range data for all tested US- and EU- Humira batches was provided in 3.2.R.4 Biosimilarity Appendix 1 tables 116 and 118, respectively.*

Table 8: Analytical Similarity Summary for Biological Activities tested by Quality Range Approach

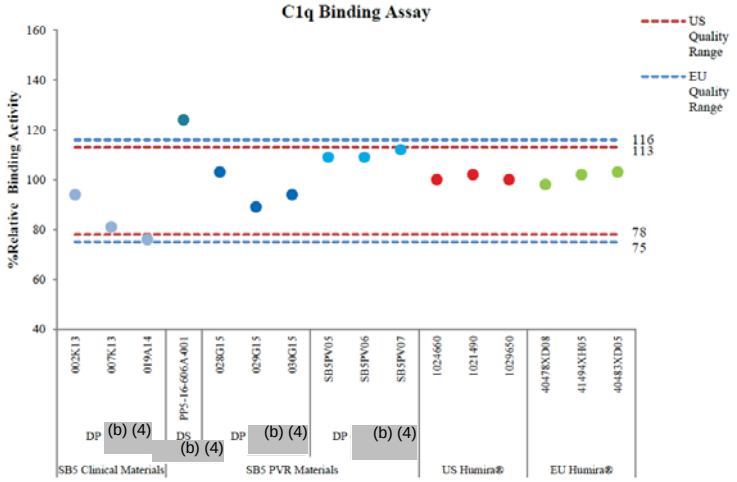
Quality Attribute	Test Method	Number of Batches (SB5: US- licensed Humira: EU-approved Humira)	SB5 min –max Range	US-licensed Humira Quality Range or Visual Range	EU- approved Humira Quality Range or Visual Range	SB5 vs. US-licensed Humira / SB5 vs. EU- approved Humira / US- licensed Humira vs EU-approved Humira
Stimulation of mTNF-α induced apoptosis	Caspase Assay	10:36:39	98-112%	87-117%	87-114%	Similar/similar/comparable
CDC Effector	CDC Assay	10:37:40	89-99%	86-112%	87-110%	Similar/similar/comparable

Function	C1q Binding ELISA	10:40:41	70-111%	78-113%	75-116%	**Not similar (2 batches OOR)**/similar / Comparable
ADCC Activity	NK Cell ADCC Assay	10:40:40	81%-114%	71-145%	80-141%	Similar/similar/comparable
Fcγ Receptor Binding by Alpha Assay	FcγRIIa	10:34:35	76-103%	61-162%	71-136%	Similar/similar/comparable
	FcγRIIb	10:28:34	91-102%	76-151%	72-146%	Similar/similar/comparable
	FcγRIIIa High Affinity (158V/V)	10:40:42	90-116%	82-126%	95-118%	Similar/similar/comparable
Additional Fcγ Receptor Binding assays	FcγRIa by FRET	10:37:36	89-110%	87-113%	87-113%	Similar/similar/comparable
	Binding to FcγRIIIb (M) by SPR	10:5:6	9.74E-06 to 1.24E-05M	9.47E-06 to 1.17E-05M	7.93E-06 to 1.14E-05M	**Not similar (4 batches OOR) /Not Similar (4 batches OOR)/ non-comparable (3 EU batches OOR)**
Neonatal Fc receptor binding	Binding to FcRn by AlphaScreen	10:39:40	85-111%	81-115%	80-120%	Similar/similar/ comparable

Table prepared by assessor.

C1q Binding ELISA

C1q is a glycoprotein component of the C1 enzyme complex that activates serum complement system. The binding of C1q to the Fc CH2 region of antigen-antibody immune complexes on target cell surfaces is the required first step in the complement cascade leading to complement dependent cytotoxicity (CDC). Binding of human C1q to SB5 was assessed by an ELISA binding assay. The ELISA method was developed and qualified for determination of relative binding to C1q of SB5 to US- or EU-Humira. Results for batches tested side-by-side are summarized in the Sponsor's Figure 35 in 3.2.R.4 below.



The relative C1q binding activity was 76-124% for SB5. One SB5 batch (SB5 clinical DP, 019A14,) showed slightly lower binding activity and fell outside the US-Humira quality range. Another SB5 batch (SB5 PVR DS, PP5-16-606A-001) fell outside the US- (78-113%) and EU-Humira (75-116%) quality ranges. SB5

C1q binding met the criteria that >90% of the SB5 batches fall within the US and EU-Humira quality ranges. In addition, CDC activities of these two batches (DP 104%, DS 92%) were within both US (71-145%; n=40) and EU Humira (80-141%; n=41) quality ranges. All 41 batches of EU-Humira (80%-106%) were within the US-Humira quality range.

Assessor comment:

Some evidence in the literature suggest that higher levels of N- linked galactosylation increases C1q binding and CDC, although C1q binding appears to be necessary but not sufficient for CDC activity. As shown in the Table 9 below prepared by assessor, no consistent association is observed between binding to C1q, % Gal, and CDC activity for SB5, US-, and EU-Humira. The data provided support the similarity of SB5, US-, and EU- Humira with regards to C1q binding activity.

Table 9: Summary of %Gal-glycans, C1q Binding Activity, and CDC Similarity Data

Sample			**Galactosylation %**	**C1q %Relative Binding Activity**	**CDC % Relative Activity**
SB5 Clinical	DP (b) (4)	002K13	23.6	94	89
		007K13	19.3	81	98
		019A14	18.6	76	96
SB5 PVR	DS (b) (4)	PP5-16-606A-001	27.5	124	97
	DP (b) (4)	028G15	22.8	103	98
		029G15	22.1	89	99
		030G15	22.6	94	90
	DP (b) (4)	SB5PV05	26.5	109	97
		SB5PV06	28.3	109	99
		SB5PV07	24.7	112	95
Humira	US	1024660	19.7	100	104
		1021490	19.6	102	99
		1029650	19.5	100	96
	EU	40478XD08	20.6	98	110
		41494XH05	19.1	102	101
		40483XD05	20.4	103	101
US Quality Range (45:40:37)			18.3-21.4	78-113	86-112
EU Quality Range (45:41 :40)			16.7-22.2	75-116	87-110

Table prepared by assessor

FcγRIIIb Binding Assay

FcγRIIIb (CD16b) is a GPI anchored human IgG Fc receptor primarily expressed in neutrophils which serves a low affinity receptor of IgG containing immune complexes. FcγRIIIb and FcγRIIIa are the two CD16 Fc receptor isoforms. FcγRIIIa is mostly expressed in NK cells and macrophages. The Sponsor determined the

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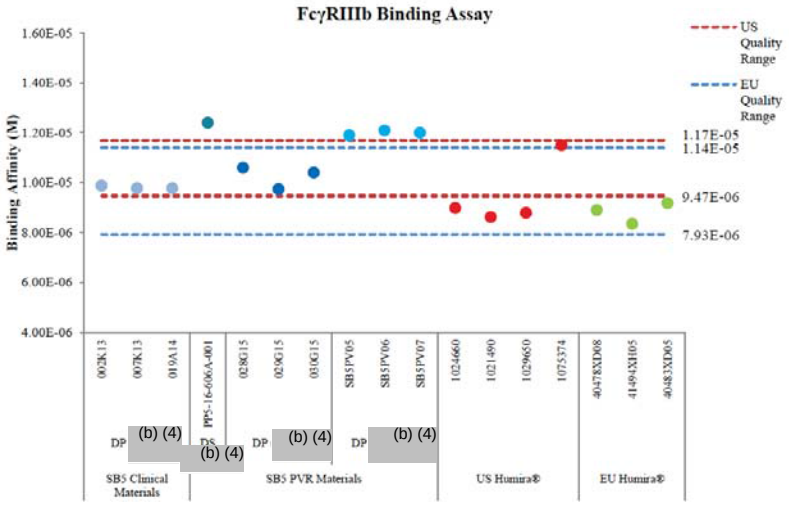
relative binding affinity of SB5 and US- and EU-Humira to FcγRIIIb using a surface plasmon resonance (SPR) assay. Data for the batches tested side-by- side is summarized in the graph below: the FcγRIIIb binding affinity for SB5 was 9.74E-06 to 1.24E-05M.



The K_D values of each three US- and EU- Humira batches tested side-by-side were lower than the US-Humira quality range. The quality ranges for US- and EU-Humira were established with 5 and 6 batches of each product, respectively

The Sponsor states when data from the four batches of US-Humira and three batches of EU-Humira tested in a side-by-side with those used in setting quality ranges, allows for the SB5 batches to fall within the quality ranges for US-Humira (6.94E-06 to 1.32E-05M). However, 4/10 SB5 batches and 1/4 US-Humira batches still showed slightly higher binding affinity than the recalculated EU-Humira quality range (7.39E-06 to 1.14E-05M).

Assessor comment:

The affinity differences in the FcγRIIIb binding between SB5, US- and EU- Humira are slight. Four batches of SB5 fall outside the US- and EU-Humira quality ranges. The Sponsor argues that the quality ranges for this attribute were set using results from 5 US- and 6 EU-Humira batches and that the limited number of batches used to set the quality ranges could explain the results. In support of this argument, when batches of US- and EU- Humira tested as part of the analytical similarity assessment are included to set the quality ranges all batches of SB5 fall within the US-Humira quality range. The Sponsors rational to support the differences observed is reasonable. Moreover, the small differences observed in affinity are not reflected in a functional assay such as ADCC and do not preclude a determination that SB5 and US-Humira are highly similar.

General Conclusion on Quality Range Similarity Data

The analyses of the data provided in the analytical similarity assessment of Fc -mediated functions indicate that the observed physicochemical differences between SB5, US- and EU-Humira measured using in vitro analytics do not substantially impact SB5 Fc function relative to US- Humira. Therefore, the observed differences do not preclude a determination that SB-5 and US-Humira are highly similar.

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3.2.R.2.3 Similarity Assessment for Quality Attributes tested using Visual Displays (Raw Data/Graphical Comparison)

The least statistically stringent approach to evaluate analytical similarity involves visual display comparisons either using raw data or graphical comparisons. Quality attributes analyzed by this method are typically lower risk attributes that have minimal impact on activity, PK/PD, safety, immunogenicity, attributes whose data are not amenable to statistical analysis, or both. For this section, Samsung categorized attributes into four groups including primary structure, carbohydrate structure, biophysical properties, and additional biological activities. QAs in this section were assessed using side-by-side graphical comparisons of the raw data, or in some cases, descriptive statistics for quantitative QAs. The Table 10 below adapted by assessor from submission provides a list of the assays analyzed using visual display approach.

Table 10: Similarity Assessment Strategy for Quality Attributes tested using Visual Displays (Raw Data/Graphical Comparison)

Category	Test and Analytical Method	Similarity Assessment Strategy	
		Raw Data/ Graphical Comparison	Mean ± 3SD Range Approach[a]
Primary Structure	Molecular weight determination by UPLC-ESI-MS	X	-
	Amino acid sequencing by UPLC-ESI-MS/MS	X	-
	N-terminal sequencing by UPLC-ESI-MS/MS	X	-
	C-terminal sequencing by UPLC-ESI-MS/MS	X	-
	Peptide mapping by UPLC-ESI-MS/MS	X	-
	Disulfide bond analysis by UPLC-ESI-MS/MS	X	-
	Free sulfhydryl group quantification by FLR	X	-
	Methionine oxidation by UPLC-ESI-MS/MS	X	-
	Deamidation by UPLC-ESI-MS/MS	X	-
Glycan Profile	N-linked glycosylation site determination by UPLC-ESI-MS/MS	X	-
	N-glycan identification by procainamide labeling and UPLC-ESI-MS/MS	X	-
	Charged and galactosylated glycan profile analysis by 2-AB labeling and HILIC-UPLC	-	X
High-order Structure	Protein secondary and tertiary structure analysis by CD (Far-UV/Near-UV)	X	-
	Protein folding analysis by intrinsic fluorescence spectroscopy	X	-
	Protein folding analysis by extrinsic fluorescence spectroscopy	X	-
	Secondary structure analysis by FTIR spectroscopy	X	-
	Tertiary structure analysis by H/DX-MS	X	-

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Category	Test and Analytical Method	Similarity Assessment Strategy	
		Raw Data/ Graphical Comparison	Mean ± 3SD Range Approach[a]
	Tertiary structure analysis by antibody conformation array	X	-
	Thermal stability analysis by DSC	X	-
	Aggregates characterization analysis by SE-HPLC/MALLS	X	-
	Aggregates characterization analysis by SV-AUC	X	-
	Protein size characterization analysis by DLS	X	-
	Extinction coefficient determination by amino acid analysis	X	-
	Subvisible particles analysis by MFI	X	-
Biological Assays Addressing Potential MoA	LTα3 binding assay (TNF-β binding assay) by FRET	X	-
	Transmembrane TNF-α binding assay by FACS	-	X
	FcγRIIIa binding assay (158F/F) by SPR	-	X
	Evaluation of regulatory macrophage induction by MLR	-	X
	Inhibition of IL-8 cytokine release in *in vitro* IBD model	-	X
	Apoptosis assay in *in vitro* IBD model	-	X
	Inhibition of sVCAM-1 adhesion molecule expression	-	X

[a] Mean ± 3SD ranges were established by data of US and EU-Humira analyzed during side-by-side characterization study, respectively. *Table adapted from submission by assessor.*

3.2.R.2.3.1 Primary Structure and sequence variants

Study results for primary structure assessment show that the SB5 molecular weight, primary structure and amino acid sequence for the variable and constant regions is similar to that of US-Humira and EU-Humira. Molecular weight was assessed for intact and deglycosylated drug, under reducing and non-reducing conditions. The identity and locations of post-translational modifications of SB5 and US- or EU-Humira were also similar, although some minor differences were found and are discussed below.
The experimental results using UPLC-ESI-MS/MS indicate that the disulfide bonds are at the expected cysteines and are the same in SB5, US- , and EU- Humira. Data are summarized in Table 11 below prepared by the assessor.

Table 11: Summary of Relative quantification of amino acid modifications and sequence variants

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Quality Attribute	SB5	US-licensed Humira	EU-approved Humira	SB5 vs. US-licensed Humira /SB5 vs. EU- approved Humira / US- licensed Humira vs EU- approved Humira
Free Thiol uM (%) by fluorescence (FLR) assay kit	1.1-6.2 µM (0.5-3.1%)	0.2-2.2 µM (0.1- 1.1%)	0.1-0.3 µM (0.1-0.15%)	**Not similar (3 batches OOR): not similar (9 batches OOR):** comparable
Deamidation (iso-Asp) at LH27 or LH30	HC Asn 77/84: 0-1.1% HC Asn319: 0-1.7 LC Asn137/138: 0-0.9%	HC Asn 77/84: 0-1.0% HC Asn319:0-1.1% LC Asn137/138: 0-0.9%	HC Asn 77/84: 0.7-0.8% HC Asn319:0.5-0.7% LC Asn137/138: 0.4-0.6%	Similar: similar: comparable
Methionine Oxidation	Met 256: 3.0-6.4% Met 83: 0-0.4% Met 34: 0.2-0.5%	Met 256: 2.3-3.9% Met 83: 0-0.4% Met 34: 0.1-0.7%	Met 256: 2.9-3.5% Met 83: 0-0.5% Met 34: 0.4-0.5%	**Met 256: Not similar (3 batches OOR)/Not similar (3 batches OOR)** /comparable
N-terminal Pyro glutamate	0.7-1.3%	0.9-1.6%	1.5-1.7%	Similar: similar: comparable
C-terminal lysine variants	1.3-3.3%	5.7-9.6%	6.8-8.1%	**Not similar (9 batches OOR): not similar (9 batches OOR)**: comparable
N-Glycan Identification using Procainamide label	13/14 glycans detected	14/14 glycans detected	14/14 glycans detected	Similar: similar: comparable
HMW variants by SV-AUC	0.94-1.37%	1.46-1.84%	1.72-2.44%	**Not-similar (9 batches OOR)/not-similar (9 batches OOR)**/comparable

Deamidation

The Sponsor monitored deamidation of peptides LH27 and LH30, Deamidation data were reported as being similar, with all results <1%. As reported in amendment 27 (Dec 31, 2019), Samsung provided the deamidation levels for Asn 54, Asn 77 or 84, and Asn 319 in the heavy chain, and Asn 317 or 138 in the light chain for 9 batches of SB5 DP, 4 batches of US-, and 3 batches of EU-Humira. Table 11 above includes the updated deamidation ranges observed. HC Asn 319 was the most prominent, but it ranged from not detectable to 1.7% for SB5 batches, and from not detectable to 1.1% in US-Humira. Asn 319 is located in the HC framework region, away from Fab and Fc regions.

Assessor comment:

The only notable deamidation difference was in Asn 319 levels, that went up to 1.7% in SB5. However, the levels of deamidated Asn 319 are still low and because Ans 319 is located in the HC framework region, away from the regions of the molecules implicated in functional activities, the observed difference do not preclude a determination that SB5 and US Humira are highly similar

Free Thiol Quantification

Samsung quantified free thiol groups in SB5, US- and EU- Humira using a fluorescence (FLR) assay kit. The molar concentration of free thiol content in SB5, US- and EU-Humira was 1.1-6.2 µM (0.5-3.1%), 0.2-2.2 µM (0.1-1.1%) and 0.1-0.3 µM (0.1-0.15%). The free thiol content of the 9 batches of SB5 was

higher compared to US (n=4) and EU-Humira (n=3). The higher levels were observed in the DP batches manufactured in (b) (4) (4.3-6.2 µM). The US- and EU-Humira free sulfhydryl and thioester levels were comparable. The relative percentage of free thiol group was low (< 3.1%) in all SB5 and US-, and EU-Humira batches.

Assessor comment:
Although the free thiol levels were higher for SB5 when compared to US- and EU-Humira, the differences are small. The relative percentage of free thiol group was low (< 3.1%) in all SB5, US-, and EU-Humira batches suggesting that mostly of 32 Cys residues were linked by disulfide bonds and that there were no free Cys residues. Although thiol content could impact structural integrity and stability, there was no difference in hydrogen/deuterium exchange (H/DX), antibody conformational array and differential scanning calorimetry (DSC) analysis for tertiary structure, and thermal stability between SB5, US-, and EU-Humira suggesting that the differences observed do not impact the conformation or stability of the product.

C-terminal Lysine Variants
C-terminal sequencing was performed by UPLC-ESI-MS/MS after digestion with Lys-C. In the case of heavy chain, two forms of C-terminal peptide were found for SB5 and US and EU-Humira: Intact form: 444-SLSLSPGK-451; Lys deleted: 444-SLSLSPG-450. C- terminal sequences were identical between SB5 and US and U-Humira.
The results showed that the relative content of the intact form for SB5 (1.3-3.3%; n=9) was slight lower than that of US (5.7-9.6%; n=4) and EU-Humira (6.8-8.1%; n=3), respectively. EU-Humira was comparable to those of US Humira.

Assessor comment
SB5 shows greater processing of C-terminal Lysine than US- and EU-Humira. The SAR study on SB5 basic fractions purified from CEX-HPLC showed that its C-terminal Lys variation has no effect on TNF-α binding and ADCC. In addition, information in the literature indicates that C-terminal Lys variants do not impact pharmacokinetic of monoclonal antibodies, when administered intravenously, and that the C-terminal, because of the distal location from the antigen-binding domain and the sites involved in interactions with Fc receptors, has little impact the biological activity of monoclonal antibodies in general. Therefore, the observed differences do not preclude a determination that SB-5 and US-Humira are highly similar.

Methionine Oxidation
Oxidation of proteins can serve as a stress signal leading to protein degradation in the body, potentially impacting PK and immunogenicity. Adalimumab contains five methionine residues (HC 34, 83, 256 and 432; LC 4). Met 256 is located in the FcRn binding region, and its oxidation has the potential to affect Fc-related biological activity. The oxidation contents of Met residues were quantified using UPLC-ESI-MS/MS after trypsin digestion. Met 256 was the most oxidized of the Met residues- the levels in SB5 ranged from 3.0-6.4% (n=9), which are slightly higher than those in US (2.3-3.9%; n=4) and EU Humira (2.9-3.5%; n=3), respectively. No evident differences in the level of oxidation were observed in the other Met residues. The %Met oxidation content of EU-Humira was comparable to that of US -Humira for all met residues.

Assessor comment:
The levels of oxidized Met 256 are higher in SB5 primarily in the three clinical batches, which were manufactured using an early process. The levels of oxidized Met 256 in the six remaining SB5 batches are

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similar to both US- or EU-Humira. Met256 is located in the neonatal Fc receptor (FcRn) binding region. However, the FcRn binding affinity was shown to be similar across SB5, US-, and EU-Humira: SB5 (85-111% n=10); US-Humira (81-115%, n=39); and EU-Humira (80-120%, n=40). Therefore, the observed differences do not preclude a determination that SB-5 and US-Humira are highly similar.

N-glycan Identification by Procainamide Labeling

Samsung identified specific N-glycan structures of SB5, US-, and EU-Humira using UPLC-ESI-MS/MS by procainamide labeling. The overall chromatography patterns were similar across SB5, US-, and EU-Humira. In addition, all three products had a single N-linked glycosylation site at Asn301. There were 14 identified glycan peaks, which were identical across the three products. The only exception was one glycan species, M4 ($Hex_4HexNAc_2$), which was only detected in US- and EU-Humira and at very low levels.

Assessor comment:
Although M4 was not detectable in SB5, the amount of M4 was very low in both US- and EU-Humira. The primary carbohydrate characterization data obtained using HILIC was discussed under the Quality Range analytical methods section.

HMW variants by Sedimentation Velocity-Analytical Ultracentrifugation (SV-AUC)

Samsung used SV-AUC as an orthogonal method to SE-HPLC, to investigate the purity and the main molecular species in a protein solution. Per cent HMW variants, aggregates, in SB5 (n=4) were 0.94-1.37% and in US-, and EU-Humira (n=2 each) were 1.46-1.84% and 1.72-2.44%, respectively. The frictional ratio, which gives information of the asymmetry of molecules, was similar across SB5 (1.61-1.74), US-Humira (1.59-1.63) and EU-Humira (1.59-1.63). The molecular weights for HMW were also similar across SB5 (264.0 to 295.5 kDa), US (262.0 to 279.0 kDa) and EU-Humira (280.0 to 289.5 kDa).

Assessor comment:
There was a slightly lower level in HMW for SB5 compared to US- and EU-Humira. This was not observed with SE-HPLC (SB5: 0.2-0.4%; US and EU-Humira: 0.3-0.5%), which included much greater number of batches tested (10:45:46). The slight difference seen with SV-AUC is likely within assay variability and could be accounted by the low number of batches tested. Monomer levels by SV-AUC were similar for all 3 products (99.2-99.9%). Data for monomer and low molecular weight impurities measured by SE-HPLC are consistent wtih SV-AUC data (see discussion SE-HPLC). Because HMW is an unwanted impurity lower levels of HMW species in SB5 do not preclude a determination of highly similar.

Biophysical Properties

Higher Order Structure

The similarity of the higher order structure of SB5, US-, and EU-Humira was evaluated by orthogonal biophysical techniques. These techniques include far and near-UV circular dichroism (CD), Intrinsic and Extrinsic Fluoresce Spectroscopy (IFS and EFS, respectively), Fourier transform infrared (FTIR), H/D exchange mass spectrometry, antibody confirmation array (Array Bridge), differential scanning calorimetry (DSC), size exclusion chromatography coupled to multi angle laser light scattering (SEC/MALLS), and sedimentation velocity- analytical ultracentrifugation (SV-AUC). These tests were primarily performed at

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Assessor comment: *The Sponsor conducted higher order structure analyses to assess the similarity between SB5, , US-, and EU-Humira. Four independent batches of SB5, 2 batches of US- ,and 2 batches of EU-Humira were tested by far- and near-UV CD, IFS and EFS, FTIR, DSC, SEC/MALLS, and SV-AUC. Two batches of SB5 and one lot each of US- and EU-Humira were analyzed by H/D exchange MS, and Antibody Array Bridge. The graphical data for all these assays were provided in the submission but not reproduced in this review. Data from the biophysical techniques support the conclusion that the secondary and tertiary structure of SB5 is similar to that of US- and EU- Humira.*

Particulate Levels

Samsung compared SB5 with US- and EU-Humira for particles of difference size ranges. Samsung used micro-flow imaging (MFI) to detect subvisible particles (SVP) ≥1, ≥2, ≥5, ≥10 and ≥25 µm. SB5 DP has similar SVP levels to US and EU-Humira. Samsung used Dynamic Light Scattering (DLS) as an orthogonal method to evaluate particles size and polydispersity, and the results indicated that SB5 exhibited similar particle size and polydispersity to US- and EU-Humira.

Assessor comment: *Samsung compared SVP levels between SB5, US-, and EU-Humira. Two batches of SB5 and one lot each of US- and EU- Humira were analyzed by MFI, and 4 batches of SB5 and 2 batches US- and EU- Humira were analyzed by DLS.SVP levels were similar between SB5, US- and EU- Humira.*

Additional Biological Activities:

Samsung provided data on additional biological activities that could play a role in the MOA in inflammatory Bowel Disease (IBD) and analyzed them by visual display comparisons either using raw data or graphical comparisons. These include transmembrane TNF-β (LTα3) binding assay by FRET, membrane bound TNF-α (mTNF- α) binding assay by FACS, inhibition of sTNF-α induced HCT-116 cell apoptosis (in vitro IBD model), Inhibition of IL-8 cytokine release (in vitro IBD model), Inhibition of sVCAM-1 adhesion molecule expression, FcγRIIIa binding assay (158F/F low affinity variant) by SPR, evaluation of regulatory cell function by MLR, and concurrent regulatory macrophage induction (CD206 marker expression) by flowcytometry. Table 12 below was prepared by the assessor and provides a summary of these data.

Assessor Note: *Discussion in subsequent section will focus on quality attributes where similarity was not met.*

Table 12: Relative quantification of additional Biological Activities (prepared by assessor)

Biological Activity	Number of Batches (SB5: US- licensed Humira: EU-approved Humira)	SB5 min –max Range	US-licensed Humira Quality Range or Visual Range	EU- approved Humira Quality Range or Visual Range	SB5 vs. US-licensed Humira /SB5 vs. EU-approved Humira / US-licensed Humira vs EU-approved Humira
Binding to TNF-β (LTα3) by FRET	3:2:1	Not detected	Not detected	Not Detected	Similar/similar/comparable

Binding to mTNF by flowcytometry	10:7: 6	87-99%	66-116%	73-118%	Similar/similar/comparable
Inhibition of sTNF-α induced HCT-116 cell apoptosis (in vitro IBD model)	10:7: 6	92-101%	82-113%	93-105%	Similar/similar/comparable
Inhibition of IL-8 Cytokine Release by HCT-116 cells in in vitro IBD model	9:7: 6	95-108%	88-120%	84-116%	Similar/similar/comparable
Inhibition of sVCAM-1 adhesion molecule expression	9:7: 6	95-120%	76-139%	81-139%	Similar/similar/comparable
FcγRIIIa binding (158F/F Low Affinity)	6:4:3	1.65E-06 to 1.86E-06 M	1.26E-06 to 2.01E-06 M	1.31E-06 to 1.92E-06 M	Similar/similar/comparable
Regulatory Macrophages (CD206 expression) by flowcytometry	9:7: 6	87-114%	69-120%	81-112%	Similar/ Similar (**1 lot OOR)**/comparable
Regulatory Cell induction by MLR Assay BrdU incorporation by Flowcytometry	9:7:6	17-52%	0-70%	9-41%	Similar/**Not similar (3 batches OOR)/ Not comparable (2 batches OOR)**

Adalimumab Induction of Regulatory Cells in a Mixed Lymphocyte Reaction (MLR) Assay

One of the adalimumab mechanisms of action thought to operate in inflammatory bowel disease involves the induction of regulatory cell populations, including $CD206^{hi}$ $CD14^{hi}$ $HLA\text{-}DR^{hi}$ regulatory macrophages and $TNFR2^{hi}$ T reg cell populations. Culturing monocytes with activated T cells in the presence of adalimumab can induce $CD206^{hi}$ $CD14^{hi}$ macrophages with immunosuppressive capacities, which inhibit allospecific T-cell proliferation in mixed lymphocyte reactions (MLR). As with ADCC effector function, binding to both mTNF-α and to Fc receptor appear to be required for the generation of regulatory populations. Samsung compared the ability of SB5 DP, and US-, EU-Humira to induce CD206 (mannose receptor) expression in regulatory macrophages by an MLR assay. The MLR assay uses peripheral blood mononuclear cells (PBMCs) from two different donors that are co-cultured with adalimumab or an IgG isotype control. The populations of putative regulatory macrophages were identified using flow cytometry by gating on CD206+ high forward scatter/side scatter cells. In the same MLR reaction, T cell proliferation was measured by flowcytometry using 5-ethynyl-2'-deoxyuridine (EdU) incorporated into genomic DNA. The greater the level of regulatory cells (CD206+ cells and others), the lower the levels of EdU incorporation detected in the gated CD3+ T cell population.

Nine batches of SB5, 7 batches of US-, and 6 batches of EU-Humira were tested at different concentrations against an IgG isotype control for induction of CD206+ cells and for EdU incorporation in MLR assays. Table 13 below prepared by the assessor provides a summary of the data, with corresponding data graphs provided: CD206 induction (left figure) and Tcell proliferation (right figure). The data ranges of US- and EU-Humira were set as mean ± 3SD from the data presented in Table 13 below.

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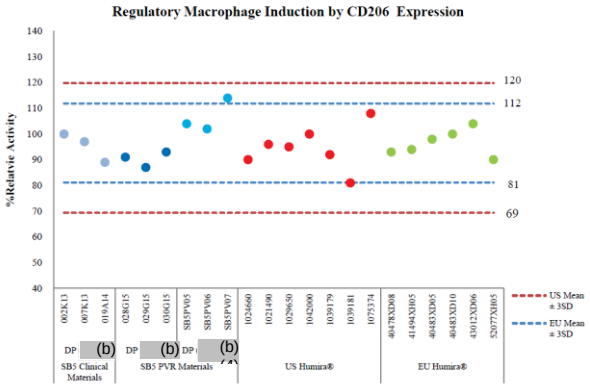
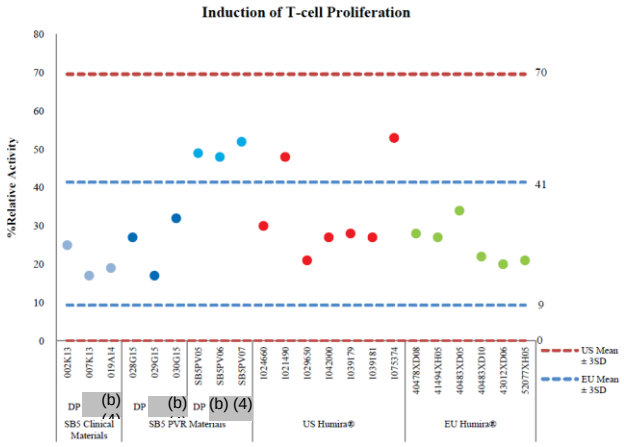
Table 13: Summary of Regulatory Macrophage Induction Activity of SB5 and Humira (prepared by assessor)

Adalimumab Source		Batch #	CD206 Induction %Relative Activity	T cell proliferation %Relative Activity
SB5 Clinical	DP (b) (4)	002K13	100	25
		007K13	97	17
		019A14	89	19
SB5 PVR	DP ((b) (4)	028G15	91	27
		029G15	87	17
		030G15	93	32
	DP (b) (4)	SB5PV05	104	49
		SB5PV06	102	48
		SB5PV07	114	52
Humira	US	1024660	90	30
		1021490	96	48
		1029650	95	21
		1042000	100	27
		1039179	92	28
		1039181	81	27
		1075374	108	53
	EU	40478XD08	93	28
		41494XH05	94	27
		40483XD05	98	34
		40483XD10	100	22
		43012XD06	104	20
		52077XH05	90	21
Mean ± 3SD of Humira			US: 69-120	US: 0-70
			EU: 81-112	EU: 9-41





The relative CD206+ cell (putative regulatory macrophages) induction activity was 87-114% for SB5 compared to IgG isotype control. The induction activity of all SB5 batches was within the range of US-Humira (69-120%). All SB5 batches were within the range of EU-Humira (81-112%) except for SB5 PVR DP batch manufactured at (b) (4) (SB5PV07 of 114%), which was slightly above the EU-Humira range. The allospecific T-cell anti-proliferation activity relative to the negative control (IgG isotype control) was 17-52% for SB5 batches and was within the range of US-Humira (0-70%). Three SB5 PVR DP batches manufactured at (b) (4) (SB5PV05, SB5PV06, and SB5PV07) were outside the range of EU-Humira (9-41%), while all six (b) (4) manufactured SB5 DP batches were within this range. Two batches of the US-Humira were also outside the EU-Humira range.

Assessor comment:
The induction of regulatory cells by MLR assay using human PBMCs is a complex assay involving interactions between multiple cell populations. Based on published literature, PBMCs can have CD3+ T cells (45 – 70%), B cells (5 – 15%), NK cells (5-15%), monocytes (10 – 30%) and DCs (1 – 2%). The assay was run using cells from two different donors in the presence of either adalimumab (SB5, US or EU-Humira) or IgG Isotype control. The induction of putative CD206+ regulatory macrophages was similar across SB5, US- and EU-Humira. The inhibition of EdU incorporation, attributed to decreased allospecific T cell proliferation, showed greater variability, with 3 batches of (b) (4) SB5 DP and 2 batches of US-Humira falling outside the EU-Humira range. This is likely to be due to inherent assay variability rather than true differences in the products. In addition, as seen from the table, there is no apparent correlation between CD206+ cell induction and decreased EdU incorporation as the (b) (4) batches that show higher %CD206 induction also show the higher % T cell proliferation activity.

Comparative Stability Studies with SB5 and Humira
Samsung performed comparative stability studies to demonstrate similarity in the degradation profiles of SB5 DP, US- and EU-Humira to support the analytical similarity assessment.

Assessor comment*: Comparative stability data were collected from the studies described below.*

- *3 studies performed under heat stress (40°C) conditions: Study 1: 3 SB5 clinical batches (002K13, 007K13, 019A14), 1US-Humira and 1 EU-Humira lot; Study 2: pilot SB5 DP lot (TR-(b) (4)-003611), and 1 EU-Humira lot; Study 3: (b) (4) SB5 DP (SB5PV01, SB5PV02, SB5PV03, SB5PV05, SB5PV06, SB5PV07), and 1US-Humira lot.*

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- *One accelerated temperature study (25°C) performed with pilot DP lot (TR-(b) (4)-003611), 1US-, and 1 EU- Humira lot,*
- *Two oxidation studies with H2O2 0.1% and 0.01%, performed with pilot DP lot (TR-(b) (4)-003611), 1US-, and 1 EU-Humira lot or SB5 (b) (4)* PVR DP#5 and SB5 *(b) (4) PVR lot 2 (029G15) and 1 US-Humira lot*
- *Two photostability studies: study 1 used SB5 clinical lot (002K13); 1US-, and 1 EU- Humira lot; Study 2 used SB5 (b) (4) PVR DP#5 and 1 US- Humira lot*
- *One basic and acidic stress study used 1 SB5 clinical lot (002K13), 1US-, and 1 EU-Humira lot each.*

In amendment 27 (12/31/2018) Samsung clarified that all studies were performed at Samsung except the photostability studies, which were performed at (b) (4) using methods qualified at Samsung and transferred to (b) (4) Samsung also provided summaries of the method transfer data, which indicate that method performance is similar at the two sites. Regarding the selection of batches used in the comparative stability studies, Samsung explained that for the heat stress study, the first three consecutively manufactured SB5 DP batches were used for long-term stability and characterization studies. For the accelerated, oxidative stress, pH stress, photostability studies, the first batch of first 3 consecutively manufactured batches were used. However, if the number of DP syringes remaining were insufficient to conduct the studies, a second batch was used, as was the case with lot 029G15 (second batch of PVR DP manufactured at (b) (4)) in the oxidative and pH stress studies. The US-, and EU-Humira batches were chosen due to availability and expiry dating during the study period.
Tests used as part of stability studies are summarized in Table 14 below prepared by the assessor.

Table 14: Stress conditions and analytical methods applied for different stress conditions (prepared by assessor)

Stress conditions		Appearance	pH	Protein Concentration	SEC	CE (NR)	icIEF	CEX	Peptide Map	TNFa binding by FRET	TNF neutralization by NF-kb reporter gene	FcRn binding by SPR
Initial		X	X	X	X	X	X	X	X	X	X	NP
40±2°C Temperature for 1, 2, and 3mo (Studies 1 and 3) Study 2: 1, 2, 3 and 6mo	Study 1 3 clinical (b) (4) DP batches	X	X	X	X	X	X	X	X	X	X	NP
	Study 2 (b) (4) Pilot DP lot	X	X	X	X	X	X	X	NP	X	X	NP
	Study 3 6 (b) (4) PV DP batches	X	X	X	X	X	X	NP	X	X	X	NP
25±2°C Temperature for 1, 3, 6, 9, &12mo	(b) (4) Pilot DP lot	X	X	X	X	X	X	X	NP	X	X	NP
Oxidation for 0, 3 and 6	0.1% H_2O_2 Pilot DP lot	X	X	X	X	X	X	X	X	X	X	X

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hrs. at 40±2°C	0.01% H_2O_2 1 (b) (4) PVR lot 1 (b) (4) PVR lot											
Base Stress 25±2°C for 0, 1 and 2 d	NaOH 1 (b) (4) PVR lot 1 (b) (4) PVR lot	X	X	NP	X	X	NP	X	X	X	X	NP
Acid Stress 25±2°C for 0, 1 and 2 d	HCl 1 (b) (4) PVR lot 1 (b) (4) PVR lot	X	X	NP	X	X	NP	X	NP	X	X	NP
Photostability 1.2 million Lux hrs. at 25 ± 2°C	Clinical DP lot 1 (b) (4) PVR lot 5	X	X	X	X	X	X	X	X	X	X	NP

NP Not Performed.

The reference standards used in comparative stability studies are provided in the Sponsor's Table 3 below.

Table 3: Description of Reference Standards Used in Comparative Stability Studies

Test Site	Test Material	Comparative Study	Used Reference Standard per Test Category	
			Purity and Impurities	Biological Activity
(b) (4)	SB5 Clinical DP US-licensed Humira® EU-approved Humira®	Heat Stress	(b) (4)	
		Photo Stress		
Samsung Bioepis	SB5 Pilot DP US-licensed Humira® EU-approved Humira®	Heat Stress		
		Accelerated		
		Oxidative Stress		
	SB5 Clinical DP US-licensed Humira® EU-approved Humira®	Heat Stress (for additional test)		
		Photo Stress (for additional test)		
	SB5 PVR DP US-licensed Humira®	Heat Stress		
		Oxidative Stress		
		Base Stress		
		Acid Stress		
		Photo Stress		

Assessor comment: *Samsung provided tabular comparability data for purity for all the above RS in STN27 (12/31/2018). The data included SEC (%HMW), CEX-HPLC (%Acidic, Main and Basic), icIEF (pI, %Acidic, Main and Basic); CE-SDS-NR (%IgG and 2H1L) and demonstrated that the various RS were comparable.*

Stability data were provided in summary tables for all the various studies, with acceptance criteria, with the exception of Study 3 for stress temperature (40°C) which listed "report results" for all the tests.
For all stability studies, trending plots were provided for %HMW species by SE-HPLC, % Total purity by CE-SDS (NR), and potency by FRET and NF-kb reporter gene assays. Oxidation with H2O2 included additional plots for %oxidized Met256 and %FcRn binding. Photostability studies included additional plots of %oxidized Met256 and Met432, and %Main peak by CEX, and icIEF. Table 15 below prepared by the assessor lists the graphical results provided for the different stress conditions.

Table 15: Graphical Trending Data presented for different stress conditions (prepared by assessor)

Stress conditions		Appearance And Quantity	SEC % HMW Main* LMW*	CE (NR) %total purity	icIEF % Acidic Main Basic	CEX %Main	% MetOx (M256, M434)	% TNFa binding by FRET	%TNF neutralization by NF-kb reporter gene	%FcRn binding by SPR
Heat Stress (40±2°C) for 1, 2, and 3m (Studies 1 and 3) Study 2: 1, 2, 3 and 6 months	Study 1 3 clinical DP batches	X	X	X	NS	NS	NS	X	X	NP
	Study 2 Pilot DP lot	X	X	X	NS	NS	NS	X	X	NP
	Study 3 6 (b) (4) PV DP batches	X	X	X	NS	NS	X	X	X	NP
Accelerated Temperature (25±2°C) for 1, 3, 6, 9, & 12 months	(b) (4) Pilot DP lot	X	X	X	NS	X	NS	X	X	NP
Oxidation 0, 3 and 6 hrs at 5±2°C	0.1% H_2O_2 Pilot DP lot	NS	X	NS	NS	NS	X	NP	NP	NP
	0.01% H_2O_2 1 (b) (4) PVR lot 1 (b) (4) PVR lot	NS	X	X	NS	X	X	X	X	X
Base Stress 25±2°C for 0, 1 and 2 d	NaOH 1 (b) (4) PVR lot 1 (b) (4) PVR lot	NS	X	X	NP	NS	NP	X	X	NP
Acid Stress 25±2°C for 0, 1 and 2 d	HCl 1 (b) (4) PVR lot 1 (b) (4) PVR lot	NS	X	X	NP	NP	NP	X	X	NP
Photostability 1.2 million Lux hrs at 25 ± 2°C	Clinical DP lot 1 (b) (4) PVR lot	NS	X	X	X	X	X	X	X	NP

NS Not Shown; NP Not Performed.

In amendment 27 (12/31/27), Samsung provided primary data for CEX-HPLC, SE-HPLC, and potency dose response curves for stability results under real time, accelerated, and stress conditions for SB5 and US- Humira batches. % FcRn binding activity was included in the assessment of comparative oxidation stress as an additional assessment of oxidation of Met256.

The stability trending data graphs showed similar degradation profiles between SB5, US- and EU-Humira under stress (40°C) and accelerated storage (25°C) temperatures, and for oxidation with H2O2.

Exposure to stress and accelerated temperature conditions of 40°C and 25°C resulted in decreased purity measured by CE-SDS (NR), SE-HPLC (increase in aggregation) and CEX-HPLC and icIEF (increase in acidic variants with decrease in main peak and basic variants). Decrease in potency measured by % TNFa binding by FRET and %TNF neutralization by NF-kb reporter gene was only observed under stress temperature conditions. Treatment under oxidative conditions resulted in increased oxidation of Met_{246}, increase in basic variants evaluated by icIEF and CEX-HLC end decrease in binding to FcRn.

Photostability study 1 was performed in the immediate package and showed increased degradation for both US and EU-Humira compared to (b) (4) Clinical DP lot 1 ((002K13) for %HMW by SEC, % Met256 and Met432 oxidation (see graphs below).

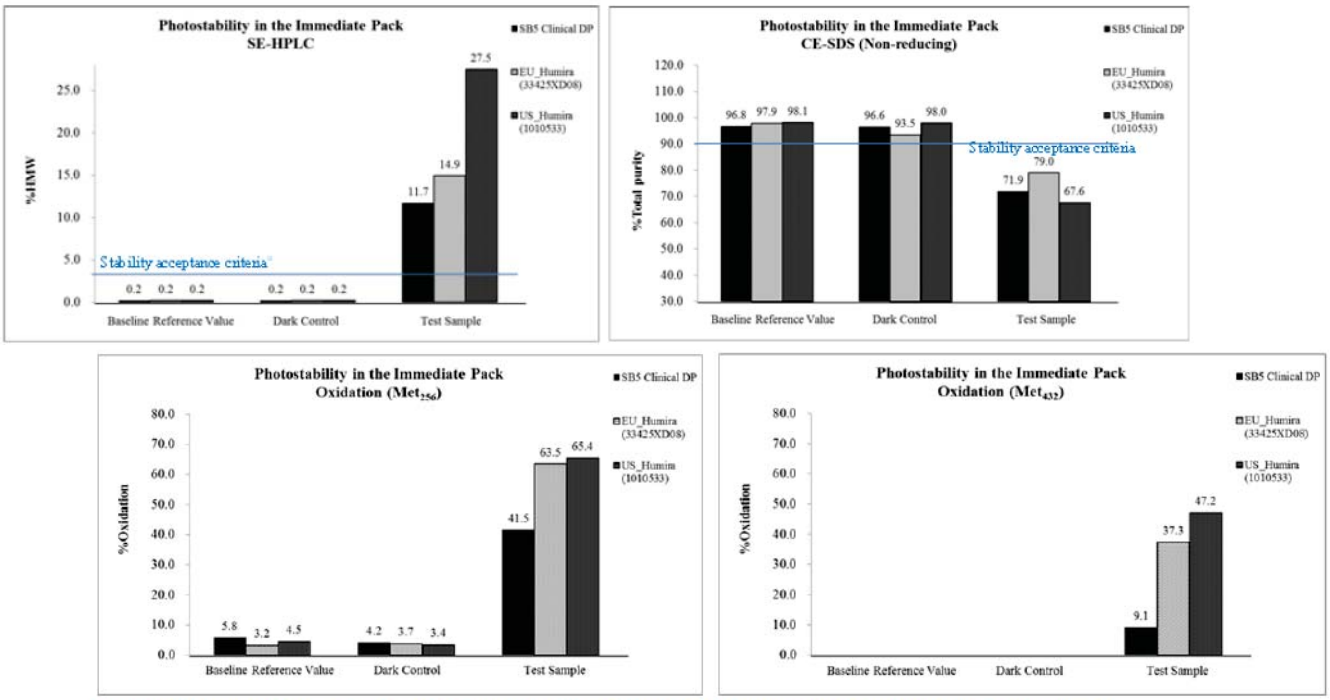
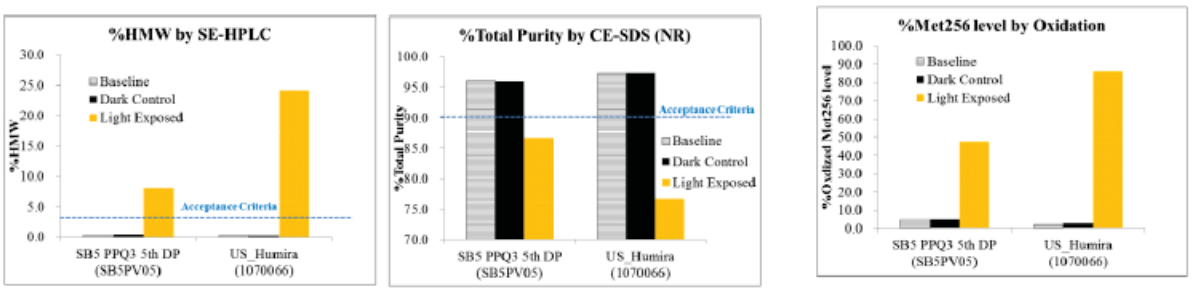


Figure 109 : Similarity of Comparative Photostability between SB5 Clinical DP and Humira® (Continued)

Photostability study 2 showed increased degradation for US Humira compared to (b) (4) PVR DP lot 5 (SB5PV05) for %HMW by SEC, Total Purity by CE-SDS (NR), and, % Met256 oxidation (see graphs below).



Assessor comment:

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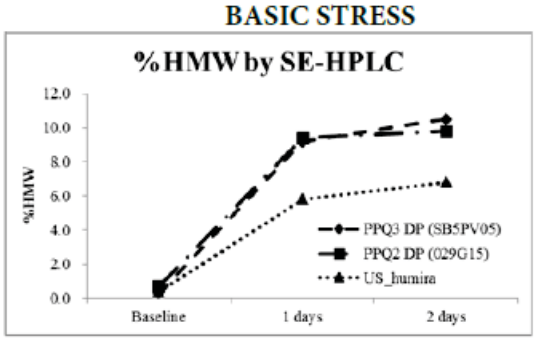
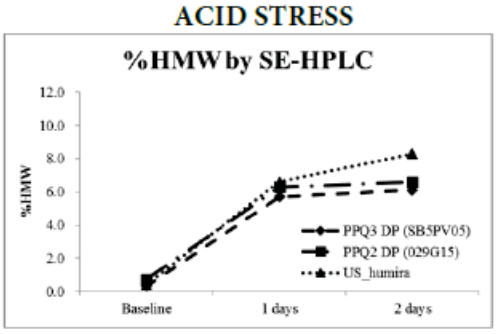
The data suggesting higher photo-resistance of SB5 compared to US-, and EU-Humira is limited by the number of batches tested (2 SB5:2 US Humira: 1 EU Humira), and the lack of kinetic sampling. However, differences could be due to the differences in formulation between SB5 and Humira and the age of the reference product batches used. Higher order structure studies indicate it is less likely these differences are due to differences in higher order structure; therefore, the differences do not preclude a determination that SB5 and US-Humira are Similar.

Comparative stability studies under base and acidic stress conditions showed decreased in purity measured by SE-HPLC with increase in HMW species and in CEX-HPLC with increased in basic variants and decrease in acidic variants and main peak in SB5 and US and EU-Humira. No degradation was observed in biological activity measured by % TNFa binding by FRET and %TNF neutralization by NF-kb reporter gene.

Assessor comment: *Differences in the degradation profiles between SB5 and US and EU-Humira were observed after treatment under basic and acidic conditions. According to Samsung, formulation differences also account for the increased sensitivity of SB5 to basic stress (NaOH treatment) and conversely increased resistance to acidic stress (HCL), as detected by %HMW by SEC (see trending graphs below). The sponsor claims that these differences are not seen when SB5 is formulated as Humira, however the data were not shown. These data were requested as part of the IR dated 12/7/2018.*





In their IR response submitted in STN27 (12/31/2018) Samsung provided data from buffer exchange experiments in which (b) (4) *lot SB5PV3 and US-Humira lot 1070006 formulation were swapped by dialysis and assessed under basic stress and acidic stresses. For basic stress (Fig 2 below) the SE-HPLC data show an %HMW increase over a 2-day exposure at RT to NaOH for both conditions. When, SB5 is buffer exchanged with Humira the %HMW increase is lower than Humira buffer exchanged with SB5 buffer (left panel vs right panel).*

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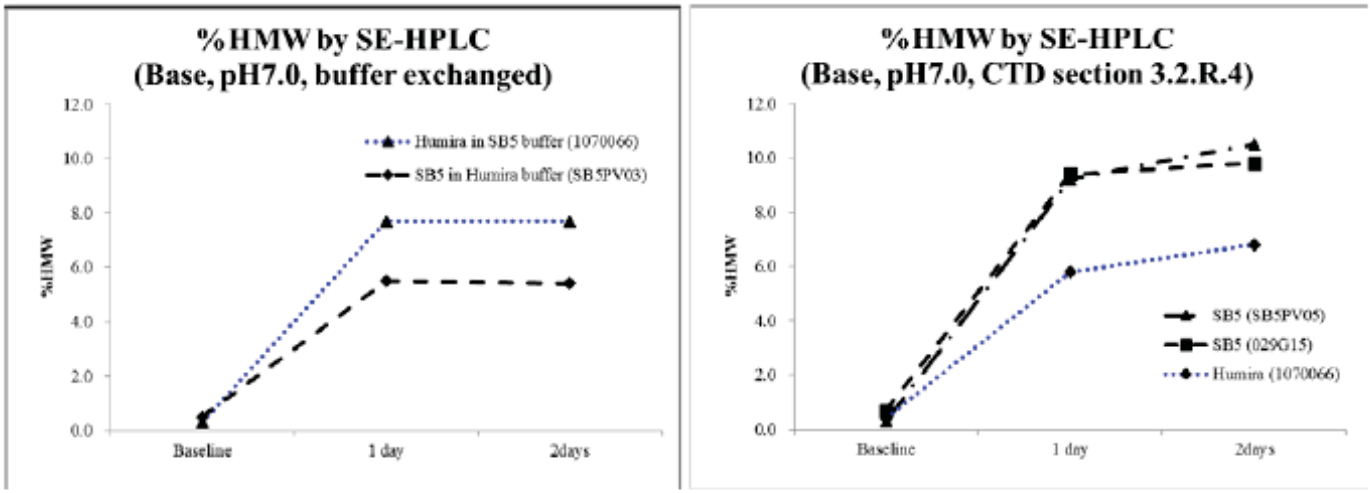

Figure 2: pH Stress Study Result Trends: Basic Stress Condition

For acidic stress (Fig 3 below), buffer exchanging Humira with SB5 buffer appears to reduce %HMW to SB5 levels over the course of two days (left panel vs right panel), but the converse was not the case for SB5 in Humira buffer. It is noted that while the Humira lot is the same (lot 1007066) in both panels, the SB5 lot is not (SB5PV003 in left panel and SB5PV005 in right panel), so the data primarily confirms the effect for Humira.

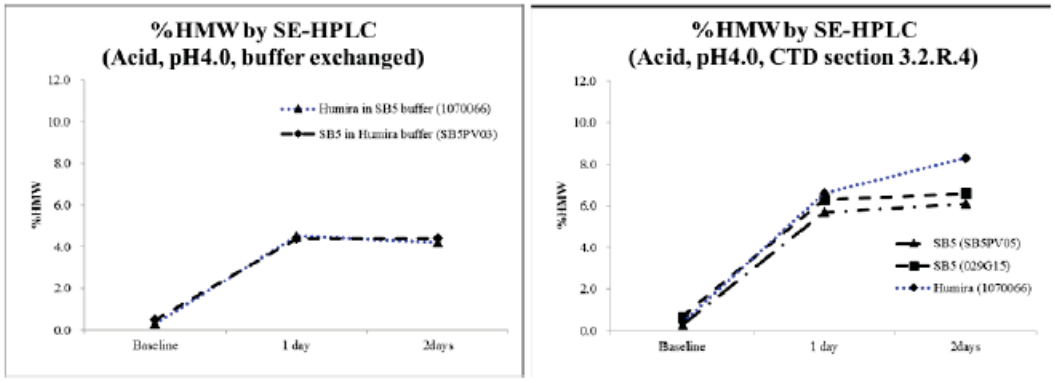

Figure 3: pH Stress Study Result Trends: Acidic Stress Condition

For photostress, Samsung did not provide buffer exchange data, probably because the photostress studies were previously performed at (b) (4) *and not at Samsung. Samsung referred to the literature as to the role of histidine in the photoprotection afforded by SB5 formulation buffer, and state that a stability study is underway to generate the requested data and will be provided by April 2019. This is acceptable currently.*

The commitment will be tracked, and information provided will be added in an addendum to primary review as it will be submitted after internal primary memo dates.

As part of STN27, Samsung also provided %LMW and %Main SE-HPLC tabular data for all comparative stability studies. For Heat stress studies 1-3 there was a 6-13% increase in %LMW and a similar decrease in %Main for both SB5 and Humira over the 3-6 months. For accelerated temperature study, there was a similar ~3-4% increase in %LMW and ~5% decrease in %Main for both SB5 and Humira over the 12 months. For oxidative stress, no apparent impact on %LMW or %Main for either product over the 6hrs tested for either

product. For base stress and acid stress there was no apparent impact on %LMW, but there was a 6-10% decrease in %Main, with slightly less impact for Humira than for SB5 under basic conditions in line with %HMW data. For photo-stress study 2, there was a 20% decrease in %main for Humira and a 10% decrease for SB5, paralleling the %HMW data, but there was only 1-2% increase in %LMW for both products.

Summarizing the data from comparative stability studies, SB5 in the proposed formulation is more resistant to acidic and photo-stress, but less resistant to basic stress than Humira. SB5 and Humira show similar degradation rates at accelerated storage temperature (25°C) and heat stress (40°C) as well as oxidizing agent (H2O2) treatment. These stability differences are attributable to formulation differences, and do not preclude a conclusion of highly similar.

3.2.A Appendices

3.2.A.2 Adventitious Agents Safety Evaluation

(b) (4)

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix I

Drug Substance Information Requests

October 5, 2018 IR

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing, and Controls

(b) (4)

[redacted]

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(b) (4)

[redacted]

Analytical Similarity

2. Section 3.2.S.5 Reference Standards or Materials indicates that a total of eight reference standard lots were used during development of SB5. In Table 47 of this section, you list the Research reference standards (RRS) used to determine relative potency of SB5, US- licensed Humira, and EU-approved Humira by TNF-α binding assay by FRET and TNF- α neutralization assay by NF-κB reporter gene using equivalence testing. However, it is unclear which RRS lots(s) were used in the analytical similarity assessment for the other potency assays that report a result relative to a reference standard that were evaluated using quality ranges such asapoptosis ADCC, CDC, and binding to FcγRIa, FcγRIIa,

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FcγRIIb, FcγRIIIa, FcγRIIIb, FcRn and C1q.

a. Provide a detailed list of the RRS lot(s) used in each biological activity assay other than TNF-α binding assay by FRET and TNF-α neutralization assay by NF-κB reporter gene for each lot of SB5, US-licensed Humira, or EU- approved Humira. If more than one reference standard (RS) lot was used for a particular method, evaluation of a particular quality attribute, or both, provide data that support a bridge between those reference standards. Clearly describe the relationship between the RRSs and provide your rationale as to how the data support the bridge. In the absence of an adequate bridge, relative activity data determined using different RRSs cannot be pooled for analysis.

3. Your assessment of similarity of the carbohydrate structure of SB5, US-licensed Humira, or EU-approved Humira includes evaluation of the sum of afucosylated glycans (%Afucose) and mannosylchitobiose core without L-fucose (%High Mannose (HM)) using quality ranges, and assessment of neutral galactosylated glycans (%Gal), and of charged glycans (%Charged) using visual display comparisons. The reason for assessing combined %Afucose and %High Mannose content by HILIC is unclear. Afucosylated glycans and high mannose glycans can impact FcγRIIIa binding and ADCC activities. However, higher afucosylation is expected to increase ADCC activity while lower high mannose content is expected to lower ADCC activity. Therefore, differences in the relative levels of %Afucose and %High Mannose may be undetected with this approach. Reassess the available data for %Afucose and %High Mannose and perform analytical similarity assessment of %Afucose and %High Mannose content separately. Submit these data to the BLA.

4. You propose to measure potency using an NF-κB reporter gene assay to measure TNF-α activity neutralization and a FRET assay to measure competitive inhibition binding to TNF-α at release and stability testing of DS and DP. These assays are insufficient to control potency because both assays measure only the early steps of the TNFα signaling cascade. The TNFα-induced apoptosis inhibition assay is a more appropriate approach to controlling potency because better reflects a dominant mechanism of action of adalimumab. To improve your control strategy over the potency of SB5, implement a bioassay that assesses the impact of adalimumab on TNFα-induced apoptosis and establish appropriate DS and DP release and stability specifications.

5. The legends in some of the (b) (4) Manufacturing facility maps are not legible. Update the BLA with maps of higher resolution.

ii) Some of your proposed acceptance criteria described in Table 24 of section 2.3 are report results. Revise your protocol to include numerical acceptance criteria with upper and/or lower limits for purity measured by iCIEF and CE-SDS (non-reduced).

c. The requalification protocol does not include [redacted] (b) (4)

October 17, 2018 IR

We are reviewing your submission and have the following request. We request a prompt written response to continue our evaluation of your submission. Please submit your response by close of business **(COB):** Tuesday November 6, 2018.

We are currently reviewing your control strategy for SB5 drug substance and drug product under BLA 761059. To facilitate the Agency's review of your drug substance and drug product process control strategies, provide a table with the following information for each of your process parameters and IPCs:

- Unit operation
- Parameter and in-process control name
- Classification (CPP, KPP, non-CPP/KPP, IPC)
- Justification for parameter classification
- Proposed acceptance range for the commercial manufacturing process
- Acceptable range determined during process development studies (if applicable)
- Range evaluated during commercial-scale process validation
- Justification of the proposed acceptance range

December 7, 2018 IR

We are currently reviewing your 351(k) BLA 761059 submission and your responses to the Agency's day 74 letter comments submitted to BLA 761059 in amendment 22 on November 5, 2018, and we have the following information request. We request a prompt written response by COB December 31, 2018, to continue our evaluation of your application:

1. It is unclear from your submission whether the data provided to support that SB5 is highly similar to US-licensed Humira and to establish the analytical bridge with EU-approved Humira were obtained from a single or from multiple analytical similarity exercises and whether there were differences in the protocols used. Provide a

description of the analytical similarity protocols executed to generate the data provided in the submission. Confirm that the all the analytical similarity data generated were submittedin your 351(k) BLA application.

2. Provide a list describing all the US-licensed Humira and EU-approved Humira lots acquired until the time of submission of the 351(k) BLA application and their disposition (e.g., analytical similarity, clinical studies, stability studies, etc.).

3. During the analytical similarity inspection, the investigator noted that some of the lots of US- licensed Humira and EU-approved Humira were retested. Provide a complete list of all retested lots and the reason for the retests.

4. For each analytical method used in the analytical similarity exercise(s), provide the basis for the selection of the specific lots evaluated when only a subset of the total lots of SB5, US- licensed Humira, and EU-approved Humira were tested.

5. In your analytical similarity exercise, you include SE-HPLC assay as a purity method for size species. You use the SE-HPLC method to assess high molecular weight (HMW) species in SB5, EU-approved Humira and US-licensed Humira. However, you do not assess the SE- HPLC data collected for low molecular weight (LMW) species or main peak. Provide the following:
    a. Analytical similarity data and comparative stability data for main peak and LMW species measured by SE-HPLC for SB5, US-licensed Humira and EU-approved Humira.
    b. A description of the integration criteria for the SE-HPLC method used for assessment of purity and product-related species. Indicate whether the same integration criteria were consistently applied to all samples tested by SE-HPLC used to support analytical similarity, including data in the comparative stability study.
    c. An example of SE-HPLC peak integration data for SB5, US-licensed Humira and EU-approved Humira.

6. As part of the analytical similarity assessment, you utilized CEX-HPLC and icIEF to assess the charge variants profiles of SB5, US-licensed Humira and EU-approved Humira. You provided data on the identification of acidic and basic species present in each peak of the CEX-HPLC chromatogram. However, you did not identify the nature of all product-related species observed by icIEF. Provide information on the identity of the charge species that are present in each peak of the icIEF chromatogram and an assessment on the impact of product- related species identified by icIEF on the safety, purity, and potency of the product.

7. In response to our request to implement a bioassay that assesses the impact of SB5 on

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TNF-α induced apoptosis, you provided data comparing the performance of your TNF-α neutralization reporter gene assay (NRGA) with the L929 cell cytotoxicity/apoptosis inhibition bioassay. The data presented in table 18 of your IR response dated November 5, 2018, suggest that the two assays have comparable performance with regards to precision, accuracy and linearity. You also provided data in table 19 that show that the NRGA potency assay is more sensitive to changes in product quality than the L929 apoptosis inhibition

assay. However, you provide data from one lot of SB5 and one lot the reference standard to support this conclusion. To bolster your conclusion that the NRGA assay is more capable of detecting small differences in potency than the L929 apoptosis inhibition assay and is therefore a suitable assay to control for the potency of SB5, provide the following:

a. The detailed study report describing the materials and conditions used in the comparative study, including primary dose response curves of the comparative results described in Table 19.
b. Additional comparative data with both assays, testing different lots of SB5 and multiple testing replicates under accelerated or stress conditions. Include data from lots of US-licensed Humira. Provide tabular and primary data of the comparative results.

8. You assessed deamidation and iso-aspartic acid modifications using trypsin digested samples and UPLC-ESI-MS/MS. You state that the calculated relative content of deamidation was less than 1.0% for any of the Asn residues in SB5, US-licensed Humira and EU-approved Humira. However, these data were not provided in the submission. Provide the tabular analytical similarity data you collected for deamidation. Provide information of which lot(s) of SB5, US-licensed Humira and EU-approved Humira were used in the study.

9. As part of the analytical similarity exercise, you performed comparative stability studies between SB5, US-licensed Humira and EU-approved Humira. You selected a subset of stability indicating assays and provided tabular data and regression plots of some of the data obtained under accelerated and stress temperature conditions, exposure to light as well as oxidative, acid, and base stress conditions. You describe that testing for the comparative stability study under heat stress conditions was performed at (b) (4) for the QC tests and at Samsung Bioepis for the additional tests. However, the following information was not provided:
   a. The location(s) where the additional comparative stability studies for conditions other than heat stress were performed
   b. Information and data supporting that the methods used for the comparative stability assessment have a similar performance to the same methods performed at Samsung

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Bioepis in the analytical similarity exercise.

c. The selection criteria for the lots tested in the comparative stability study and the rationale for choice of presentation.

d. Primary data for CEX-HPLC, SE-HPLC and potency dose response for stability results under real time, accelerated and stress conditions for SB5 and US-licensed Humira lots.

e. A description of the reference standards used in the comparative stability studies. Update your 351(k) BLA with the information described above.

10. As part of the comparative stability studies, you provide data suggesting that SB5 has higher photo-resistance and acidic stress resistance and increased sensitivity to basic stress, compared to US-licensed Humira and EU-approved Humira. These conclusions are based on the levels of HMW species assessed by SE-HPLC and % Met 256 oxidation assessed by peptide mapping. You attribute these differences to differences in formulation. However, you did not provide data to support this conclusion. Provide the data you generated to support that the differences in the stability profile of SB5, US-licensed Humira, and EU-approved Humira under stress conditions are due to differences in the formulation.

11. You provided general descriptions for the analytical procedures used for the characterization (Section 3.2.S.3.1) and analytical similarity testing of SB5, US-licensed Humira, and EU-approved Humira (Section 3.2.R). However, no method qualificationn data and/or information were included in your 351(k) BLA application to support that the methods are fit for purpose.

a. Provide method qualification data and/or information (i.e., descriptive summaries) for each analytical procedure used in the characterization of SB5 and in the analytical similarity assessment. Include information on how each experiment was performed for each parameter (e.g., precision, accuracy and specificity, etc.) tested for method qualification at Samsung Bioepis.

b. Provide data and/or information to support comparable performance of the assays used in the analytical similarity exercise that are also used for release and stability testing of SB5 at Samsung Bioepis Co, at (b) (4) as appropriate.

c. For the biological activity assays assessed by either equivalence testing, or quality ranges, include dose-response curves for each reference standard used and tested sample from at least three lots each of SB5, US-licensed Humira and EU-approved Humira.

12. In the characterization section 3.2.S.3.1, you provide glycan data expressed as combined levels and individual levels %Afucose and %High Mannose (%HM), and other N-glycans (%G0F, %G1F, and %G2F). The glycan analysis for %Charged

(Sialylated) and % Gal was not provided. In the analytical similarity section 3.2.R.4, you provide glycan data expressed as %Charged (Sialylated) glycans and %Gal as well as %Afucose and %HM data combined. In your IR response dated November 5, 2018, you provided the analytical similarity assessment of %Afucose and %HM content separately. However, the amounts of N-glycans like G0F, G1F, and G2F in SB5, US-licensed Humira and EU-approved Humira were not provided in section 3.2.R.4 Biosimilarity. Update your characterization section to include glycan assessment of %Charged (Sialylated) and % Gal and update the analytical similarity assessment to include glycan assessment of %G0F, %G1F, and %G2F for SB5, US-licensed Humira and EU-approved Humira.

February 27, 2019
We are reviewing your submission and have the following request. We request a prompt written response to continue our evaluation of your submission. Please submit your response by close of business (COB): Monday March 4, 2019 for CMC section responses and (COB): Thursday March 14, 2019 for Microbiology responses.

CMC:

(b) (4)

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Joao Pedras Vasconcel

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

BLA STN 761059
Drug Product Assessment

Product SB5
Proposed Trade Name: Hadlima
Manufacturer: Samsung Bioepis Co, Ltd

Primary Assessor: Tracy Denison

ATL: Maria Cecilia Tami, Ph.D.
Review Chief: Susan Kirshner, Ph.D.

Division of Biotechnology Review and Research III
Office of Biotechnology Products

OBP CMC Assessment Data Sheet

1. BLA#: 761059

2. Assessment Date: March 22, 2019

3. Primary Assessment Team:

Clinical	DPARP – Raj Nair / Nikolay Nikolov DDDP –Roselyn Epps / David Kettl DGIEP –Anil Rajpal
Clin/Pharm	Lei He / Anshu Marathe
Clin Stats	Becky Rothwell / Nie Lei
Pharm/Tox	David Klein / Tim Robison
TBBS	Cristina Ausín-Moreno /Stacey Ricci
Product Quality & Immunogenicity	João Pedras-Vasconcelos (AS, DS Imm)/ Tracy Denison (DP) / Merry Christie (Method Validation)/ Maria Cecilia Tami
CMC Stats	Yu-Ting Weng / Meiyu Shen
Process and Facilities	DIA— Viviana Matta / Peter Qiu DMA – Bo Chi (DS)/ Jessica Hankins (DP) /Maria Candauchacon
CDRH	OC/ODE- Sarah Mollo/Stevens Alan / Carolyn Dorgan

4. Major GRMP Deadlines:

Milestone	Target Date for Completion
Filing Action Date (60 Day Letter)	September 21, 2018
74 Day Letter	October 5, 2018
Mid Cycle Communication	January 22, 2019
Primary Assessments	March 22, 2019
Secondary Assessments	March 30, 2019
Wrap Up Meeting	June 3, 2019
BsUFA Action Date (12 months)	July 23, 2019

5. Information Requests to the Sponsor:

The communications listed below are information requests that were needed to complete the assessment for this Drug Product CMC Quality. Refer to the Drug Substance Quality assessment memo for a more complete listing of OBP communications during the BLA assessment.

Reference ID: 4466647

Date of Information Request* Communication	Date Response Received	Response Submission	Assessment Completed
October 5, 2018	November 5, 2018	761059/0022	Yes
October 17, 2018	November 6, 2018	761059/0023	Yes
February 4, 2019	February 12, 2019	761059/0036	Yes
February 28, 2019	March 6, 2019	761059/0041	Yes
March 8, 2019	March 13, 2019	761059/0043	Yes
March 22, 2019 *(sent on or approximately this date)*	*Pending*	*Pending*	*Will be included in an addendum*

*The Information Request language is provided in the Appendix of this memo.

6. Drug Product Name/Code/Type:
   a. Proprietary Name SB5
   b. Trade Name (proposed) Hadlima/Hadlima PushTouch
   c. Non-Proprietary Name/USAN/INN adalimumab-xxxx
   d. CAS Name 331731-18-1
   e. Common Name
   g. Compendial Name not applicable
   h. OBP systematic name MAB HUMAN (IGG1) ANTI P01375 (TNFA_HUMAN) [SB5]

7. Pharmacological Category: Immunosuppressant, TNF-α inhibitor

8. Dosage Form: Autoinjector (Hadlima PushTouch)
   Pre-filled syringe (Hadlima)
9. Strength/Potency:
   (i): The concentration/strength of the Drug Product: 40 mg/0.8 mL
   (ii): Type of potency assay(s): Reporter Gene bioassay, FRET binding assay

10. Route of Administration: subcutaneous injection

11. Referenced Drug Master Files (DMF):

Refer to the Drug Substance Product Quality assessment memo for this information. No DMFs were assessed to complete this memo because sufficient information was provided in the BLA submission.

12. Inspectional Activities:

Reference ID: 4466647

Three pre-licensing inspections were performed for BLA 761059, including an inspection of the Drug Substance manufacturing site, the Drug Product manufacturing site, and the Sponsor's facility in Korea to assess the analytical similarity data. Details of all three inspections are included in the Drug Substance Quality assessment. A summary of the Drug Product manufacturing site inspection only is duplicated here for its relevance to this memo.

A PLI of the DP manufacturing site was conducted from February (b) (4). Information about the facility and FDA personnel involved is described below:

Firm:	(b) (4)	
Location:		
FEI:		
Dates of inspection:		
Days in the facility:	7	
Participants:	Viviana Matta, Ph.D.,	CDER/OPQ/OPF/DIA
	Jessica Hankins, Ph.D.	CDER/OPQ/OPF/DIA

A five-item 483 form was issue to (b) (4) at the end of the DP facility inspection on (b) (4) (Appendix III). The inspection recommendation, following responses from the firm, is VAI. The 483 observations included:

(b) (4)

13. Consults Requested by OBP:

Refer to the Drug Substance Product Quality assessment memo for this information.

14. Quality by Design Elements:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

15. Precedents: None

16. Administrative:

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation

From the perspective of the quality of the drug product, we recommend approval of BLA 761059. The data submitted in this Biologics License Application support the conclusion that the drug product manufacturing process for SB5 can produce a product that consistently meets acceptable purity and potency. Refer to the assessment memos for the conclusions regarding drug substance manufacturing, analytical similarity, and assessor conclusions from other disciplines.

II. List of Deficiencies to be Communicated

There are no CMC-Product Quality deficiencies related to drug product identified at this time that preclude approval of this BLA.

III. List of Post-Marketing Commitments/Requirements

No PMCs for drug product have been identified at this time. However, there are pending information requests that may result in a Post Marketing Commitment.

IV. Primary Container Labeling Assessment

Reference ID: 4466647

The primary container labeling was assessed by Vicky Borders-Hemphill. Refer to Vicky Borders-Hemphill's assessment in Panorama.

V. Assessment of Common Technical Document- Quality Module 3.2.P

CTD Module 3.2.P was assessed by Tracy Denison regarding product quality. Relevant portions of 3.2.P may also be covered in the assessment of the device by CDRH, or for microbial control by DMA in their respective assessment memos.

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Reference ID: 4466647

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

SB5 DP is a clear to opalescent, colorless to pale brown, sterile and preservative-free solution for injection. It is presented as a single-use safety pre-filled syringe (SPFS) and a single-use autoinjector (AI), each containing 0.8 mL of solution and 40 mg adalimumab. The Safety PFS consists of a pre-filled syringe (PFS) assembled into secondary packaging components (safe-shield body, finger flange, and plunger rod). The AI consists of a PFS assembled into device components as well as front and rear subassemblies. The PFS consists of a clear glass syringe with a stainless-steel needle, rigid needle shield, and a plunger stopper. The Sponsor's Table 1 below summarizes the composition of SB5 DP:

Table 1: Composition of SB5 Solution for Injection

Component	Nominal Quantity/0.8 mL	Function	Quality Standard
Adalimumab	40 mg	Active substance	In-house
Sodium citrate dihydrate	1.6 mg	(b) (4)	Ph. Eur./USP/JP
Citric acid monohydrate	0.544 mg		Ph. Eur./USP/JP
L-Histidine	0.96 mg		Ph. Eur./USP/JP
L-Histidine hydrochloride monohydrate	8.64 mg		Ph. Eur./JP
Sorbitol	20.0 mg		Ph. Eur./USP/JP
Polysorbate 20	0.64 mg		Ph. Eur./NF/JP
Water for injection	*q.s.*		Ph. Eur./USP

3.2.P.2 Pharmaceutical Development

(b) (4)

[redacted]

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(b) (4)

[redacted]

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

Proposed Shelf Life and Storage Conditions

The Sponsor proposes a 36-month shelf life for [redacted] (b) (4) DP when stored at 5 ± 3 °C, [redacted] (b) (4) The 36-month shelf life is based on real-time data from clinical lots produced at [redacted] (b) (4). The shelf-life for both Safety PFS and AI is dependent on the shelf-life of the nude PFS component of the final assembled device. It is not allowed to mix nude PFS from different lots to a single batch of Safety PFS or AI. The storage conditions are the same for PFS compared to the final assemblies of Safety PFS and AI.

Assessor's Comment: Based on the comparability assessment (see Section 3.2.P.2.3.2 Comparability Assessment) between (b) (4) *lots (both PVR and clinical) and* (b) (4) *lots, the Sponsor is justified to propose a 36-month shelf life of SB5 DP from a product quality perspective. CDRH concurs that the device components can support a shelf-life of 36 months.*

3.2.P.8.2 Post-Approval Stability Commitment

The Sponsor commits to place at least one lot of SB5 DP on stability testing each year, unless no lots are made that year. The following Table 1 copied below, which is an updated version provided by the Sponsor in amendment 0043 (March 13, 2019), shows the testing commitment for SB5 DP. Storage of samples will be at real-time conditions of 5 ± 3 °C.

Table 1: Post-approval Stability Plan for SB5 DP

Category	Test Item		Shelf Life Acceptance Criteria	Time Points (Month) Shelf Life: 36 Months[a]	(b) (4)
General test	Appearance	Clarity	(b) (4)	0[c], 3, 6, 9, 12, 18, 24, 36	
		Color		0, 3, 6, 9, 12, 18, 24, 36	
		Visible particles		0, 3, 6, 9, 12, 18, 24, 36	
	pH			0, 3, 6, 9, 12, 18, 24, 36	
Quantity	Protein concentration (A_{280})			0, 3, 6, 9, 12, 18, 24, 36	
Biological activity	Competitive inhibition binding assay to TNF-α by FRET			0, 3, 6, 9, 12, 18, 24, 36	
	TNF-α neutralization by NF-κB reporter gene			0, 3, 6, 9, 12, 18, 24, 36	
Purity and impurity	SE-HPLC			0, 3, 6, 9, 12, 18, 24, 36	
	CE-SDS (non-reducing)	%Total purity		0, 3, 6, 9, 12, 18, 24, 36	
		%2H1L			
	icIEF	%Acidic		0, 3, 6, 9, 12, 18, 24, 36	
		%Main			
		%Basic			
Safety	Container closure integrity[d]			12, 24	
	Sterility[e]			0, 36	
	Particulate matter			0, 3, 6, 9, 12, 18, 24, 36	

[a] Post-approval stability plan if the approved shelf life is 36 months. (b) (4)
[c] Data from release testing will be used for the initial time point.
[d] CCIT will be performed annually, except at the initial time point and at the end of shelf life, where the sterility of SB5 DP will be demonstrated by the sterility test.
[e] The sterility test will be performed at the initial time point, and at the end of shelf life.

The annual testing for the AI presentation also includes the following tests.

Table 2: Post-approval Functional Stability Plan for SB5 AI

Test Item	Shelf Life Acceptance Criteria	Time Points (Month) Shelf Life: 36 Months[a]	(b) (4)
Deliverable volume	(b) (4)	0[c], 12, 24, 36	
Needle extension		0, 12, 24, 36	
Injection time		0, 12, 24, 36	

[a] Post-approval stability plan if the approved shelf life is 36 months. (b) (4)
[c] Data from release testing will be used for the initial time point.

The Sponsor does not propose additional functionality testing beyond release to include on stability for the Safety PFS (see also section *3.2.P.5.1 Specifications*).

Assessor's Comment: The Sponsor updated the stability protocol for Nude PFS SB5 DP to match ICH recommended testing frequency, and the testing frequency is now acceptable. An assessment of the specifications for both release and stability is found in Section 3.2.P.5.1., as well as in Section 3.2.S.4.1 of the DS assessment memo for assessment of shared specifications. The adequacy of functional stability testing is deferred to CDRH. Stability testing for sterility and CCIT is deferred to DMA assessment.

3.2.P.8.3 Stability Data

DP Stability Results

The Sponsor provides the tabular data for stability testing of the three clinical DP lots, the three (b) (4) PVR lots, a pilot lot TR (b) (4)-003611, and six PVR lots from (b) (4). These lots were tested at real-time conditions of 5 ± 3 °C, accelerated conditions of 25 ± 2 °C/60 ± 5% RH, and stressed[5] conditions of 40 ± 2 °C/75 ± 5 %RH. The three clinical lots produced at (b) (4) and Pilot lot TR- (b) (4)-003611 have available testing results completed to 36 months at real-time conditions. The ongoing (b) (4) PVR stability testing include test results out to 24 months of real time for three lots. The PVR batches from (b) (4) have 3-6 months of available real-time data. All testing results of accelerated conditions were available for 3-6 months, and all stressed condition testing results were tested to their 3-month completion.

The stability data for clinical lot 019A14, completed out to 36 months, are shown in Table 3 below copied from the Sponsor as a representative example of stability data at real-time conditions.

Table 5: SB5 Clinical DP (007K13): Stability Data at Long Term Condition (5 ± 3°C, Completed)

Category	Test Item	Initially Proposed Acceptance Criteria	0[a] month	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
General test	Appearance: Colour	(b) (4)	B8 ≤ sample < B7	B7 ≤ sample < B6	B7 < Sample < B6	B8 ≤ Sample < B7	Water < Sample < B9	Water < Sample < B9	Water < Sample < B9	B9 < Sample < B8	B7 ≤ sample < B6	B7 ≤ sample < B6
	Appearance: Clarity		19	18	18	17	17	18	17	11	17	16
	Appearance: Visible particles		Con-forms	Con-forms	Con-forms	Con-forms	Con-forms	Con-forms	Con-forms	Con-forms	Con-forms	Con-forms
	pH		5.3	5.3	5.2	5.2	5.3	5.3	5.2	5.3	5.2	5.2
Quantity	Protein concentration (A_{280})		49.3	50.3	49.0	49.9	49.1	49.6	49.4	50.2	49.7	50.5
Purity and impurity	SE-HPLC		0.2	0.2	0.2	0.3	0.3	0.3	0.4	0.5	0.5	0.6
	CE-SDS (non-reducing)		95.2	96.0	96.0	96.3	96.6	96.3	96.3	96.2	96.6	96.0
			3.0	2.0	2.2	2.1	1.9	2.0	2.0	2.0	2.0	2.2
	icIEF		20.8	24.7	22.6	27.3	23.2	23.1	25.6	25.6	25.1	25.3
			69.5	65.7	68.2	63.3	67.7	67.9	65.1	64.6	66.0	64.9
			9.7	9.6	9.2	9.4	9.1	9.0	8.8	9.9	8.9	9.8
Biological activity	Competitive inhibition binding assay to TNF-α by FRET		92	92	98	97	102	89	100	113	91	100
	TNF-α neutralisation assay by NF-kB reporter gene		108	108	98	102	94	99	94	100	95	100
Safety	Particulate matter		1,448	1,290	2,019	1,043	1,559	1,468	1,999	1,211	1,342	1,364
			16	12	21	11	20	36	40	28	10	14
	Endotoxin		< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5
	Container closure integrity		N/S	N/S	N/S	N/S	N/S	Pass	N/S	N/S	N/S	N/S
	Sterility		No growth	N/S	N/S	N/S	N/S	N/S	N/S	No growth	No growth	No growth
Additional test	CEX-HPLC		22.5	23.3	22.7	23.8	23.7	23.4	24.1	22.8	26.0	26.7
			68.2	67.6	68.0	67.3	67.6	66.8	66.4	70.0	64.4	62.7
			9.3	9.1	9.3	8.9	8.7	9.8	9.5	7.3	9.6	10.6

[5] (b) (4) PVR lots 030G15 and 029G15 do not include stressed stability testing

Category	Test Item	Initially Proposed Acceptance Criteria	0[a] month	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
	Oxidation	(b) (4)	0.2	0.4	2.9	0.1	1.5	1.2	0.2	0.2	0.2	0.3
			N/D	0.1	1.4	N/D	0.8	0.7	N/D	0.1	0.4	N/D
			2.9	4.0	6.4	3.7	8.5	5.5	5.7	7.2	5.2	4.8
			N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D	N/D
			N/D	N/D	1.5	N/D	0.9	0.6	N/D	N/D	N/D	N/D
	Sub-visible particles		12,141	10,890	14,018	12,187	11,853	10,994	13,676	10,932	16,639	12,584
			6,376	5,378	8,167	5,764	5,991	5,787	6,237	4,006	6,655	6,405
			2,429	2,099	3,426	1,879	2,438	2,352	3,109	1,812	2,435	2,460

[a] Data from release testing was used for the initial stability time point for SB5 clinical DP.

Assessor Comment: The available real-time data from four lots, including clinical lots, indicate that the product remains stable for out to 36 months, however only 24 months of stability data are available for lots manufactured using the commercial process at (b) (4) *and up to 6 months of data from the commercial process at* (b) (4)*. The comparability established between* (b) (4) *DP lots (both clinical and PVR) and* (b) (4) *DP lots supports that* (b) (4) *DP should have comparable stability to* (b) (4) *lots. The comparability assessment is assessed in Section 3.2.P.2.3.2. The three* (b) (4) *clinical DP lots tested to 36 months each derived from a different DS batch, so they represent unique process material. The levels of acidic variants in icIEF and CEX-HPLC, as well as oxidized Met256 increase under accelerated and stressed conditions. However, the trend is comparable for SB5 lots from both* (b) (4)*. This supports the expectation that* (b) (4) *clinical lots with their 36 months of real-time data can support a dating period of 36 months from a product quality perspective. Other available data provided in the submission from ongoing studies support the stability of SB5 to date of testing available. Establishing the dating period using results from stability studies with material manufactured using a representative process and in representative containers is consistent with ICH Q5C. ICH Q5C also encourages requesting stability updates during the review cycle when a complete data set from material manufactured using the commercial process are not included in the initial submission. Therefore, we will request a stability update and make a final recommendation on the dating period in an addendum to this memo.*

Additional Stability Testing

The Sponsor tested stability under other conditions, including photostability, patient convenience stability study, and temperature cycling.

Assessor's Comment: Photostability testing exposed samples to at least 1.2 million lux hours of cool white fluorescent lamp light and at least 200 watt hours/square meter of near ultraviolet lamp light at 25 °C. Control samples were wrapped in aluminum foil to protect from light, or for one study the sample was left in commercial secondary packaging to demonstrate the effectiveness of packaging to protect from effects of light. The photostability results for (b) (4) *lots 002K13 (clinical) and 028G15 (PVR) and* (b) (4) *PVR lot SB5PV05 had similar results. The results show that light exposure increases HMW species in SEC-HPLC, reduced purity by NR CE-SDS, increases oxidized Met256, and increases acidic forms by icIEF and CEX-HPLC. The commercially packed sample from 028G15 had similar results to the dark control and mitigated the impact of light exposure (Table 24). This supports that the commercial*

packaging will protect from effects of light. The label indicates to store in carton until use to protect from light, which is appropriate.

The SB5 product quality attributes were resilient to stress from short-term temperature cycling, with no significant differences between treated and control samples. Testing included three cycles, with each cycle exposing samples to 48 hours at 30 °C followed by 48 hours at -5 °C.

The patient convenience study tested the stability of SB5 after real-time storage for 24 or 36 months followed by two and four weeks or storage at 25 ± 2 °C/60 ± 5% RH. The results support the label claim that product left at room temperature for 14 days can be used, even if it at the end of shelf-life.

Supply Chain Cycling Study

The following table describes the study design for the supply chain cycling study.

Table 13: Supply Chain Cycling Study Design for SB5 PVR DP

Description	Temperature (°C)	Exposure Time
Low temperature excursion	(b) (4)	5 days
Normal shipping temperature		20 days
Manufacturing (DP filling/visual inspection/assembly/label/pack), pack out, receipt time, end user time		23 days
High temperature excursion		12 hours

Assessor's Comment: The SB5 product quality did not exhibit changes in product quality attributes measured compared to baseline levels (Table 22). The data support that SB5 product would be resilient to potential temperature excursions that might occur during shipping.

DP Functional Stability Study Conditions and Testing Schedule

Functional stability of the Safety PFS and AI are also being performed. The study designs are similar for Safety PFS and AI. Each design has four studies, two are accelerated and two are long-term. Study 1 applies accelerated conditions (45 ± 2ºC/19.8 ± 5% RH for Safety PFS or 45 ± 2ºC/50 ± 10% RH for AI) to an assembled AI or Safety PFS to simulate storage equivalent of out to three years. Study 2 tests functionality of the device at timepoints out to 48 months in real-time at long-term storage conditions. Study 3 and Study 4 represent worst case where the device components are aged to their 2-year limit and then tested for functionality out to 48 months after assembly of the device. The aging is simulated for Study 3 and done in real-time for Study 4. The estimation of simulated aging of packaging components is based on extrapolation guidelines from ASTM-F1980, and involves treatment of components with a higher temperature than intended storage temperature.

Assessor's Comment: The study results are assessed by CDRH. The CDRH assessor communicated that the data can support a 36-month shelf life for the device components.

Appendix

Information Requests related to Drug Product Quality are listed below. Requests from other disciplines from the same information request are not shown.

Information Request Sent October 5, 2018

2. Regarding your release and shelf life specifications for Drug Substance (DS) and Drug Product (DP), we have the following preliminary comments:

a. For purity by SE-HPLC, you propose to monitor only %HMW (b) (4) for both release and stability. This approach is inadequate. Propose numerical acceptance criteria for main peak and low molecular weight impurities, where appropriate.

b. For purity by icIEF you propose to monitor %acidic, % main and %basic. However, you did not establish acceptance criteria for pI of the main peak. Update the acceptance criteria for purity by icIEF to include pI values for the main peak.

c. For purity by CE-SDS (non-reduced) you propose to monitor %Total purity (b) (4) and %2H1L (b) (4), but do not provide specifications for other impurities such as LC, HC, HL, and HH. Propose acceptance criteria for these various impurities or provide a justification why these impurities are not specified.

Information Request Sent October 17, 2018

We are currently reviewing your control strategy for SB5 drug substance and drug product under BLA 761059. To facilitate the Agency's assessment of your drug substance and drug product process control strategies, provide a table with the following information for each of your process parameters and IPCs:

- Unit operation
- Parameter and in-process control name
- Classification (CPP, KPP, non-CPP/KPP, IPC)
- Justification for parameter classification
- Proposed acceptance range for the commercial manufacturing process
- Acceptable range determined during process development studies (if applicable)
- Range evaluated during commercial-scale process validation
- Justification of the proposed acceptance range

Information Request Sent February 4, 2019

We are reviewing Module 3.2.P in BLA 761059. We request the following information. Provide responses by February 12, 2019.

1. Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls is incomplete because it lacks sufficient information regarding the manufacturing process description and controls. We provide below examples of the type of information that should be included in the updated section; however, this

list in not comprehensive and provides only some specific examples of the information to be included in this section.

(b) (4)

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Susan Kirshner

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Tracy Denison

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 03/22/19
To: Administrative File, STN 761059/0
From: Viviana Matta, Consumer Safety Officer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: 2046
Applicant: Samsung Bioepis Co., Ltd.
Mfg Facility: Drug Substance: (b) (4)
Drug Product: (b) (4)
Product: Hadlima and Hadlima Pushtouch (adalimumab/SB5)
Dosage: 40mg / Single-dose pre-filled syringe, autoinjector
Indication: For the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps)
Due Date: 07/23/19

Recommendation: The proposed manufacturing and testing sites are recommended for approval from a facilities assessment standpoint for the (b) (4) inspection of the (b) (4)), for the 11/12/18 to 11/14/18 inspection of the Samsung Bioepis Co., Ltd. (FEI: 3010031951), and for the (b) (4) inspection of the (b) (4)

SUMMARY

The subject BLA proposes manufacture of adalimumab (SB5) Drug Substance and Hadlima and Hadlima Pushtouch Drug Product at the following facility.

(b) (4) is responsible for DS manufacturing. A PLI was conducted from (b) (4). This inspection was a system-based covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 6-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection for the following:

(b) (4)

(b) (4)

The inspection was classified as VAI. *The facility and inspection recommendation is approve. Proposed corrective actions appear adequate.*

Samsung Bioepis Co., Ltd. (FEI: 3010031951) in South Korea is responsible for DS Drug substance QC in-process testing on (b) (4). A PLI was conducted from 11/12/2018 to 11/14/2018 in order to assess the analytical similarity data at the site. The pre-approval inspection covered the in-process testing of adalimumab drug product. The profile covered was CTL. No Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. *The facility and inspection recommendation is approve. Proposed corrective actions appear adequate.*

(b) (4) is responsible for DS QC in-process testing. Last inspection was completed (b) (4) and was a surveillance inspection. Inspectional coverage included the Quality System, Laboratory Control System and at the conclusion of the inspection, a two item FDA-483, Inspectional Observations form, was issued for inadequate electronic records and backup system management. Inspection was classified as VAI. The laboratory system is acceptable. *The facility review recommendation is approve.*

(b) (4) is responsible for DP manufacturing. A PLI was conducted from (b) (4). This inspection was a system-based covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 6-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection for the following:

(b) (4)

Reference ID: 4466647

(b) (4)

The initial recommendation was withhold. *The facility and inspection EIR review recommendation is approve and the PLI is classified as VAI. Proposed corrective actions appear adequate.*

(b) (4) is responsible for DS QC stability testing. Last inspection was completed (b) (4) and was a surveillance inspection. Inspectional coverage included the Quality System and Laboratory Control System. The profile covered was CTL. No Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. *The facility review recommendation is approve.*

(b) (4) is responsible for DS QC release testing. Last inspection was completed (b) (4) and was a surveillance inspection. Inspectional coverage included the Quality, Laboratory and Facility and Equipment Systems. The profile covered was CTL. No Form FDA 483, Inspectional Observations, was issued to the firm at the end of the inspection. *The facility review recommendation is approve.*

(b) (4) is responsible for DS QC release testing. Last inspection was completed (b) (4) and was a surveillance and pre-approval inspection. The inspection covered the Quality System and Laboratory System. Profile class covered was CTL. No Form FDA 483, Inspectional Observations, was issued to the firm at the end of the inspection. *The facility review recommendation is approve.*

(b) (4) is responsible for release and stability testing for functionality of auto-injector. Last inspection was completed (b) (4) and was a surveillance and pre-approval inspection. Medical device areas covered during this inspection were the following: Management Controls, CAPA, MDR, Purchasing Controls, and Production and Process controls. For drug areas labeling and storage were covered which involved the Quality and Materials systems. At the close of the inspection an FDA 483, Inspectional Observations form, was issued for the following deficiency: Management with executive responsibility has not reviewed the suitability and effectiveness of the quality system at defined intervals. Inspection was classified as VAI. The site has an acceptable profile (PRF) for kit assembler. *The facility review recommendation is approve.*

The facility descriptions submitted in this BLA have been reviewed and are approved. Facility and inspection EIR reviews determined the sites are adequate to support the manufacture and/or testing of adalimumab Drug Substance and Hadlima and Hadlima Pushtouch Drug Product.

ASSESSMENT

Reference ID: 4466647

DRUG SUBSTANCE
3.2.S.2.1 Manufacturers

The proposed adalimumab DS manufacturing, storage, release testing, and stability testing sites are listed below in Table 1.

Table 1. Adalimumab Drug Substance Facility

Site Name	Address	FEI	Responsibilities
(b) (4)			Drug substance manufacturer
Samsung Bioepis Co., Ltd.	107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Korea, Republic Of	3010031951	Drug substance QC in-process testing (b) (4)
(b) (4)			Drug substance QC in-process testing (b) (4)

Review comment: The facilities for the manufacturing, storage, release testing, and stability testing for the adalimumab drug substance are adequately described.

—Satisfactory—

<u>Facility Inspection:</u>

Prior Inspection History

(b) (4) is responsible for DS manufacturing. The last inspection was a pre-approval inspection conducted (b) (4). The following systems were covered: Quality, Production, Materials, Facilities and Equipment, Laboratory Controls, Packaging and Labeling. CBI profile was covered. A 3-item Form FDA 483, Inspectional Observations, was issued to the firm at the end of the inspection for the following: (b) (4) The inspection was classified as VAI and approval was recommended for the pending application. *PLI was requested.*

Reference ID: 4466647

Samsung Bioepis Co., Ltd. (FEI: 3010031951) in South Korea is responsible for DS Drug substance QC in-process testing (b) (4). The last inspection was conducted 03/07/2018 and was a pre-approval inspection. CTL profile was covered. No Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. The inspection was classified as NAI and approval was recommended for the pending application. *A PLI was requested. in order to assess the analytical similarity data at the site.*

(b) (4) is responsible for DS QC in-process testing. Last inspection was completed (b) (4) and was a surveillance inspection. Inspectional coverage included the Quality System, Laboratory Control System and at the conclusion of the inspection, a two item FDA-483, Inspectional Observations form, was issued for inadequate electronic records and backup system management. Inspection was classified as VAI. The laboratory system is acceptable. *PLI was not requested.*

Current PLI Outcome

(b) (4) is responsible for DS manufacturing. A PLI was conducted from (b) (4). This inspection was a system-based covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 6-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection for the following:

(b) (4)

The initial recommendation was VAI. *The facility and inspection recommendation is approve. Proposed corrective actions appear adequate.*

Samsung Bioepis Co., Ltd. (FEI: 3010031951) in South Korea is responsible for DS Drug substance QC in-process testing (b) (4). A PLI was conducted from (b) (4). The pre-license inspection covered the in-process testing of adalimumab drug product. The profile covered was CTL. No Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. The initial recommendation was

Reference ID: 4466647

NAI/approve. *The facility and inspection recommendation is approve. Proposed corrective actions appear adequate.*

Review comment: The compliance status of the facilities associated with the manufacture of adalimumab drug product is approve.

—Satisfactory—

3.2.A.1 Facilities and Equipment

Facility Overview and Adalimumab Manufacturing Areas

(b) (4)

[redacted]

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Reference ID: 4466647

(b) (4)

[redacted]

—Satisfactory—

DRUG PRODUCT

3.2.P.2.1 Manufacturers

The manufacturing, storage, release testing, and stability testing for the Hadlima and Hadlima Pushtouch drug product is shown in Table 2.

Table 2. Hadlima and Hadlima Pushtouch Drug Product Facility

Site Name	Address	FEI	Responsibilities

Reference ID: 4466647

(b) (4)	Drug product manufacturer
	Drug product QC stability testing (endotoxin and microbial enumeration)
	Drug product QC release testing (all tests excluding appearance, protein concentration, endotoxin, and microbial enumeration) Drug product stability testing (all tests)
	Drug product QC release testing (all tests excluding appearance, protein concentration, endotoxin, and microbial enumeration) Stability testing (all tests except endotoxin and microbial enumeration)
	Release test for functionality of AI Functional stability testing of AI (all tests except container closure integrity test (CCIT))

Review comment: *The facilities for the manufacturing, storage, release testing, and stability testing for the Hadlima and Hadlima Pushtouch drug product are adequately described*

—Satisfactory—

Prior Inspection History

Reference ID: 4466647

(b) (4) is responsible for DP manufacturing. The last inspection was a pre-approval inspection completed 0 (b) (4). Profile classes SVS and IDD were covered. The inspection covered the Laboratory Control, Quality, Facilities and Equipment, and Production systems. The inspection concluded with a four-item FDA-483 for the following observations: (b) (4)

(b) (4) is responsible for DS QC stability testing. Last inspection was completed (b) (4) and was a surveillance inspection. Inspectional coverage included the Quality System and Laboratory Control System. The profile covered was CTL. No Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection. *PLI was not requested.*

(b) (4) is responsible for DS QC release testing. Last inspection was completed (b) (4) and was a surveillance inspection. Inspectional coverage included the Quality, Laboratory and Facility and Equipment Systems. The profile covered was CTL. No Form FDA 483, Inspectional Observations, was issued to the firm at the end of the inspection. *PLI was not requested.*

(b) (4) is responsible for DS QC release testing. Last inspection was completed 0 (b) (4) and was a surveillance and pre-approval inspection. The inspection covered the Quality System and Laboratory System. Profile class covered was CTL. No Form FDA 483, Inspectional Observations, was issued to the firm at the end of the inspection. *PLI was not requested.*

(b) (4) is responsible for release and stability testing for functionality of auto-injector. Last inspection was completed (b) (4) and was a surveillance and pre-approval inspection. Medical device areas covered during this inspection were the following: Management Controls, CAPA, MDR, Purchasing Controls, and Production and Process controls. For drug areas labeling and storage were covered which involved the Quality and Materials systems. At the close of the inspection an FDA 483, Inspectional Observations form, was issued for the following deficiency: (b) (4) Inspection was classified as VAI. The site has an acceptable profile (PRF) for kit assembler. *PLI was not requested.*

The facility descriptions submitted in this BLA have been reviewed and are approved. Facility and inspection EIR reviews determined the sites are adequate to support the manufacture and/or testing of adalimumab Drug Substance and Hadlima and Hadlima Pushtouch Drug Product.

Reference ID: 4466647

Current PLI Outcome

(b) (4) is responsible for DP manufacturing. A PLI was conducted from (b) (4). This inspection was a system-based covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 6-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection for the following:

(b) (4)

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Reference ID: 4466647

(b) (4)

[redacted]

Review comment: The compliance status of the facilities associated with the manufacture of adalimumab drug product is approve.

—Satisfactory—

3.2.A.1 Facilities and Equipment

Facility Overview

(b) (4)

[redacted]

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(b) (4)

—Satisfactory—

Conclusion:

Adequate description was provided for the following sites proposed for adalimumab DS and DP manufacture: (b) (4)

The proposed manufacturing and testing site are recommended for approval from a facilities assessment standpoint (b) (4)

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Viviana Matta
Consumer Safety Officer
OPF Division of Inspectional Assessment Branch 1

Zhihao Qiu -S

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Zhihao (Peter) Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment Branch 1

Reference ID: 4466647

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: **3/21/2019**
To: Administrative File, **STN 761059/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead, CDER/OPQ/OPF/DMA/Branch IV
Subject: New 351(k) Biologic License Applications (BLA)
Applicant: Samsung Bioepis Co., Ltd.
US License: **2046**
Facility: (b) (4)
Product: SB5
Dosage: Single-dose pre-filled syringe, autoinjector, 40 mg, subcutaneous injection
Indication: Rheumatoid Arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), adult Crohn's disease (CD), ulcerative colitis (UC), plaque psoriasis (Ps)
BsUFA date: July 23, 2019

Recommendation: The drug substance part of this BLA is recommended for approval from quality microbiology perspective. The hold time validation for (b) (4) will be reviewed in an addendum review memo.

Review Summary

Samsung has submitted this Biologics License Application (BLA) under 351(k) of the Public Health Service Act for SB5, a proposed adalimumab (Humira®) biosimilar. This submission is a resubmission of the original 351(k) application for SB5 which was previously submitted on August 29, 2016 but received refusal-to-file (RTF) on October 28, 2016. The drug substance (DS) is manufactured at (b) (4). The drug product (DP) is manufactured at (b) (4). The application contains CMC information in an eCTD format.

This review contains an assessment of the SB5 drug substance section of the BLA from microbiology perspective. The amendments reviewed are provided in the table below:

Sequence number	Date	Description
0012	7/23/2018	BLA resubmission after RTF
0032	1/25/2019	Response to IR

0044	3/14/2019	Response to IR

Assessment

Drug Substance (3.2.S)

General Information (3.2.S.1)

SB5 is a recombinant human monoclonal antibody manufactured in [redacted] (b) (4) cells. It binds to tumor necrosis factor alpha (TNF-α) and neutralizes/modulates the biological activities of TNF-α. [redacted] (b) (4)

Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1)

Drug substance manufacturing, Drug substance in-process and release testing

[redacted] (b) (4)

Description of Manufacturing Process and Process Controls (3.2.S.2.2) and Controls of Critical Steps (3.2.S.2.4)

[redacted] (b) (4)

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Candau-Chacon

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Jessica Hankins, Ph.D.
Quality Assessment Lead: Reyes Candau-Chacon, Ph.D.

BLA:	761059
Applicant:	Samsung Bioepsis Co, Ltd.
US License Number:	2046
Submission Reviewed:	Original 351k BLA (resubmission after of original 351(k) BLA following refusal-to-file determination by FDA)
Product:	SB5 (proposed biosimilar to U.S. licensed Humira)
Indication:	Rheumatoid arthritis (RA), juvenile iodiopathic arthritis (JIA), psoriatic arthritis (PsA), Chron's disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis
Dosage Form:	Single-dose pre-filled syringe, autoinjector for subcutaneous injection (40 mg)
Manufacturing Sites:	(b) (4)
FDA Receipt Date:	July 23, 2018
Action Date:	July 23, 2019

Conclusion and Approvability Recommendation

The drug product portion of this BLA, as amended, was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for approval. The following postmarketing commitment should be communicated to the applicant.

1. Implement (b) (4) monitoring (b) (4) of the SB5 drug product.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0012	07/23/18	Resubmission of original BLA after resubmission after of original 351(k) BLA following refusal-to-file determination by FDA
0015	09/10/18	Updated Modules of BLA in response to IR
0029	01/10/19	Response to IR
0038	02/21/19	Response to IR
0042	03/08/19	Response to IR

Drug Master Files (DMF) Reviewed

DMF #	DMF Holder	Review Date	Review Number	File Name	Conclusion
(b) (4)		3/1/19	62	(b) (4)	Adequate
		7/12/18	37		Adequate
		10/9/18	7		Adequate
		1/8/18	3		Adequate

Module 1

1.14 Labeling

The drug product (DP) is supplied as preservative-free sterile solution for subcutaneous administration by a single-dose, 1 mL pre-filled syringe (PFS) or by a single-dose autoinjector (AI), which contains the 1 mL PFS. The DP must be refrigerated at 2-8°C.

Module 3.2

P.1 Description and Composition of the Drug Product

The DP is presented as a single-use Safety PFS and a single-use AI containing 0.8 mL of solution (40 mg of DP). The composition of the DP was provided in Table 1 of P.1 (sequence 0015) and includes the DP, sodium citrate dihydrate, citric acid monohydrate, L-Histidine, L-Histidine hydrochloride monohydrate, sorbitol, polysorbate 20, and WFI.

The container closure system (CCS) consists of a 1 mL long clear glass syringe and stainless-steel needle, rigid needle shield, and plunger stopper. The safety PFS consists of the PFS assembled into the secondary packaging components (e.g., safe-shield body, finger flange, and plunger rod). The AI consists of the PFS assembled into the device components. Refer to section 3.2.P.7 for additional information on the PFS.

Reviewer comment: The primary packaging for the DP is a pre-filled syringe (PFS). The components in direct contact with the DP are the (b) (4) *glass syringe barrel,*

Reference ID: 4466647

stainless steel needle, and rubber plunger stopper. The syringe and plunger stopper are reviewed below in section 3.2.P.7.

SATISFACTORY

P.2 Pharmaceutical Development

(b) (4)

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Reyes Candau-Chacon

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