CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA NO.:	761100
SERIAL NO.:	0000
DATE RECEIVED BY THE CENTER:	October 20, 2017
DRUG NAME:	SB3 (proposed biosimilar to US-licensed Herceptin)
DOSAGE FORM:	Prefilled vials, 150 mg
INDICATIONS:	Same indications of use as approved for US-licensed Herceptin
APPLICANT:	Samsung Bioepis Co., Ltd.
REVIEW FINISHED:	July 24, 2018
NAME OF PRIMARY STATISTICAL REVIEWER:	Yu-Ting Weng
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1 INTRODUCTION

On October 20, 2017, Samsung Bioepis Co., Ltd. (the applicant) submitted to the US Food and Drug Administration (FDA) a 351(k) BLA which included analytical similarity assessments of comparing SB3, US-licensed Herceptin (US), and EU-approved trastuzumab (EU).

Two Tier 1 QAs are relative activities of Anti-proliferation and ADCC. The CMC statistical reviewer found out the following review issues and discussed internally with OBP CMC reviewers.

On April 9, 2018, the FDA sent the applicant the first Information Request (IR). The request related to the CMC statistics team is described below.

SB3 drug product (DP) batch (b) (4)-002175 (manufactured at a (b) (4) scale), was included in the tier 1 statistical testing of anti-proliferation (Section 2.2.1) and ADCC activity (Section 2.2.2) along with SB3 DP lots produced at the intended commercial scale (i.e., (b) (4)). The scale and conditions of a production bioreactor can significantly impact certain quality attributes (e.g., glycosylation) that are shown to play an important role in product potency and ADCC activity. The data provided in Section 3.2.R.4 demonstrate that lot (b) (4)-002175 is not representative of the clinical and commercial scale lots. Specifically, the relative potency values for anti-proliferation (b) (4) and ADCC activity (b) (4) of lot (b) (4)-002175 are outside of the potency ranges derived from the intended commercial scale lots for both tier 1 evaluated quality attributes (i.e., anti-proliferation range 92-103%; ADCC range 86-104%). Therefore, lot (b) (4)-002175 should not be included in the analytical similarity assessment. Remove SB3 batch (b) (4)-002175 from the dataset used to conduct equivalence testing for the ADCC and anti-proliferation assays, and conduct equivalence testing using the remaining 8 lots of SB3 drug product. If available, include data from additional independent lots of SB3 that are representative of the clinical and commercial scale lots to allow for a sufficiently robust statistical evaluation of the attributes evaluated by Tier 1 equivalence testing. Alternatively, provide a justification (which could include a statistical assessment) as to how the analytical data and equivalence testing from the current number of SB3 lots (i.e., 8 lots) that are included in the tier 1 assessments supports a meaningful analytical similarity assessment among SB3, US-licensed Herceptin® and EU-approved trastuzumab.

On April 20, 2018, the applicant provided the following clarifications to the FDA IR dated April 9, 2018:

- Data correction for four lots (H4365B01, H4519H01, H4577H03, and H4723H01) of EU used in the equivalence test due to the error found during the internal review.
- Analysis excluding the pilot DP lot ((b) (4)-002175).

On June 29, 2018, the FDA sent the applicant the second IR. The request related to the CMC statistics team is described below.

Regarding the applicant's April 12, 2018 response to comment 4 of the FDA IR dated March 29, 2018, which was sent by OBP CMC team, and to the data provided in Section 3.2.S.5.4 of the BLA: Insufficient information and data have been provided to establish a bridge for potency between the four Research Reference Standard (RRS) lots (1st RRS (b) (4); 2nd RRS (b) (4); 3rd RRS (b) (4); 4th RRS (b) (4)) used in the analytical similarity assessment (Section

3.2.R.4). The data provided for RRS (b) (4) indicates a potential drift in antiproliferation (12% increase) and ADCC activity (12% decrease) as compared to RRS (b) (4). Based on the data provided to date and the qualification program used at the time of the RRS (b) (4) implementation (e.g. insufficient replicates and inappropriate acceptance criteria), the Agency does not agree that RRS (b) (4) was appropriately qualified with respect to potency or appropriately bridged to RRS (b) (4). Therefore, we do not agree that the data generated from lots of SB3, US-licensed Herceptin, and EU-approved trastuzumab evaluated against RRS (b) (4) and RRS (b) (4) can be pooled to support the assessment of a single product quality attribute in the analytical similarity assessment. Remove lots of SB3, US-licensed Herceptin, and EU-approved trastuzumab evaluated against RRS (b) (4) and RRS (b) (4) from the analytical similarity assessment for the product quality attributes where data are evaluated against a RRS (i.e., antiproliferation, ADCC activity, HER2 binding, Fcγ receptor binding, FcRn binding, and C1q binding). Provide a complete revised analysis of the remaining data (i.e., SB3, US-licensed Herceptin and EU-approved trastuzumab lots only evaluated against RRS (b) (4) and RRS (b) (4)) and update Section 3.2.R.4.

On July 13, 2018, the applicant provided the following clarifications to the FDA IR dated June 29, 2018:

- Justification of using the data tested against 2nd RRS in the similarity assessment.
- Analysis excluding the data tested against 1st RRS.
- Analysis excluding the data tested against 1st RRS and 2nd RRS.

The FDA CMC statistics reviewers carefully evaluated data for the relative activities of Anti-proliferation and ADCC provided in the BLA resubmission. The applicant's statistical equivalence testing (Tier 1 approach) is provided in Section 3, and CMC statistical reviewer's independent statistical equivalence testing analyses using modified Wald test are present in Section 4.

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 Anti-proliferation activity and the relative ADCC activity.

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 October 20, 2017 and the data is corrected on May 11, 2018. The summary of SB3 lots for Tier 1 analysis is provided in Table 1. The CMC statistical reviewer conducted Tier 1 statistical equivalence testing based on these eight independent lots for each QA.

Table 1. Summary of SB3 Lots for Tier 1 Analysis

Source	DS lot number
PVR DS	HP5-14-604-003
	HP5-14-604-005
Clinical DP	P51702A
	P51704A
	P51705A
PVR DP	P51708A
	P51710A
	P51712A

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 $\theta_1 = -1.5\sigma_R$, $\theta_2 = 1.5\sigma_R$, 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 independent. $\overline{X}_i = \sum_{j=1}^{n_i} X_{ij} \Big/ n_i$, and $S_i^2 = \sum_{j=1}^{n_i} \left(X_{ij} - \overline{X}_i\right) \Big/ \left(n_i - 1\right)$, 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:

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

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):

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

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

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.

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 addressing the issue.

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.

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:

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

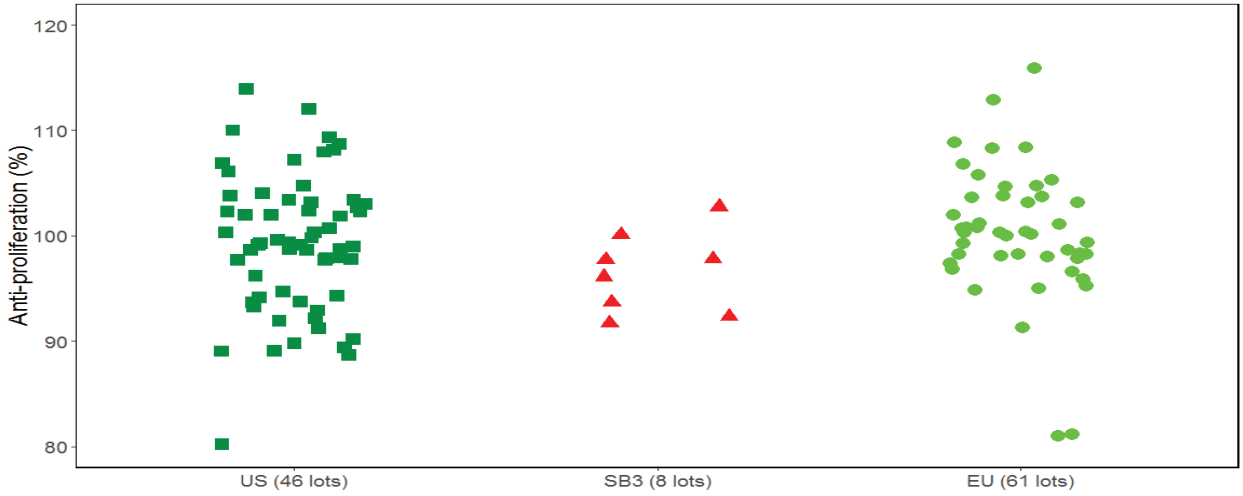
where the sample sizes of adjusted reference lots, n_R^* , is equal to $\min(1.5 \times n_T, n_R)$. n_T and n_R denote the sample sizes of test product lots and the sample sizes of reference product lots, respectively.

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

3.3 FDA statistical equivalence testing for the relative Anti-proliferation activity

The relative Anti-proliferation activity's data points of SB3, US, and EU are displayed in Figure 1. SB3 has the smallest sample mean and sample variability among three products.

Figure 1. Scatter plot of the relative Anti-proliferation activity for SB3, US-licensed Herceptin, and EU-approved Herceptin



Eight SB3 lots, 46 US lots, and 61 EU lots were included for the statistical equivalence testing for the relative Anti-proliferation activity. Descriptive statistics for the relative Anti-proliferation activity's data are listed in Table 2.

Table 2. Descriptive statistics for the relative Anti-proliferation activity data

Product	Number of lots	Sample mean, %	Sample standard deviation, %	Minimum, %	Maximum, %
SB3	8	96.63	3.89	92	103
US	46	100.33	6.35	81	116
EU	61	99.28	6.54	80	114

From Table 3, the result shows that the three-way pairwise comparisons (SB3 vs. US, SB3 vs. EU, and US vs. EU) for the relative Anti-proliferation activity, using the current practice for fixed margin, pass equivalence testing.

Table 3. Equivalence testing results for the relative Anti-proliferation activity using the current practice for fixed margin

Comparison	Number of lots	Mean difference, %		Equivalence margin, %	Statistical Equivalence
		Estimate	90% CI [1]		
SB3 vs. US	(8, 46)	-3.70	(-7.57, 0.17)	(-9.53, 9.53)	Yes
SB3 vs. EU	(8, 61)	-2.65	(-6.58, 1.28)	(-9.81, 9.81)	Yes
EU vs. US	(61, 46)	-1.05	(-3.13, 1.04)	(-9.53, 9.53)	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 (SB3 vs. US, SB3 vs. EU, and US vs. EU) for the relative Anti-proliferation activity, using the MWCMLE method for parameter margin, also pass equivalence testing.

Table 4. Equivalence testing results for the relative Anti-proliferation activity using the MWCMLE for parameter margin

Comparison	Number of lots	Mean difference, %		Equivalence margin, %	Statistical Equivalence
		Estimate	90% CI [1]		
SB3 vs. US	(8, 46)	-3.70	(-8.63, 5.02)	(-10.80, 10.80)	Yes
SB3 vs. EU	(8, 61)	-2.65	(-8.34, 5.78)	(-11.11, 11.11)	Yes
EU vs. US	(61, 46)	-1.05	(-3.61, 1.71)	(-10.80, 10.80)	Yes

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

3.4 FDA statistical equivalence testing for the relative ADCC activity

The relative ADCC activity's data points of SB3, US, and EU are displayed in Figure 2. SB3 has the largest sample mean and smallest sample variability among three products.

Eight SB3 lots, 48 US lots, and 56 EU lots were included for the statistical equivalence testing for the relative ADCC activity. Descriptive statistics for the relative ADCC activity's data are listed in Table 5.

From Table 6, the result shows that the three-way pairwise comparisons (SB3 vs. US, SB3 vs. EU, and US vs. EU) for the relative ADCC activity, using the current practice for fixed margin, pass equivalence testing.

From Table 7, the result shows that the three-way pairwise comparisons (SB3 vs. US, SB3 vs. EU, and US vs. EU) for the relative ADCC activity, using the MWCMLE method for parameter margin, also pass equivalence testing.

Figure 2. Scatter plot of the relative ADCC activity for SB3, US-licensed Herceptin, and EU-approved Herceptin

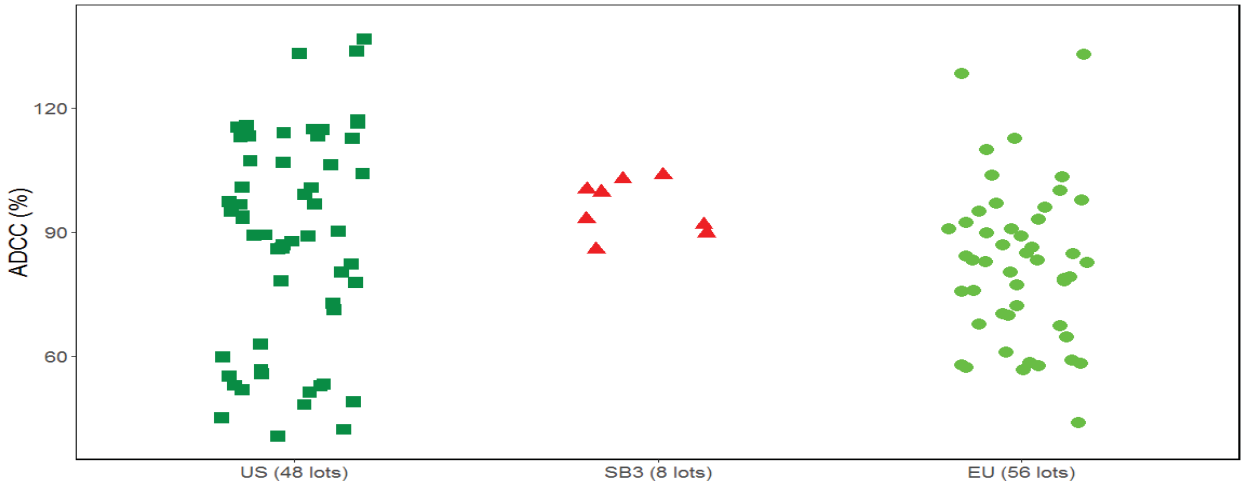


Table 5. Descriptive statistics for the relative ADCC activity data

Product	Number of lots	Sample mean, %	Sample standard deviation, %	Minimum, %	Maximum, %
SB3	8	96	6.61	86	104
US	48	82.27	18.63	44	133
EU	56	87.61	26.07	41	137

Table 6. Equivalence testing results for the relative ADCC activity using the current practice for fixed margin

Comparison	Number of lots	Mean difference, %		Equivalence margin, %	Statistical Equivalence
		Estimate	90% CI [1]		
SB3 vs. US	(8, 48)	13.73	(3.91, 23.55)	(-27.95, 27.95)	Yes
SB3 vs. EU	(8, 56)	8.39	(-4.77, 21.55)	(-39.10, 39.10)	Yes
EU vs. US	(56, 48)	5.34	(-1.97, 12.64)	(-27.95, 27.95)	Yes

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

Table 7. Equivalence testing results for the relative ADCC activity using the MWCMLE for parameter margin

Comparison	Number of lots	Mean difference, %		Equivalence margin, %	Statistical Equivalence
		Estimate	90% CI [1]		
SB3 vs. US	(8, 48)	13.73	(-12.96, 25.32)	(-31.68, 31.68)	Yes
SB3 vs. EU	(8, 56)	8.39	(-22.85, 30.18)	(-44.31, 44.31)	Yes
EU vs. US	(56, 48)	5.34	(-4.52, 14.15)	(-31.68, 31.68)	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 Anti-proliferation and ADCC supported a demonstration that the proposed biosimilar SB3 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

[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

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