STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA NO.:	761054
SERIAL NO.:	0000
DATE RECEIVED BY THE CENTER:	March 21, 2016
DRUG NAME:	SB2 (proposed biosimilar to Remicade, Samsung Bioepis)
DOSAGE FORM:	Lyophilized powder,100 mg/vial
INDICATIONS:	Crohn's Disease (CD), Pediatric Crohn's Disease (Pediatric CD), Ulcerative Colitis (UC), Pediatric Ulcerative Colitis (Pediatric UC), Rheumatoid Arthritis (RA) in combination with methotrexate, Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA) and Plaque Psoriasis (PsO).
APPLICANT:	Samsung Bioepis Inc.
REVIEW FINISHED:	December 12, 2016
NAME OF STATISTICAL REVIEWER:	Yu-Ting Weng
NAME OF PROJECT MANAGER:	Christine Ford

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1 EXECUTIVE SUMMARY AND RECOMMENDATION

The CMC statistics reviewer in the Office of Biostatistics analyzed the comparative results of two critical quality attributes (QAs): TNF-α neutralization assay and TNF-α binding assay, which were recommended for equivalence testing analysis by the Office of Biotechnology Products. Tier 1 statistical equivalence testing was conducted using equivalence margins of $\pm 1.5\sigma_R$, where σ_R represents US-licensed reference product variability or the comparator variability. 10 batches of SB2 (test product) combined 6 batches of Drug Product (DP) and 4 batches of Drug Substance (DS) and 46 batches of US-licensed Remicade (reference product), and 40 batches of EU-approved Remicade were used for equivalence testing of TNF-α neutralization assay (potency). The results are summarized in Table 1.

Table 1. Results of equivalence testing for TNF-α neutralization assay (potency)

Comparison	# of lots	Mean difference, %	90% CI for mean difference, %	Equivalence margin, %	Equivalent
SB2 vs. US	(10, 46)	-3.76	(-7.10, -0.44)	(-9.33, 9.33)	Yes
SB2 vs. EU	(10, 40)	-3.35	(-6.92, 0.22)	(-10.36, 10.36)	Yes
EU vs. US	(40, 46)	-0.41	(-2.79,1.96)	(-9.33, 9.33)	Yes

*The 90% confidence interval (CI) is adjusted by the sample size imbalance.

10 batches combined 6 batches of DP and 4 batches of DS of SB2, 41 batches of US-licensed Remicade, and 37 batches of EU-approved Remicade were included in the TNF-α binding assay dataset for the statistical equivalence testing. The results are shown in Table 2.

Table 2. Results of equivalence testing for TNF-α binding assay

Comparison	# of lots	Mean difference, %	90% CI for mean difference, %	Equivalence margin, %	Equivalent
SB2 vs. US	(10, 41)	-2.11	(-4.49, 0.26)	(-5.90, 5.90)	Yes
SB2 vs. EU	(10, 37)	-2.40	(-5.05, 0.25)	(-7.21, 7.21)	Yes
EU vs. US	(37, 41)	0.29	(-1.38,1.96)	(-5.90, 5.90)	Yes

*The 90% confidence interval (CI) is adjusted by the sample size imbalance.

As shown in Tables 1 and 2, the results from the statistical equivalence testing of TNF-α neutralization assay (potency) and TNF-α binding assay demonstrate that the proposed biosimilar SB2 is highly similar to US-licensed Remicade. In addition, the results support the analytical bridge between US-licensed Remicade and EU-approved Remicade.

2 INTRODUCTION

On March 21, 2016, the applicant (Samsung Bioepis) submitted to the US Food and Drug Administration (FDA) a 351(k) BLA which included an analytical similarity assessment of comparing SB2 and US-licensed Remicade.

On May 13, 2016, the Agency requested the sponsor to provide more data for all Tier 1 QAs.

Question 1. The applicant's analytical similarity exercise included five independent DP lots. As the Agency noted in the meeting minutes for the BPD Type 2 and Type 4 meetings held July 20, 2015 and December 14, 2015, respectively, data from only five lots may not be sufficient for the analytical similarity assessment. The Agency notes that five intended-commercial DS lots have been produced that are not included in the analytical similarity assessment. It is unclear whether DP lots have been produced from these additional DS lots. To support the analytical similarity assessment, provide data for all Tier 1 (equivalence testing) analytical tests for these five DS lots or their subsequently produced DP lots. If feasible to obtain, DP data will provide the strongest evidence to support analytical similarity to the US-licensed reference product. DS data may be acceptable for attributes that do not change significantly between DS lots and their resulting DP lots.

Question 2. For Tier 1 QAs (TNF-α neutralization assay and TNF-α binding assay), please provide the testing results from each block (each block has one relative potency) as the relative potency is determined as an average (geometric mean) from 3 to 4 blocks of data. For example, for batch A, the individual relative potency values from the 4 blocks are 96%, 101%, 102%, 98%, then you calculate the relative potency for this batch as (96% × 101% × 102% × 98%)1/4. Those individual block values, 96%, 101%, 102%, 98%, are the data points we are requesting.

On August 5, 2016, the applicant provided the following data:

- All Tier 1 QAs' testing results from each block for 4 intended-commercial DS, 1 intended-commercial DP, and 5 independent DP SB2 lots.
- All Tier 1 QAs' testing results from each block for all US-licensed Remicade and EU-approved Remicade lots.

The applicant characterized multiple batches of US-licensed Remicade and EU-approved Remicade using a comprehensive set of analytical methods during the SB2 development. In addition, the applicant recalculated the 90% Confidence Intervals for all Tier 1 QAs based on the Agency's recommended sample size imbalanced adjusted approach.

The Agency carefully evaluated data for the TNF-α neutralization assay and TNF-α binding assay provided in the initial BLA submission. Samsung Bioepis' statistical equivalence testing (Tier 1 approach) is provided in Section 4, and our independent statistical equivalence testing analyses are present in Section 5.

3 DATA ANALYZED

Samsung Bioepis submitted the analytical data on August 5, 2016. The TNF-α neutralization assay data of 46 US-licensed Remicade lots, 40 EU-approved Remicade lots, and 10 SB2 lots are summarized in Table 3. The TNF-α binding assay data of 41 US-licensed Remicade lots, 37 EU-approved Remicade lots, and 10 SB2 lots are also summarized in Table 3.

Table 3. Number of batches from each product

Product	Number of batches	
	TNF-α neutralization assay (potency)	TNF-α binding assay
US-licensed Remicade	46	41
SB2	10	10
EU-approved Remicade	40	37

4 APPLICANT'S STATISTICAL EQUIVALENCE TESTING

In this submission, Samsung Bioepis conducted Tier 1 statistical equivalence testing with the margin defined as $1.5\hat{\sigma}_R$ for TNF-α neutralization assay (potency) and TNF-α binding assay. To demonstrate statistical equivalence for TNF-α neutralization bioassay (potency) and TNF-α binding assay in this context, the entire two-sided CI must fall within$(-1.5\hat{\sigma}_R, 1.5\hat{\sigma}_R)$. Samsung Bioepis applied the Agency's recommended sample size imbalanced adjusted CI approach to calculate the two-sided CI. In addition, Satterthwaite approximation was applied for obtaining the degree of freedom (DF) of the sample size imbalanced adjusted CI because there is no assumption of equal variance between the test and reference products. However, the DF using in Satterthwaite method is incorrect and the correct version is provided in the following section. After the communication, Samsung Bioepis recalculated the 90% CIs for all Tier 1 QAs using the sample size imbalanced adjusted approach with the correct DF in the amendment on August 5, 2016.

5 FDA STATISTICAL ANALYSES

To evaluate analytical similarity, the Agency recommended Samsung Bioepis to apply a tiered approach in the Agency's responses to IND meetings with Samsung Bioepis. That is, product QAs amendable to statistical evaluation are assigned to three tiers based on their criticality. The quality attributes 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.

5.1 Statistical method

Let μ_T and μ_R be respectively the population mean of the QA for the test product and the population mean of the QA for the reference product. Let σ_R be the standard deviation of the QA

of interest for the reference product. In order 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:

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

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

We reject H_0 if 90% confidence interval 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% confidence interval 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 quality attribute 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 $\pm(-1.5\sigma_R, 1.5\sigma_R)$ 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 (or by the sample variability of EU-approved Remicade in the comparison between SB2 and EU-approved Remicade), 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 Batch *j* of the test product (the proposed biosimilar product) and X_{Rj} be the observed value of the QA of interest for Batch *j* of the reference product. Since the two products are manufactured by two manufacturers, two products are independent. $\overline{X}_i = \sum_{j=1}^{n_i} X_{ij} \Big/ n_i$, and $S_i^2 = \sum_{j=1}^{n_i} \left(X_{ij} - \overline{X}_i\right) \Big/ (n_i - 1)$, where n_i is the number of lots in the i^{th} 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:

$$\left(\overline{X}_T - \overline{X}_R - t_\alpha(\nu)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}}, \overline{X}_T - \overline{X}_R + t_\alpha(\nu)\sqrt{\frac{S_T^2}{n_T} + \frac{S_R^2}{n_R}} \right). \quad (1)$$

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:

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

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 α=0.05.

5.2 FDA statistical equivalence testing for TNF-α neutralization assay

The TNF-α neutralization assay data points of SB2, US-licensed Remicade, and EU-approved Remicade are displayed in Figure 1. There appears a small mean difference among the three products. The variability of SB2 is smallest among three products.

10 batches of SB2, 46 batches of US-licensed Remicade, and 40 batches of EU-approved Remicade are included for the statistical equivalence testing for the TNF-α neutralization assay. Descriptive statistics for the TNF-α neutralization assay data are listed in Table 4.

Figure 1. Scatter plot of TNF-α neutralization assay for US-licensed Remicade, SB2, and EU-approved Remicade

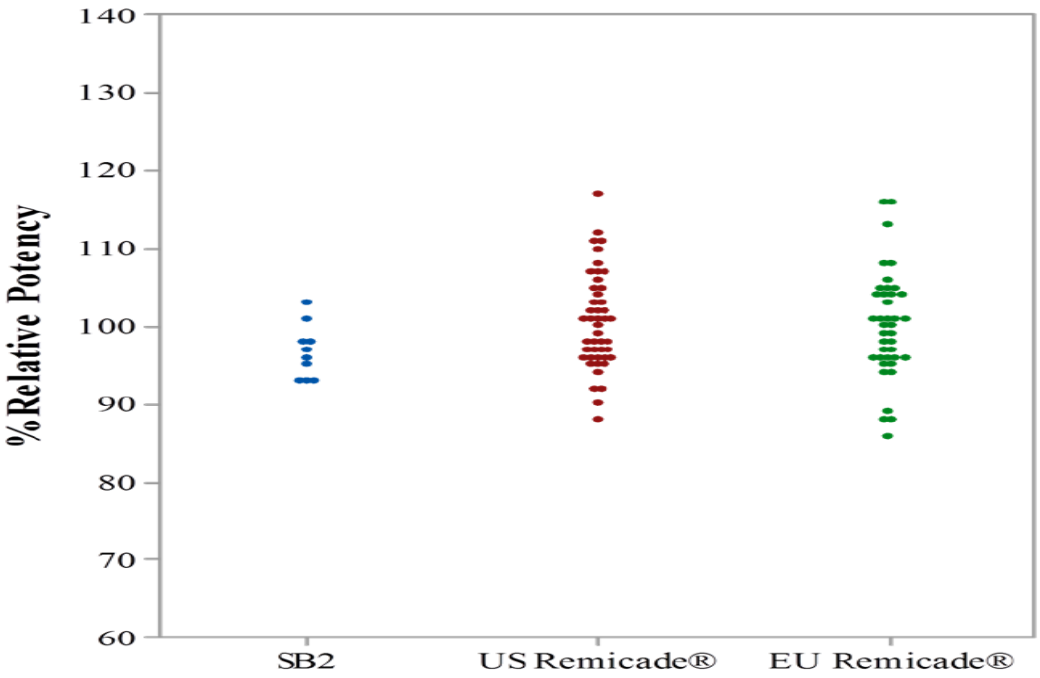

Table 4. Descriptive statistics for the TNF-α neutralization assay data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Minimum, %	Maximum, %
US-licensed Remicade	46	100.74	6.22	88	117.51
SB2	10	96.98	3.67	92.63	103.54
EU-approved Remicade	40	100.33	6.91	86.26	116.44

Because there is no assumption of equal variance between the test and reference products, Satterthwaite approximation is applied for obtaining the degree of freedom of the 90% sample size imbalanced adjusted CI for the mean difference between US-licensed Remicade and SB2. From Table 5, the result shows that the TNF-α neutralization assay of SB2 is equivalent to the TNF-α neutralization assay of US-licensed Remicade. Similarly, the TNF-α neutralization assay of SB2 is equivalent to the TNF-α neutralization assay of EU-approved Remicade, and the TNF-α neutralization assay of EU-approved Remicade is equivalent to the TNF-α neutralization assay of US-licensed Remicade.

Table 5. Equivalence testing results for the TNF-α neutralization assay

Comparison	# of lots	Mean difference, %	90% CI for mean difference, %	Equivalence margin, %	Equivalent
SB2 vs. US	(10, 46)	-3.76	(-7.10, -0.44)	(-9.33, 9.33)	Yes
SB2 vs. EU	(10, 40)	-3.35	(-6.92, 0.22)	(-10.36, 10.36)	Yes
EU vs. US	(40, 46)	-0.41	(-2.79,1.96)	(-9.33, 9.33)	Yes

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

5.3 FDA statistical equivalence testing for TNF-α binding assay

The TNF-α binding assay data points of SB2, US-licensed Remicade, and EU-approved Remicade are displayed in Figure 2. There appears a small mean difference among the three products. The variability of SB2 is smallest among three products.

10 batches of SB2, 41 batches of US-licensed Remicade, and 37 batches of EU-approved Remicade are included in the TNF-α binding assay dataset for the statistical equivalence testing. Descriptive statistics for the TNF-α binding assay data of SB2, US-licensed Remicade, and EU-approved Remicade are listed in Table 6.

From Table 7, the result shows that the equivalence of TNF-α binding assay between SB2 and US-licensed Remicade is supported. The equivalence of TNF-α binding assay between SB2 and

EU-approved Remicade is supported. The equivalence of TNF-α binding assay between US-licensed Remicade and EU-approved Remicade is supported.

Figure 2. Scatter plot of TNF-α binding assay for US-licensed Remicade, SB2, and EU-approved Remicade

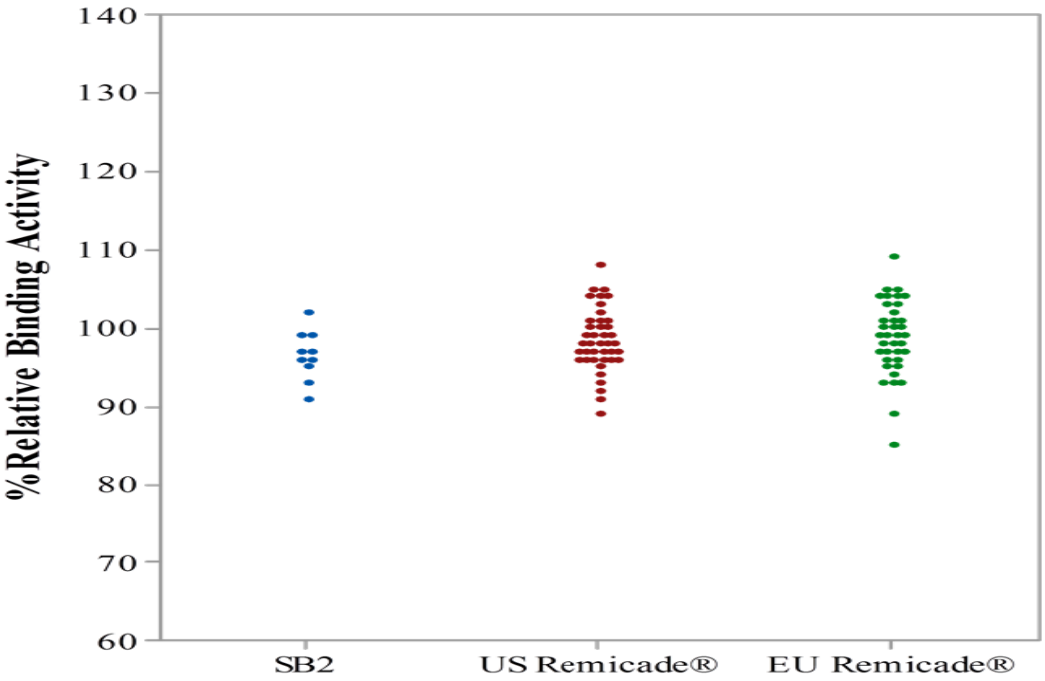

Table 6. Descriptive statistics for the TNF-α binding assay data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Minimum, %	Maximum, %
US-licensed Remicade	41	98.64	3.94	89.49	107.77
SB2	10	96.53	3.05	91.14	101.94
EU-approved Remicade	37	98.93	4.80	84.87	108.89

Table 7. Equivalence testing results for the TNF-α binding assay

Comparison	# of lots	Mean difference, %	90% CI for mean difference, %	Equivalence margin, %	Equivalent
SB2 vs. US	(10, 41)	-2.11	(-4.49, 0.26)	(-5.90, 5.90)	Yes
SB2 vs. EU	(10, 37)	-2.40	(-5.05, 0.25)	(-7.21, 7.21)	Yes
EU vs. US	(37, 41)	0.29	(-1.38,1.96)	(-5.90, 5.90)	Yes

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

5.4 Sensitivity analysis

For some batches, the number of within-batch replicates is different due to the failure of the sample parallelism test and the fraction of batches with parallelism failure is summarized in Table 8.

Table 8. Fraction of lots with parallelism failure for each product

Product	Quality Attribute	Fraction of batches with parallelism failure
SB2	TNF- α Neutralization	3/10
	TNF- α Binding	0/10
US-licensed Remicade	TNF- α Neutralization	10/46
	TNF- α Binding	7/41
EU-approved Remicade	TNF- α Neutralization	11/40
	TNF- α Binding	6/37

Then, the descriptive statistics and 90% CI for both Tier 1 QAs are recalculated after we take out batches with the failure of the sample parallelism test.

5.4.1 TNF-α neutralization assay

Seven batches of SB2, 36 batches of US-licensed Remicade, and 29 batches of EU-approved Remicade are included for the statistical equivalence testing for the TNF-α neutralization assay. Descriptive statistics for the TNF-α neutralization assay data are listed in Table 9. There appears a small mean difference among the three products. The variability of SB2 is smallest among three products.

Table 9. Descriptive statistics for the TNF-α neutralization assay data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Minimum, %	Maximum, %
US-licensed Remicade	36	100.76	6.64	88	117.51
SB2	7	95.97	3.39	92.63	101.85
EU-approved Remicade	29	99.41	6.69	86.26	115.83

The 90% sample size imbalanced adjusted CI for the mean difference between US-licensed Remicade and SB2 is recalculated in Table 10. The result shows that the TNF-α neutralization assay of SB2 is equivalent to the TNF-α neutralization assay of US-licensed Remicade. Similarly, the TNF-α neutralization assay of SB2 is equivalent to the TNF-α neutralization assay of EU-approved Remicade, and the TNF-α neutralization assay of EU-approved Remicade is equivalent to the TNF-α neutralization assay of US-licensed Remicade.

Table 10. Equivalence testing results for the TNF-α neutralization assay

Comparison	# of lots	Mean difference, %	90% CI for mean difference, %	Equivalence margin, %	Equivalent
SB2 vs. US	(7, 36)	-4.79	(-8.81, -0.77)	(-9.96, 9.96)	Yes
SB2 vs. EU	(7, 29)	-3.44	(-7.50, 0.60)	(-10.03, 10.03)	Yes
EU vs. US	(29, 36)	-1.35	(-4.12, 1.44)	(-9.96, 9.96)	Yes

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

5.4.2 TNF-α binding assay

10 batches of SB2, 34 batches of US-licensed Remicade, and 31 batches of EU-approved Remicade are included in the TNF-α binding assay dataset for the statistical equivalence testing. Descriptive statistics for the TNF-α binding assay data of SB2, US-licensed Remicade, and EU-approved Remicade are listed in Table 11. There appears a small mean difference among the three products. The variability of SB2 is smallest among three products.

From Table 12, the result shows that the equivalence of TNF-α binding assay between SB2 and US-licensed Remicade is supported. The equivalence of TNF-α binding assay between SB2 and EU-approved Remicade is supported. The equivalence of TNF-α binding assay between US-licensed Remicade and EU-approved Remicade is supported.

Table 11. Descriptive statistics for the TNF-α binding assay data

Product	Number of batches	Sample mean, %	Sample standard deviation, %	Minimum, %	Maximum, %
US-licensed Remicade	34	98.94	4.12	89.49	107.77
SB2	10	96.53	3.05	91.14	101.94
EU-approved Remicade	31	98.48	4.83	84.87	108.89

Table 12. Equivalence testing results for the TNF-α binding assay

Comparison	# of lots	Mean difference, %	90% CI for mean difference, %	Equivalence margin, %	Equivalent
SB2 vs. US	(10, 34)	-2.41	(-4.84, 0.02)	(-6.18, 6.18)	Yes
SB2 vs. EU	(10, 31)	-1.95	(-4.62, 0.71)	(-7.25, 7.25)	Yes
EU vs. US	(31, 34)	-0.46	(-2.33, 1.41)	(-6.18, 6.18)	Yes

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

6 CONCLUSION AND RECOMMENDATION

The results from the statistical equivalence testing of the TNF-α neutralization and the TNF-α binding assay support a demonstration that the proposed biosimilar SB2 is highly similar to US-licensed Remicade. The statistical analyses of the TNF-α neutralization and the TNF-α binding

assay in the three pair-wise comparisons (SB2, US-licensed Remicade, and EU-approved Remicade) also support the scientific bridge to justify the relevance of the data obtained from clinical studies that compared EU-approved Remicade and the SB2 product to support a demonstration of biosimilarity to US-licensed Remicade.

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/s/

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12/12/2016

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12/13/2016

YI TSONG
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