

## Medical Officer Review

### Division of Gastroenterology & Inborn Errors Products

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**Application Type and Number:** 351(k) BLA 761054

**Applicant:** Samsung Bioepis Co.

**Date of Submission:** 3/21/2016

**PDUFA Goal Date:** 1/21/2017

**DGIEP Clinical Reviewer:** Tara Altepeter, MD

**DGIEP Clinical Team Leader:** Jessica J. Lee, MD MMSc

**DGIEP Division Director:** Shari Targum, MD

**Date Review Completed:** 12/22/2016

**Drug:** SB2 / “Renflexis” (a proposed biosimilar to US licensed Remicade (infliximab))

**Drug Class:** TNF- $\alpha$  antagonist

**Dosage Form/Presentation:** Sterile lyophilized powder in a 20ml capacity vial / 100mg per vial

**Route of Administration:** Intravenous infusion

**Proposed Indications:** Crohn’s disease, pediatric Crohn’s disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis

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## 1 Introduction

On March 21, 2015, Samsung (the applicant) submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for SB2, a proposed biosimilar to US-licensed Remicade (infliximab). US-licensed Remicade (US-Remicade) (BLA103772) received marketing approval in the U.S. on August 24, 1998 and its license is currently held by Janssen Biotech, Inc.

This application (BLA761054) was submitted to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for review. The application included three-way analytical similarity studies between US-Remicade, EU-approved Remicade (EU-Remicade) and SB2; in-vitro and in-vivo nonclinical studies between US-Remicade, EU-Remicade, and SB2; a pharmacokinetic, safety/tolerability and immunogenicity similarity study in healthy subjects (SB2-G11-NHV); and a single randomized, double blind, parallel group comparative clinical study to assess the efficacy, safety/tolerability and immunogenicity of SB2, compared to EU-Remicade, in patients with moderate to severe rheumatoid arthritis (SB2-G31-RA). As a part of the collaborative review process of this application, this memorandum provides DGIEP’s assessment on the justification for extrapolating data, including clinical safety and efficacy data from studies of RA patients, to support approval of SB2 for the inflammatory bowel disease (IBD) indications (which include Crohn’s disease (CD), pediatric Crohn’s disease, ulcerative colitis (UC) and pediatric ulcerative colitis<sup>1</sup>). The reader is referred to the primary clinical review by Dr. Juwaria Waheed (DPARP), and the CDTL memo by Dr. Nikolay Nikolov for detailed review of the submitted clinical studies in patients with rheumatoid arthritis (RA).

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<sup>1</sup> The reviewer notes that Remicade’s indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. Accordingly, FDA will not be able to license SB2 for this indication until the orphan exclusivity expires.

## 2 Extrapolation of Existing Data to Support Biosimilarity to IBD indications

The applicant seeks licensure for the same indications for which US-Remicade is licensed (Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis). If a proposed product meets the statutory requirements for licensure as a biosimilar 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 is licensed.<sup>2</sup> However, the applicant would need to provide sufficient scientific justification for extrapolating data, including clinical data, to support a determination of biosimilarity for each condition of use for which licensure is sought. Hence, it is potentially acceptable for the applicant to conduct a clinical study only in RA patients to support licensure for additional indications that the reference product is licensed for (including IBD indications), provided that adequate scientific justification is included. The scientific justification for extrapolation should address the following issues as described in the FDA guidance<sup>2</sup>:

- 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 and efficacy of the product in each condition of use and patient population for which licensure is sought.

As discussed below, the mechanisms of action of infliximab that are relevant to RA (the clinical study population) are also relevant to IBD, which supports extrapolation to these indications.

### 1. Mechanism of Action

The primary mechanism of action of infliximab is to neutralize the biological activity of tumor necrosis factor alpha (TNF- $\alpha$ ) by binding to the soluble and transmembrane forms of TNF- $\alpha$  and inhibit binding of TNF- $\alpha$  with its receptors.<sup>3</sup> Similar to the studied indication (RA), TNF- $\alpha$  plays a central role in the pathogenesis of IBD, and TNF- $\alpha$  inhibition is important in treating the disease, as evidenced by the efficacy of the approved TNF- $\alpha$  monoclonal antibodies, though the detailed cellular and molecular mechanisms involved have not been fully elucidated.<sup>4</sup> However, the available scientific evidence suggests that for TNF- $\alpha$  inhibitors in IBD, in addition to binding and neutralization of the soluble form of TNF- $\alpha$  (sTNF- $\alpha$ ), other mechanisms of action, listed in Table 1, may play a role.<sup>5</sup> Binding to sTNF- $\alpha$  and transmembrane TNF- $\alpha$  (tmTNF- $\alpha$ ) involves the fragment antigen-binding (Fab) region of the antibody, while the other plausible mechanisms of action involve the fragment crystallizable (Fc region) region of the antibody.

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<sup>2</sup> FDA Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (April 2015), available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf>

<sup>3</sup> Prescribing Information for Remicade (last revised on October 2, 2015), accessed on August 26, 2016: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/103772s5373lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103772s5373lbl.pdf)

<sup>4</sup> Oikonomopoulos A, et al. "Anti-TNF Antibodies in Inflammatory Bowel Disease: Do We Finally Know How it Works?" *Current Drug Targets* 2013;14:1421-32.

<sup>5</sup> Tracey D, et al. "Tumor necrosis factor antagonist mechanisms of action: A comprehensive review." *Pharmacology & Therapeutics* 2008;117:244-79.

**Table 1: Mechanisms of Action of Infliximab across indications**

MOA of Remicade	RA	AS	PsA	PsO	CD, Pediatric CD	UC, Pediatric UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible
ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; MOA: mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; UC: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF						

(source: FDA table, based on summary of current literature<sup>4,5</sup>)

The Product Quality reviewers determined that the applicant has adequately addressed each of the known and potential mechanisms of action of US-licensed Remicade listed in *Table 1* through the analytical similarity assessment. TNF-α binding and neutralization, believed to be the primary function of infliximab, were demonstrated to be statistically equivalent between SB2 and US-licensed Remicade. Other mechanisms of action, such as reverse signaling, antibody dependent cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), were within the quality range set by the applicant's data on US-Remicade, with no shift in activity evident between the test batches of SB2 and US-Remicade. Refer to the Product Quality review by Xianghon Jing, PhD, for additional detail

Based on review of the data included in the BLA submission, the product quality reviewers have concluded that the applicant provided adequate data to support a conclusion that SB2 is highly similar to US-Remicade. For attributes where there were minor potential differences detected, additional data supports that there are no impacts on function, activity or stability in vitro. This reviewer agrees that the totality of data support a conclusion that SB2 is highly similar to US-Remicade.

## 2. Pharmacokinetics (PK)

The data included in the applicant's BLA submission demonstrated similar PK between SB2, US-licensed Remicade, and EU- Remicade, on the basis of in-vitro assays, as well as in-vivo study in the mouse model. Refer to the clinical pharmacology review by Le Hei, PhD, for additional details.

Data on US-Remicade do not indicate any major differences in PK based on disease state.<sup>3</sup> Therefore, it is reasonable to conclude that PK for SB2 is expected to be similar between RA patients (the studied population) and those with IBD. In addition, it should be noted that the PK of infliximab is also

influenced by immunogenicity. Specifically, the clearance of infliximab has been shown to be higher in patients who developed anti-drug-antibodies (ADA).<sup>3</sup> Similarity in immunogenicity data is discussed below.

### **3. Immunogenicity**

Immunogenicity, measured by the development of anti-drug antibodies (ADA), is an important factor influencing safety and efficacy of anti-TNF  $\alpha$  agents. Immunogenicity data are highly dependent on assay methodology, and may be influenced by sample handling, timing of sample collection, underlying disease and concomitant medication use.<sup>3</sup> Acknowledging these limitations, the immunogenicity data submitted support the determination of similarity between SB2 and the US-Remicade.

In the SB2 development program, immunogenicity assessment was conducted in healthy subjects, as well as RA patients. In the healthy subjects, there was no statistically significant difference in the rates of ADA development post-dose between SB2 and US-Remicade, SB2 and EU-Remicade, or EU-Remicade and US-Remicade. In RA patients receiving concomitant methotrexate therapy, there was no statistically significant difference in the rates of ADA development at Week 30 or Week 54, in patients treated with SB2 or EU-Remicade. Safety outcomes were similar between the SB2 and EU-Remicade treated patients.

As the sponsor has demonstrated similarity in ADA development in both healthy subjects and RA patients, and acknowledging that ADA development is thought to be driven mostly by dose, dosing interval, and concomitant therapies, it is reasonable to conclude that the immunogenicity results support a determination of similarity, and that these data can be extrapolated to the IBD population.

### **4. Toxicity**

In controlled clinical trials that supported approval of the US-licensed Remicade, patients with IBD experienced similar adverse reactions as other indications, including RA. Similar common and serious adverse reactions have been reported across licensed indications and are described in the prescribing information. Since the safety profile of SB2 has been shown to be similar to that of US-licensed Remicade (see Dr. Juwaria Waheed's primary clinical review and Dr. Nikolay Nikolov's CDTL memorandum) and submitted analytical data did not identify reasons to expect differential safety profiles between patient populations, a similar safety profile would be expected for pediatric and adult patients with IBD receiving SB2. Major toxicities of infliximab are serious infections, including tuberculosis and opportunistic infections, and malignancies, which are shared amongst disease populations. Given the similar product quality attributes, PK, and immunogenicity, there is no reason to expect that the safety profile in the IBD population would be different from that demonstrated in RA patients.

## **3 Summary and conclusions**

Consistent with the principles of the FDA Guidance outline above, this reviewer concludes that the applicant has provided sufficient scientific justification (based on the mechanism of action, PK, immunogenicity and toxicity profile) to support extrapolation of data, including clinical data from the studied population (RA patients on concomitant methotrexate therapy), to the inflammatory bowel disease indications.

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/s/  
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TARA A ALTEPETER  
12/22/2016

JESSICA J LEE  
12/22/2016

SHARI L TARGUM  
12/29/2016