**Medical Officer's Review of BLA 761054**
**Division of Dermatology and Dental Products**

**Type:** Biosimilar 351(k)
**Serial Amendment:** 000
**Supporting Document Number:** 001

**Correspondence date:** 21-MAR-2016
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**Review Date:** 16-DEC-2016

**Applicant:** Samsung Bioepis
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**Drug:** RENFLEXIS (SB2)[1] a proposed biosimilar to US-licensed Remicade (infliximab)
**Route of Administration:** Intravenous
**Strength and Dosage Form: For injection,** 100mg/vial Powder for reconstitution
**Pharmacologic Category:** Anti-human tumor necrosis factor alpha (TNFα) human-murine immunoglobulin G1 (IgG1) monoclonal antibody
**Proposed Indications:**

1) Crohn's Disease (CD):
    - reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
    - reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.
2) Pediatric Crohn's Disease:
    - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
3) Ulcerative Colitis (UC):
    - reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
4) Pediatric Ulcerative Colitis:
    - reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.[2]
5) Rheumatoid Arthritis (RA) in combination with methotrexate:

[1] Renflexis has been developed as a proposed biosimilar to US-licensed Remicade (infliximab). Since the proper name for Renflexis has not yet been determined, SB2 is used throughout this review in place of the nonproprietary name for this product.
[2] We note that Remicade's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. Accordingly, FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

- reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.

6) Ankylosing Spondylitis (AS):
   - reducing signs and symptoms in patients with active disease
7) Psoriatic Arthritis (PsA):
   - reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.
8) Plaque Psoriasis (PsO):
   - treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

**Project Manager:** Paul Phillips
**Team Leader:** David Kettl, MD
**Medical Officer:** Gary Chiang, MD, MPH.

**Executive Summary:**

The Division of Dermatology and Dental Products (DDDP) has concluded that the applicant's 351(k) BLA for the proposed drug product RENFLEXIS (SB2), a proposed biosimilar to US-licensed Remicade (infliximab), provides adequate scientific justification to support extrapolation of data, including clinical data from the studied populations, to support approval of SB2 for the indication sought under the dermatology review purview (plaque psoriasis).

The dermatology indications were not directly studied in the SB2 clinical program. For additional information on the indications evaluated in this application, please refer to the clinical review from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), the review memo from the Division of Gastrointestinal and Inborn Errors Products (DGIEP), or the Cross-Discipline Team Leader (CDTL) review for details of the submitted application.

**Introduction:**

Samsung Bioepis is developing SB2 as a proposed biosimilar to US-licensed Remicade. Remicade was licensed in the United States (US) in 1998. Remicade is also licensed in many countries worldwide, including the European Union (EU) via the Centralized Procedure.

SB2 is a chimeric human-murine immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to human tumor necrosis factor alpha (TNFα). The active substance is a glycoprotein with 1 N-linked glycosylation site in the CH2 domain of each heavy chain. Each heavy chain consists of 450 amino acids with 11 cysteine residues,

and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteines in the heavy and light chains are involved in either intra- or inter- disulfide bonding.

The results from primary structural analysis showed that the molecular weights (MWs), N-terminal and C-terminal sequences, peptide maps, disulfide bonds, levels of free thiol group, and N-linked glycosylation site were similar between SB2 and US-licensed Remicade. During C-terminal sequencing, SB2 was found to possess a lower C-terminal lysine content and a higher C-terminal α-amidated proline content compared to the US Remicade. However, C-terminal lysine content does not affect the efficacy of infliximab products.

As part of the totality of the evidence for a demonstration of biosimilarity, the clinical development program for SB2 was designed to support a demonstration that no clinically meaningful differences exist between SB2 and the reference product, US-licensed Remicade in terms of its pharmacokinetics, efficacy, safety, and immunogenicity. The following two controlled studies provided the primary evidence to support the determination of no clinically meaningful differences between SB2 and the reference product, US-licensed Remicade:

- Study SB2-G11-NHV is a randomized, single-blind, three-arm, parallel group, single-dose study to compare the PK, safety/tolerability and immunogenicity of SB2, US-licensed Remicade, and EU-approved Remicade in healthy subjects. The study demonstrated similarity of PK between SB2, US-licensed Remicade, and EU-approved Remicade, and supported the PK element of the scientific bridge between SB2, US-licensed Remicade and EU-approved Remicade. This scientific bridge between the products is necessary to justify the relevance of comparative data generated using EU-approved Remicade to support a demonstration of biosimilarity of SB2 to US-licensed Remicade.
- Study SB2-G31-RA is a randomized, double-blind, parallel-group, multicenter study to evaluate the efficacy, safety/tolerability and immunogenicity of SB2 compared to EU-approved Remicade. This clinical study is the comparative clinical study that provides the efficacy and safety data of SB2 in subjects with moderate to severe rheumatoid arthritis (RA) despite MTX therapy, to support a demonstration of no clinically meaningful differences.

Additional long-term safety and immunogenicity data for patients who underwent a single transition at week 54 from EU-approved Remicade to SB2 or continued to receive SB2 came from study SB2-G31-RA, which collected data up to 78 weeks.

**Extrapolation to Plaque Psoriasis:**

Samsung Bioepis is seeking licensure for the indications studied in the clinical program, RA, as well as for ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, adult and pediatric Crohn's disease, and adult and pediatric ulcerative colitis[2] which were not directly studied in the clinical program. To support the use of SB2 for the non-studied

indications, Samsung Bioepis has provided adequate scientific justification for the extrapolation of biosimilarity to those indications.

The justification addresses the issues for the testing and extrapolation to conditions of use outlined in Guidance for Industry: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009."

As described in the guidance, if a biological product meets the statutory requirements for licensure as a biosimilar biological product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity and potency in an appropriate condition of use, the applicant may seek licensure for one or more additional conditions of use for which the reference product (i.e., US-licensed Remicade) is licensed.[3] However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.

Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action (MOA) in each condition of use for which licensure is sought
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations
- The immunogenicity of the product in different patient populations
- Differences in expected toxicities in each condition of use and patient population
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought

As further described in FDA guidance, differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity.

Consistent with the principles outlined in the above FDA guidance, Samsung Bioepis has provided sufficient justification to extrapolate data, including data from the comparative clinical studies of SB2 in RA, to support a determination of biosimilarity for the plaque psoriasis indication for which US-licensed Remicade is licensed.
Considerations specific to plaque psoriasis include:

- The primary mechanism of action (MOA) of US-licensed Remicade is direct binding and blocking of TNF receptor-mediated biological activities. US-licensed Remicade binds to both soluble (s) and transmembrane (tm) TNF, thus blocking TNF binding to its receptors TNFR1 and TNFR2 and the resulting downstream

[3] Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015
http://www fda.gov/downloads/Drugs/Guidances/UCM273001.pdf

pro-inflammatory cascade of events. The scientific literature indicates that this MOA is the primary MOA in RA, AS, PsA, PsO. The data provided by Samsung Bioepis for SB2 showed similar TNF binding and potency to neutralize TNFα, supporting the determination of analytical similarity pertinent to this MOA. Therefore, the demonstration of biosimilarity of SB2 to US-licensed Remicade, which included clinical studies in RA, can reasonably be extrapolated to adult patients with chronic severe plaque psoriasis based on common mechanism of action.

- Because similar PK was demonstrated between SB2 and US-licensed Remicade, a similar PK profile would be expected for SB2 in adult patients with chronic severe plaque psoriasis.

- As reported in the US-licensed Remicade labeling, the immunogenicity of US-licensed Remicade is generally affected by the use of concomitant immunosuppressive therapy across different indications rather than by patient population, and the results were influenced by the type of immunoassay used. In plaque psoriasis the recommended dose is 5 mg/kg. US-licensed Remicade is used without methotrexate in plaque psoriasis. Samsung Bioepis provided adequate bridging data to justify the relevance of comparative data with EU-approved Remicade in the PK healthy subject study and the RA comparative clinical study to support a demonstration of biosimilarity of SB2 to US-licensed Remicade. The applicant provided sufficient data to indicate similar immunogenicity between SB2, US-licensed Remicade, and EU-approved Remicade, including in the setting a repeat dosing in patients with RA. Accordingly, similar immunogenicity would be expected between SB2 and US-licensed Remicade in plaque psoriasis.

- No differences in expected toxicities that are relevant to the plaque psoriasis population were noted between the SB2 product and the EU-approved Remicade arms in the comparative clinical study.

- Based on the above considerations, the Division concluded that it is reasonable to extrapolate data, including clinical data, submitted by the applicant to support a demonstration of biosimilarity of SB2 in plaque psoriasis.

**Overall Conclusion:**

The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires a demonstration that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the proposed biosimilar product and the reference product in terms of the safety, purity and potency of the product.

This review by DDDP of the applicant's 351(k) BLA has determined that the applicant has provided adequate justification to support extrapolation of data, including clinical data from RA, to support approval of SB2 for the following indication: the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

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12/16/2016

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