# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761028Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **BLA Serial Number:** | 761028/ 00 |
| **Drug Name:** | ABP-215 (Biosimilar to Avastin®) |
| **Indication(s):** | NSCLC, mCRC, Glioblastoma, Renal Cell Carcinoma, Cervical Cancer |
| **Applicant:** | Amgen |
| **Submission Date:** | 11/14/2016 |
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| **Keywords:** | Objective Response Rate(ORR), Risk Ratio (RR), Similarity Margins, Progression Free Survival (PFS), Non-Small Cell Lung Cancer (NSCLC), Bevacizumab |

# Table of Contents

# LIST OF TABLES

# LIST OF FIGURES

# 1. EXECUTIVE SUMMARY

The applicant submitted data and a clinical study report of a randomized study to support approval for ABP-215 as a biosimilar to US-licensed Avastin (bevacizumab) for indications approved for US-licensed Avastin including metastatic colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, and cervical cancer. This is the first biosimilar product for US-licensed Avastin.

This application was based on extensive analytical data; a single-dose pharmacokinetic study providing a three-way comparison of ABP-215, US-licensed Avastin, and EU-approved bevacizumab; a scientific justification for extrapolation of data to support biosimilarity in each of the additional indications for which the applicant is seeking licensure; and a comparative clinical study. The purpose of the comparative clinical study is to resolve any residue uncertainties and support a demonstration of no clinically meaningful differences between the proposed biosimilar product and the reference product.

The comparative clinical study submitted was Study 20120265 (Study 265), titled "a randomized, double-blind, Phase 3 study evaluating the efficacy and safety of ABP-215 compared with bevacizumab in subjects with advanced non-small cell lung cancer." Randomization was stratified by geographic region (Eastern Europe vs. Western Europe vs. Asia Pacific/Other vs. North America), ECOG performance status (0 vs. 1), and sex (male vs. female). The primary endpoint was objective response rate (ORR). Secondary endpoints included duration of response (DoR) and progression free survival (PFS). The study planned to enroll 620 patients. The primary objective of the study was to compare the 90% confidence interval (CI) of the risk ratio of ORR between ABP 215 and EU-approved bevacizumab to pre-specified similarity margins based on the historical effect of bevacizumab. If the CI of the risk ratio of ORR falls within the margins, it is considered that there are no clinically meaningful differences between the two products.

A total of 642 patients were randomized in a 1:1 allocation with 328 in the ABP-215 arm and 314 in the EU-approved bevacizumab arm. The estimated risk ratio (RR) of ORR was 0.93 with 90% CI (0.80, 1.09), which falls within the FDA selected similarity margin of (0.73, 1.36), and the ORR was 39.0% with 95% CI (33.7%, 44.5%) in the ABP-215 arm and 41.7% with 95% CI (36.2%, 47.4%) in the EU-approved bevacizumab arm. The results of Study 265 demonstrated there are no clinically meaningful differences between ABP-215 and EU-approved bevacizumab.

On July 17, 2017, an Oncologic Advisory Committee was held to discuss this application. The committee voted unanimously (17-0), agreeing with FDA's conclusion that the totality of the evidence support licensure of ABP-215 as a biosimilar product to US-licensed Avastin for each of the indications for which US-licensed Avastin is currently licensed and for which the Applicant is seeking licensure. From statistical point of view, the data and analyses provided in this submission support a regulatory approval.

# 2. INTRODUCTION

The applicant submitted data and a clinical study report to seek approval for ABP-215 as a biosimilar to US-licensed Avastin (bevacizumab) for indications approved for US-licensed Avastin listed in Section 2.1.1. This is the first biosimilar product for US-licensed Avastin. This application was based on:

- Extensive analytical data intended to support (i) a demonstration that ABP-215 and US-licensed Avastin are highly similar; (ii) a demonstration that ABP-215 can be manufactured in a well-controlled and consistent manner; and (iii) a justification of the relevance of the comparative data generated using EU-approved bevacizumab to support a demonstration of biosimilarity of ABP-215 to US-licensed Avastin.
- A single-dose pharmacokinetic (PK) study (Study 20110216) providing a three-way comparison of ABP-215, US-licensed Avastin, and EU-approved bevacizumab intended to (i) support PK similarity of ABP-215 and US-licensed Avastin and (ii) provide the PK portion of the scientific bridge to support the relevance of the comparative data generated using EU-approved bevacizumab to support a demonstration of the biosimilarity of ABP-215 to US-licensed Avastin.
- A comparative clinical study (Study 20120265) between ABP-215 and EU-approved bevacizumab in patients with advanced/metastatic non-small cell lung cancer (NSCLC) to support the demonstration of no clinically meaningful differences in terms of response, safety, purity, and potency between ABP-215 and US-licensed Avastin.
- A scientific justification for extrapolation of data to support biosimilarity in each of the additional indications for which the applicant is seeking licensure.

This reviewer focuses on the comparative clinical study, Study 20120265 (referred to as Study 265), a Phase 3, randomized, double blind, multi-center study of ABP-215 and EU-approved bevacizumab in patients metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC) receiving first-line therapy with carboplatin and paclitaxel.

## 2.1 Overview

### 2.1.1. Class and Indication

ABP-215, a humanized recombinant IgG1 monoclonal antibody against vascular endothelial growth factor (VEGF), is a proposed biosimilar to US-licensed Avastin (bevacizumab). BLA125085 for Avastin was initially licensed by FDA on February 26, 2004, and the BLA license holder is Genentech. The applicant is seeking licensure of ABP-215 for the following indications for which US-licensed Avastin is approved:

- Metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment.

- Metastatic colorectal cancer, with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen.
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease.
- Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy.
- Metastatic renal cell carcinoma with interferon alfa.
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease.

### 2.1.2. Regulatory History

ABP-215 is investigated under IND 111,960. The application is submitted under Section 351(k) of the Public Health Service Act (PHS Act).

In July 2013 FDA and the applicant held a meeting and discussed the design of Study 265 intended to compare EU-approved bevacizumab with ABP-215. FDA agreed that EU-approved bevacizumab could be used in the proposed comparative clinical study if an adequate scientific bridge was established.

In December 2014 FDA issued an advice letter with recommendations for the similarity margins. At a meeting held in January 2015, the applicant clarified that at the time the study had completed enrollment. FDA acknowledged that FDA's requested change of increasing the sample size based on FDA's recommended similarity margins could not be implemented due to logistics and timing of the request. FDA stated that the applicant's margins for Study 265 would be considered in the context of the totality of the evidence.

In May 2015 and February 2016, FDA and the applicant held meetings to discuss the proposed format and contents of the BLA. The BLA was completely submitted on November 14, 2016.

### 2.1.3. Study Reviewed

Study 265 is a Phase 3, randomized, double blind, multi-center study to assess if there are any clinically meaningful differences between ABP-215 and EU-approved bevacizumab in patients with previously metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC). Patients were randomized in a 1:1 ratio to receive either ABP-215 plus or EU-approved bevacizumab plus first-line therapy with carboplatin and paclitaxel. Randomization was stratified by geographic region, ECOG performance status, and sex.

The primary objective of the study was to compare the 90% confidence interval (CI) of the risk ratio (RR) of the objective response rate (ORR) between ABP-215 and EU-approved bevacizumab to pre-specified similarity margins based on the historical effect

bevacizumab. The secondary endpoints were duration of response (DoR) and progression free survival (PFS).

A total of 642 patients were randomized with 328 in the ABP-215 arm and 314 in the EU-approved bevacizumab arm. The study was initiated on November 11, 2013 and the last patient completed the study on July 23, 2015.

## 2.2 Data Sources

Data used for review is from the electronic submission received on November 14, 2016. The network path is

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# 3. STATISTICAL EVALUATION

## 3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data as well as the related SAS programs for analysis.

The reviewer was able to perform both the primary and secondary analyses using the submitted data.

## 3.2 Evaluation of Efficacy

### 3.2.1. Study Design and Endpoints

Study 265 was a Phase 3, randomized, double-blind, parallel-group, multi-center comparative clinical study of ABP-215 and EU-approved bevacizumab in patients with previously metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC).

Patients were randomly assigned in a 1:1 ratio to ABP-215 plus BSC or EU-approved bevacizumab plus first-line therapy with carboplatin and paclitaxel. Randomization were conducted via an Interactive Voice/Web Response System (IWRS) and stratified by:

- geographic region (Eastern Europe vs. Western Europe vs. Asia Pacific/Other vs. North America),
- ECOG performance status (0 vs. 1), and
- sex (male vs. female).

ABP-215 or EU-approved bevacizumab was administered at a dose of 15 mg/kg as an IV infusion every three weeks in combination with chemotherapy (carboplatin 6 AUC and paclitaxel 200 mg/m$^2$) for 6 cycles. Patients underwent tumor imaging at baseline, Week 7 (end of Cycle 2), Week 13 (end of Cycle 4), and Week 19 (end of treatment). Patients were clinically assessed prior to each chemotherapy cycle; labs (serum chemistry, hematology, urine, etc.) were assessed every three weeks.

The primary objective of this study was to compare the 90% CI of the risk ratio of ORR between ABP-215 and EU-approved bevacizumab to the pre-specified similarity margins of (0.67, 1.5). If the 90% CI of the risk ratio of ORR is within these margins, the study results support a demonstration of no clinically meaningful differences between ABP-215 and the reference product. The secondary objectives were to assess the treatment effect of ABP-215 and EU-approved bevacizumab on DoR and PFS.

*Reviewer's Comment:*

The goal of the comparative clinical study in the biosimilar exercise is to resolve residual uncertainties and support a demonstration of no clinically meaningful differences between the proposed biosimilar product and the reference product. A statistical equivalence test for similarity is used to establish such evidence that the proposed biosimilar is neither superior nor inferior to the reference product, by demonstrating that the difference between the two products lies within pre-specified margins.

FDA selected a different set of margins, (0.73, 1.36) for this study.

A meta-analysis was conducted based on four historical trials that compared bevacizumab plus chemotherapy versus chemotherapy alone.

**Table 1. Historical Randomized Non-Squamous NSCLC Trials**

| | Chemotherapy | | Bevacizumab+Chemotherapy | |
|---|---|---|---|---|
| | **(CR+PR)/N** | **ORR** | **(CR+PR)/N** | **ORR** |
| **Johnson et al.** | 6/32 | 18.8% | 11/34 | 32.4% |
| **Nishio et al.** | 20/59 | 33.8% | 68/121 | 56.2% |
| **Reck et al.** | 71/327 | 21.7% | 114/329 | 34.7% |
| **Sandler et al.** | 59/392 | 15.1% | 133/381 | 34.9% |
| **Meta Analysis** | 156/810 | 19.3% | 326/865 | 37.7% |

A total of 1675 patients were included in the meta-analysis, with 810 in chemotherapy alone arms and 865 in the bevacizumab plus chemotherapy arms. It was estimated that the ORR for bevacizumab plus chemotherapy was 37.7%. The risk ratio of chemotherapy alone versus bevacizumab plus chemotherapy was 0.53 with 95% CI (0.45, 0.63).

Symmetrical similarity margins and 50% maintenance of the confidence limit were chosen specifications to be used in the margin selection process. Assuming the ORR of bevacizumab plus chemotherapy is 37.7% and a 10% drop-out rate, the sample sizes for various power levels and confidence levels of the ORR risk ratio can be calculated. The following table presents examples of the sample size calculations.

**Table 2. Margins and Sample Size Calculation**

| | | | Sample Size | | |
|---|---|---|---|---|---|
| **CI of RR** | | **Similarity Margins** | **80% Power** | **85% Power** | **90% Power** |
| **70%** | (0.49, 0.58) | (0.73, 1.36) | 608 | 683 | 768 |
| **75%** | (0.49, 0.59) | (0.74, 1.35) | 632 | 711 | 799 |
| **80%** | (0.48, 0.60) | (0.75, 1.34) | 662 | 744 | 837 |
| **85%** | (0.47, 0.60) | (0.75, 1.33) | 702 | 789 | 887 |
| **90%** | (0.47, 0.61) | (0.76, 1.31) | 758 | 852 | 958 |
| **95%** | (0.45, 0.63) | (0.77, 1.29) | 856 | 962 | 1082 |

Based on the meta-analysis results and clinical considerations, the margins (0.73 to 1.36) was selected.

### 3.2.2. Efficacy Measures

The primary endpoint ORR was defined as the proportion of patients with objective evidence of complete response (CR) or partial response (PR), according to the RECIST version 1.1, and assessed by central, independent, blinded radiologists.

Secondary endpoints included:

- DoR, defined as the time from the date of first objective response to disease progression per RECIST v1.1 for responders. For patients alive and progression-free at the close of the study, DoR was censored at the date of the last tumor assessment demonstrating lack of progression.
- PFS, defined as the time from randomization until the first occurrence of disease progression per RECIST v1.1 or death, whichever occurs first. For patients alive and progression-free at the close of the study, PFS was censored at the date of the last tumor assessment demonstrating lack of progression.

### 3.2.3. Sample Size Consideration

In the final Study 265 protocol, approximately 620 subjects overall (310 subjects per arm) were to be randomized. The sample size was chosen to achieve greater than 95% power to demonstrate there are no clinically meaningful differences between ABP-215 and EU-approved bevacizumab on risk ratio of ORR with a margin of (0.67, 1.5) at a 2-sided significance level of 0.05. It was assumed that the ORR is approximately 38% (Botrel et al, 2011) in both the ABP-215 and EU-approved bevacizumab arms.

No interim efficacy analysis was planned for this study.

*Reviewer's Comment:*

Please see discussions on sample size for this study in Sections 2.1.2 and 3.2.1.

### 3.2.4. Statistical Methodologies

The Intent-to-Treat (ITT) population was used for the analysis. The ITT population comprise of all randomized patients regardless of whether or not treatment was administered.

ORR and its 95% CI were calculated using the exact method. The 2-sided 90% CI of the RR of ORR was estimated using a generalized linear model adjusted for the stratification factors (region, ECOG status and sex) with a log link function.

DoR was summarized by descriptive statistics. PFS was summarized using the Kaplan-Meier estimates and the difference between the two treatment arms was analyzed using a stratified log-rank test, stratifying for stratification factors at randomization.

### 3.2.5. Patient Disposition, Demographic and Baseline Characteristics

A total of 642 patients were randomized to one of two treatment arms using a 1:1 randomization ratio with 328 patients in the ABP-215 arm and 314 patients in the EU-approved bevacizumab arm. A total of 101 study centers enrolled patients in 17 countries including 14 in the United States, 3 in Mexico, 1 in Canada, 9 in Germany, 6 in Spain, 6 in Italy, 2 in Netherlands, 11 in Russia, 7 in Hungary, 7 in Romania, 8 in Poland, 5 in Greece, 5 in Bulgaria, 3 in Czech Republic, 10 in Australia, 3 in Taiwan and 1 in Hong Kong.

The study was initiated (first patient randomized) on November11, 2013 and the last patient completed the study on July 23, 2015. A total of 820 patients were screened and 642 patients were randomized into the study. A total of 633 patients in the study were treated with 4 in ABP-215 arm and 5 in EU-approved bevacizumab arm were not treated. A total of 45 patients were enrolled in the USA. Russia enrolled 113 patients, the most number of patients. The patient disposition is summarized in Table 3.

**Table 3. Patient Disposition**

| | **ABP-215** | **EU-approved bevacizumab** |
|---|---|---|
| **Randomized** | N = 328 (100) | N = 314 (100) |
| **Patients Treated** | 324 (98.8) | 309 (98.4) |
| | | |
| **Discontinued** | 324 (100) | 309 (100) |
| **Completed All Planned Doses** | 192 (59.3) | 202 (65.4) |
| **Adverse Event** | 40 (12.3) | 37 (12.0) |
| **Death** | 13 (4.0) | 11 (3.6) |
| **Disease Progression** | 45 (13.9) | 33 (10.7) |
| **Patient Request** | 16 (4.9) | 13 (4.2) |
| **Physician Decision** | 7 (2.2) | 3 (1.0) |
| **Protocol Violation** | 4 (1.2) | 2 (0.6) |
| **Need for Alternate Therapy** | 3 (0.9) | 7 (2.3) |
| **Lost to Follow-Up** | 1 (0.3) | 1 (0.3) |
| **Other** | 3 (0.9) | 0 |

Demographic characteristics at baseline are summarized in Table 4.

**Table 4. Demographics**

| | **ABP-215** N = 328 | **EU-approved bevacizumab** N = 314 |
|---|---|---|
| **Randomized** | 328 (100) | 314 (100) |
| **Gender** | | |
| **Male** | 196 (59.8) | 188 (59.9) |
| **Female** | 132 (40.2) | 126 (40.1) |
| **Race** | | |
| **Caucasian** | 313 (95.4) | 300 (95.5) |
| **Non-Caucasian** | 15 (4.6) | 14 (4.5) |
| **Age** | | |
| **< 65** | 199 (60.7) | 191 (60.8) |
| **≥ 65** | 129 (39.3) | 123 (39.2) |
| **Region** | | |
| **North America** | 31 (9.5) | 26 (8.3) |
| **Eastern Europe** | 189 (57.6) | 186 (59.2) |
| **Western Europe** | 78 (23.8) | 76 (24.2) |
| **Asia Pacific/Other** | 30 (9.1) | 26 (8.3) |

Disease characteristics at baseline are summarized in Table 5.

**Table 5. Baseline Characteristics**

| | **ABP-215** N = 328 | **EU-approved bevacizumab** N = 314 |
|---|---|---|
| **Randomized** | 328 (100) | 314 (100) |
| **ECOG Status** | | |
| **0** | 128 (39.0) | 118 (37.6) |
| **1** | 200 (61.0) | 196 (62.4) |
| **Smoking Status** | | |
| **Current** | 100 (30.5) | 80 (25.5) |
| **Former** | 163 (49.7) | 158 (50.3) |
| **Never** | 65 (19.8) | 76 (24.2) |
| **Disease Stage** | | |
| **Stage IV** | 309 (94.2) | 290 (92.4) |
| **Recurrent Disease** | 19 (5.8) | 24 (7.6) |
| **EGFR Mutation Status** | | |
| **Positive** | 7 (2.1) | 8 (2.6) |
| **Negative** | 130 (39.6) | 130 (41.4) |
| **Unknown** | 8 (2.4) | 1 (0.3) |
| **Not Performed** | 183 (55.8) | 175 (55.7) |

**Table 5. Baseline Characteristics (Continued)**

| | ABP-215<br>N = 328 | EU-approved bevacizumab<br>N = 314 |
|---|---|---|
| **Randomized** | 328 (100) | 314 (100) |
| **ALK Status** | | |
| **Postive** | 4 (1.2) | 4 (1.3) |
| **Negative** | 80 (24.4) | 71 (22.6) |
| **Not Done** | 244 (74.4) | 239 (76.1) |
| **Metastasis Classification*** | | |
| **M1a** | 120 (36.6) | 122 (38.9) |
| **M1b** | 206 (62.8) | 191 (60.8) |
| **Missing** | 2 (0.6) | 1 (0.3) |
| **Tumor Classification*** | | |
| **T0** | 9 (2.7) | 14 (4.5) |
| **T1a** | 21 (6.4) | 20 (6.4) |
| **T1b** | 18 (5.5) | 17 (5.4) |
| **T2a** | 69 (21.0) | 69 (22.0) |
| **T2b** | 34 (10.4) | 29 (9.2) |
| **T3** | 75 (22.9) | 74 (23.6) |
| **T4** | 100 (30.5) | 91 (29.0) |
| **Missing** | 2 (0.6) | 0 |
| **Nodes Classification*** | | |
| **N0** | 63 (19.2) | 68 (21.7) |
| **N1** | 30 (9.2) | 20 (6.4) |
| **N2** | 128 (39.0) | 120 (38.2) |
| **N3** | 104 (31.7) | 106 (33.8) |
| **Missing** | 3 (0.9) | 0 |

* at screening

*Reviewer's comments:*

The demographic and baseline characteristics of the ITT population are generally balanced over the two arms.

### 3.2.6. Results and Conclusions

**Primary Endpoint Analysis: ORR**

There were 642 patients in the ITT population, with 328 in the ABP-215 arm and 314 in the EU-approved bevacizumab arm. There were a total of 259 responders, of which 128 were in the ABP-215 arm and 131 in the EU-approved bevacizumab arm.

Table 6 summarizes the analysis results of the ORR. The 90% CI of the ORR risk ratio was ABP-215 was 0.93 with 90% CI (0.80, 1.09).

**Table 6. ORR Analysis Results**

| | **ABP-215** N = 328 | **EU-approved bevacizumab** N = 314 |
|---|---|---|
| **Number of Responders (%)** | 128 (39.0%) | 131 (41.7%) |
| **95%CI of ORR** | (33.7%, 44.5%) | (36.2%, 47.4%) |
| **CR(%)** | 2 (0.6%) | 2 (0.6%) |
| **PR(%)** | 126 (38.4%) | 129 (41.1%) |
| **Risk Ratio of ORR (90% CI)** | 0.93 (0.80, 1.09) | |

*Reviewer's comments:*

The 90% CI of ORR risk ratio falls into the applicant specified margins of (0.67, 1.5) as well as FDA selected similarity margin of (0.73, 1.36). This result supports a demonstration of no clinically meaningful differences between ABP-215 and the reference product.

The ORR observed in the EU-approved bevacizumab arm was comparable to the 37.7% generated by the meta-analysis for bevacizumab effect.

**Secondary Endpoints Analysis: DoR**

Among the 259 responders in the two treatment arms, median DoRs were 5.8 months in the ABP-215 arm and 5.6 months in the EU-approved bevacizumab arm. At completion of study, 85 patients in the ABP-215 arm and 86 patients in the EU-approved bevacizumab arm were censored.

**Table 7. DoR Analysis Results**

| | **ABP-215** | **EU-approved bevacizumab** |
|---|---|---|
| **Number of Responders (%)** | 128 | 131 |
| **Median DoR (95% CI)** | 5.8 (4.9, 7.7) | 5.6 (5.1, 6.3) |
| **Patient Status** | | |
| **Disease Progression (%)** | 43 (33.6) | 45 (34.4) |
| **Censored (%)** | 85 (66.4) | 86 (65.6) |

**Secondary Endpoints Analysis: PFS**

For the PFS analysis, a total of 256 patients progressed or died at time of the primary analysis, of which 131 were in the ABP-215 arm and 125 in the EU-approved bevacizumab arm.

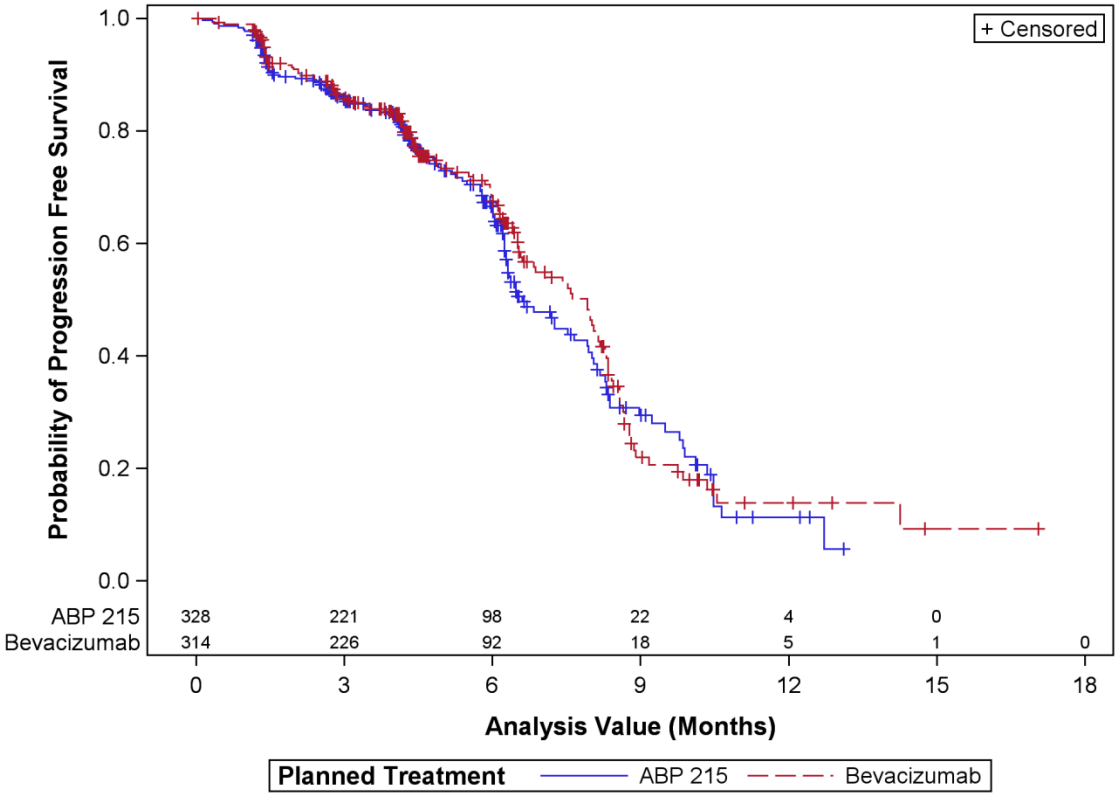
Table 8 summarizes the analysis results of PFS. The median PFS was 6.6 months in the ABP-215 arm and 7.9 months in the EU-approved bevacizumab arm. The estimated HR was 1.03 with 95% CI (0.80, 1.34) based on a Cox model stratified by geographical region, ECOG status and sex.

**Table 8. PFS Analysis Results**

| | **ABP-215** N = 328 | **EU-approved bevacizumab** N = 314 |
|---|---|---|
| **Number of Events (%)** | 131 (40%) | 125 (40%) |
| **Median PFS (95% CI)** | 6.6 (6.3, 7.9) | 7.9 (6.6, 8.2) |
| **HR (95% CI)** | 1.03 (0.80, 1.34) | |

Figure 1 shows the estimated Kaplan-Meier curves for the distribution of PFS.

**Figure 1. PFS Kaplan-Meier Curves**




*Reviewer's comments:*

The results from the secondary analyses support the demonstration that there are no clinically meaningful differences between the two products.

### 3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

# 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Gender, Race, Age, and Geographic Region

Since no hypothesis and power calculation are pre-specified in the subgroups presented in this section, all results are considered exploratory.

Table 9 summarizes the subgroup analysis of OS based the ITT population.

**Table 9. Subgroups Analyses of ORR*: Gender, Age, Race and Region**

| | Responders/N | | ORR (95% CI) | |
|---|---|---|---|---|
| | **ABP-215** | **EU-Approved Bevacizumab** | **ABP-215** | **EU-Approved Bevacizumab** |
| **Male** | 79 / 196 | 73 / 188 | 40.3 (33.4, 47.5) | 38.8 (31.8, 46.2) |
| **Female** | 49 / 132 | 58 / 126 | 37.1 (28.9, 46.0) | 46.0 (37.1, 55.1) |
| **Age <65** | 79 / 199 | 75 / 191 | 39.7 (32.8, 46.9) | 39.3 (32.3, 46.6) |
| **Age >=65** | 49 / 129 | 56 / 123 | 38.0 (29.6, 46.9) | 45.5 (36.5, 54.8) |
| **White** | 125 / 313 | 127 / 300 | 39.9 (34.5, 45.6) | 42.3 (36.7, 48.1) |
| **Non-White** | 3 / 15 | 4 / 14 | 20.0 (4.3, 48.1) | 28.6 (8.4, 58.1) |
| **North America** | 10 / 31 | 12 / 26 | 32.3 (16.7, 51.4) | 46.2 (26.6, 66.6) |
| **Western Europe** | 33 / 78 | 27 / 76 | 42.3 (31.2, 54.0) | 35.5 (24.9, 47.3) |
| **Eastern Europe** | 71 / 189 | 79 / 186 | 37.6 (30.6, 44.9) | 42.5 (35.3, 49.9) |
| **Asia Pacific/Other** | 14 / 30 | 13 / 26 | 46.7 (28.3, 65.7) | 50.0 (29.9, 70.1) |

*These analyses were not adjusted for multiplicities.

*Reviewer's comments:*

There was no outlier observed among the subgroups analyzed for ORR.

## 4.2 Other Special/Subgroup Populations

The following table summarizes other important subgroup analysis of ORR based on the ITT population.

**Table 10. Subgroup Analyses of ORR*: Baseline Characteristics**

| | Responders/N | | ORR (95% CI) | |
|---|---|---|---|---|
| | **ABP-215** | **EU-Approved Bevacizumab** | **ABP-215** | **EU-Approved Bevacizumab** |
| **ECOG=0** | 57 / 128 | 49 / 118 | 44.5 (35.7, 53.6) | 41.5 (32.5, 51.0) |
| **ECOG=1** | 71 / 200 | 82 / 196 | 35.5 (28.9, 42.6) | 41.8 (34.8, 49.1) |
| **Current Smoker** | 37 / 100 | 31 / 80 | 37.0 (27.6, 47.2) | 38.8 (28.1, 50.3) |
| **Former Smoker** | 66 / 163 | 72 / 158 | 40.5 (32.9, 48.4) | 45.6 (37.6, 53.7) |
| **Non-Smoker** | 25 / 65 | 28 / 76 | 38.5 (26.7, 51.4) | 36.8 (26.1, 48.7) |
| **M1a** | 25 / 65 | 28 / 76 | 38.5 (26.7, 51.4) | 36.8 (26.1, 48.7) |
| **M1b** | 25 / 65 | 28 / 76 | 38.5 (26.7, 51.4) | 36.8 (26.1, 48.7) |

*These analyses were not adjusted for multiplicities.

*Reviewer's comments:*
No outlier subgroup was observed among the subgroups analyzed for ORR.

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

A total of 642 patients were randomized to in 1:1 allocation with 328 in the ABP-215 arm and 314 in the EU-approved bevacizumab arm. The estimated risk ratio (RR) of ORR was 0.93 with 90% CI (0.80, 1.09), which falls within the FDA selected similarity margin of (0.73, 1.36), and the ORR was 39.0% with 95% CI (33.7%, 44.5%) in the ABP-215 arm and 41.7% with 95% CI (36.2%, 47.4%) in the EU-approved bevacizumab arm.

Median DoRs were 5.8 months in the ABP-215 arm and 5.6 months in the EU-approved bevacizumab arm. The median PFS was 6.6 months in the ABP-215 arm and 7.9 months in the EU-approved bevacizumab arm, and the estimated HR for PFS was 1.03 with 95% CI (0.80, 1.34).

## 5.2 Conclusions and Recommendations

The results of Study 265 demonstrated there are no clinically meaningful differences between ABP-215 and EU-approved bevacizumab. From statistical point of view, the data and analyses provided in this submission support a regulatory approval.

## 5.3 Labeling Recommendations

The Applicant's label would follow FDA's recommendation that in the biosimilar product labeling, applicant incorporates relevant data and information from the reference product labeling, with appropriate product specific modifications. All pre-clinical and clinical data for the indications being sought are as in the Avastin USPI.

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/s/

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WEISHI YUAN
08/02/2017

LISA R RODRIGUEZ
08/03/2017

KUN HE
08/03/2017

# STATISTICAL REVIEW AND EVALUATION

**Biometrics Division: VI**

| | |
|---|---|
| **BLA NO.** | 761028 |
| **DATE RECEIVED BY THE CENTER** | 12/13/2016 |
| **DRUG NAME** | anti-VEGF monoclonal antibody (ABP215) |
| **DOSAGE FORM** | Single use vial/Liquid |
| **STRENGTH** | 100 mg/4 mL, 400 mg/16 mL (25mg/ml) |
| **INDICATION** | Metastatic colorectal cancer, Non-squamous non-small cell lung cancer, Glioblastoma, Metastatic renal cell carcinoma, Cervical cancer |
| **SPONSOR** | Amgen, Inc. |
| **REVIEW FINISHED** | 07/18/2017 |
| **STATISTICAL REVIEWER** | Tianhua Wang, Ph.D. |
| **SECONDARY REVIEWER** | Meiyu Shen, Ph.D. |
| **PROJECT MANAGER** | Leah S. Her, MS, PMP |

_____

Tianhua Wang, Ph.D., Mathematical Statistician, CDER/OTS/OB/DB VI
Meiyu Shen, Ph.D., Lead Mathematical Statistician, CDER/OTS/OB/DB VI

Concur: _____

Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DB VI

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Meiyu Shen, Ph.D., Lead Mathematical Statistician, CDER/OTS/OB/DB VI
Yi Tsong, Ph.D., Division Director, CDER/OTS/OB/DB VI
Lillian Patrician, CDER/OTS/OB
Leah S. Her, MS, PMP, OMPT/CDER/OND/OHOP/DOPII

# TABLE OF CONTENTS

# 1 EXECUTIVE SUMMARY AND RECOMMENDATION

The CMC statistical reviewer in the Office of Biostatistics analyzed the comparative results of 2 critical quality attributes: % Relative Potency as assessed by Proliferation Inhibition Bioassay and VEGF-A Binding by ELISA, which were recommended for equivalence testing analysis by the Office of Biotechnology. Tier 1 statistical equivalence testing was conducted using equivalence margins of $\pm 1.5\sigma_R$, where R represents the reference product US-licensed Avastin or comparator product EU-approved bevacizumab. Thirteen ABP 215 drug product lots, 24 US-licensed Avastin lots, and 27 EU-approved bevacizumab lots were used for equivalence testing for % Relative Potency as assessed by Proliferation Inhibition Bioassay. The results are summarized in Table 1.

**Table 1**: Equivalence testing results for the Proliferation Inhibition Bioassay

| Comparison | # of lots | Mean Difference, % | 90% Confidence Interval for Mean Difference, % | Equivalence Margin, % | Pass the Equivalence Testing? |
|---|---|---|---|---|---|
| ABP 215 vs. US | (13, 24) | 2.92 | (+0.55, +5.29) | (-5.90, +5.90) | Yes |
| ABP 215 vs. EU | (13, 27) | 3.31 | (+0.98, +5.64) | (-5.64, +5.64) | Yes |
| EU vs. US | (27, 24) | -0.39 | (-2.21, +1.42) | (-5.90, +5.90) | Yes |

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

Thirteen ABP 215 drug product lots, 14 US-licensed Avastin lots and 13 EU-approved bevacizumab lots were used for equivalence testing for VEGF-A binding by ELISA. The results are summarized in Table 2.

**Table 2:** Equivalence testing results for the VEGF-A Binding by ELISA

| Comparison | # of lots | Mean Difference, % | 90% Confidence Interval for Mean Difference, % | Equivalence Margin, % | Pass the Equivalence Testing? |
|---|---|---|---|---|---|
| ABP 215 vs. US | (13, 14) | 0.63 | (-2.93, +4.18) | (-9.79, +9.79) | Yes |
| ABP 215 vs. EU | (13, 13) | 4.85 | (+1.23, +8.45) | (-9.57, +9.57) | Yes |
| EU vs. US | (13, 24) | -4.22 | (-8.47, +0.03) | (-9.79, +9.79) | Yes |

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

As shown in Tables 1 and 2, the results from the statistical equivalence testing of % Relative Potency as assessed by Proliferation Inhibition Bioassay and VEGF-A Binding by ELISA support a demonstration that the proposed biosimilar ABP215 is highly similar to US-licensed Avastin. The results also support the analytical portion of the scientific bridge to justify the relevance of EU-approved bevacizumab data from the comparative clinical study.

## 2 INTRODUCTION

On November 14, 2016, Amgen Inc. submitted to the U.S. Food and Drug Administration (FDA) a 351(k) BLA which included an analytical similarity assessment of comparing the Tier 1 quality attributes for ABP 215, US-licensed Avastin, and EU-approved bevacizumab.

Amgen, Inc. used 13 ABP 215 drug product lots for the Tier 1 analytical similarity assessment. This encompasses development lots, all lots used in clinical studies, and 3 process validation lots. Throughout development, no changes in scale and no significant changes to the drug substance manufacturing process have been made. All ABP 215 drug substance lots manufactured using the proposed commercial process are included to represent the expected ABP 215 process variability. For parameters primarily influenced by the drug substance manufacturing process (eg, glycan profile, purity, and potency), data from a single drug product lot representing each of the 13 unique ABP 215 drug substance lots is included in the similarity assessment. Thirteen ABP 215 lots used for analytical similarity are summarized in Table 3. The approximate ages at testing months for the 13 ABP 215 Drug Product lots used for the analytical similiarity assessement were all within the shelf lives.

Bevacizumab drug product was sourced from both the US and EU on a regular basis, over a period of approximately 6 years by Amgen, Inc. The bevacizumab drug product used in the similarity assessment had a remaining shelf life of approximately 3 to 23 months based on the expiration dates. A total of 27 US-licensed Avastin lots and 29 EU-approved bevacizumab lots, including all lots used in the clinical trials, were tested as part of the analytical similarity assessment. The US-licensed Avastin and EU-approved bevacizumab lots used in the similarity assessment are provided in Table 4 and Table 5, respectively. Some of the US-licensed Avastin and EU-approved bevacizumab lots are excluded in the final equivalence testing. FDA CMC Statistical reviewer sent out the information request letter to Amgen on Feburay 13, 2017. FDA request Amgen to provide the selection criteria of the US-licensed Avastin and EU-

approved bevacizumab lots used for testing in the 2 Tier 1 assays. The response of the information request was received on Feburay 23, 2017. Amgen justified that 1): Prior to the assay qualification, 3 US-licensed Avastin and 2 EU-approved bevacizumab lots had expired. Therefore, these lots were not evaluated using the Proliferation Inhibition Bioassay in the analytical similarity assessment. 2): Specific selection criteria were not used to determine which lots to include in the VEFG-A binding assay evaluation. Unexpired lots and those with available appropriately stored retains were included to ensure enough power to evaluate the data using the Tier 1 equivalence assessment criteria. FDA accepted Amgen's information response and agreed that a total of 24 bevacizumab (US) and 27 EU-approved bevacizumab lots were tested with the proliferation inhibition bioassay, and a total of 14 bevacizumab (US) and 13 EU-approved bevacizumab lots were testedfor VEGF-A binding by ELISA.

**Table 3:** ABP 215 Drug Product Lots Used to Demonstrate Analytical Similarity

| ABP 215 Drug Product Lot Number | Strength | ABP 215 Drug Substance Lot Number | Date of DS Manufacture | Intended Use | Site of Manufacture |
|---|---|---|---|---|---|
| 0010085282 | 400 mg | 0010092386 | Jun 2011 | Toxicology, stability | ATO |
| 0010085284 | 400 mg | 0010090537 | Jun 2011 | Development | ATO |
| 0010085286 | 400 mg | 0010094760 | Jun 2011 | Development | ATO |
| 0010095534 | 400 mg | 0010094224 | Feb 2012 | Clinical, stability | ATO |
| 0010112870 | 400 mg | 0010094225 | Feb 2012 | Clinical | ATO |
| 0010133673 | 400 mg | 0010115169 | Sep 2012 | Clinical, stability | ATO |
| 0010149803 | 400 mg | 0010137447 | Jan 2013 | Clinical, stability | ATO |
| 0010205488 | 400 mg | 0010184448 | Sep 2014 | Clinical, stability | ATO |
| 0010282118 | 100 mg | 0010208232 | Feb 2016 | Process validation, stability | (b) (4) |
| 0010282119 | 100 mg | 0010259543 | Feb 2016 | Process validation, stability | |
| 0010282121 | 400 mg | 0010259544 | Feb 2016 | Process validation, stability | |
| 0010282122 | 400 mg | 0010259545 | Mar 2016 | Process validation, stability | |
| 0010282123 | 400 mg | 0010259546 | 08 Dec 2015 | Process validation, stability | |

**Table 4:** 27 US-Licensed Avastin Drug Product Lots Information.

| Drug Product Lot Number | Presentation | Labeled Expiry Date | Used in the Equivalence Test of "% Relative Potency as assessed by Proliferation Inhibition Bioassay"? | Used in the Equivalence Test of "VEGF-A Binding by ELISA"? |
|---|---|---|---|---|
| 791839 | 100 mg | May 2011 | | |
| 794245 | 100 mg | Jun 2011 | | |
| 794253 | 100 mg | Jul 2011 | | |
| 810591 | 400 mg | Oct 2011 | Yes | |
| 861171 | 400 mg | May 2012 | Yes | |
| 927075 | 400 mg | Aug 2012 | Yes | |
| 911121 | 400 mg | Oct 2012 | Yes | |
| 913149 | 400 mg | Oct 2012 | Yes | |
| 927074 | 400 mg | Nov 2012 | Yes | |
| 970032 | 400 mg | Sep 2013 | Yes | Yes |
| 450657 | 400 mg | Oct 2013 | Yes | Yes |
| 970031 | 400 mg | Oct 2013 | Yes | Yes |
| 971630 | 100 mg | Oct 2013 | Yes | |
| 469053 | 100 mg | Apr 2014 | Yes | |
| 503227 | 100 mg | Apr 2014 | Yes | |
| 499096 | 400 mg | Jul 2014 | Yes | |
| 503224 | 400 mg | Aug 2014 | Yes | Yes |
| 605024 | 400 mg | Jan 2016 | Yes | Yes |
| 616370 | 400 mg | May 2016 | Yes | Yes |
| 640016 | 100 mg | Jun 2016 | Yes | Yes |
| 640018 | 100 mg | Jul 2016 | Yes | Yes |
| 660666 | 400 mg | Aug 2016 | Yes | Yes |
| 660705 | 400 mg | Sep 2016 | Yes | Yes |
| 3044096 | 100 mg | Aug 2017 | Yes | Yes |
| 3063923 | 100 mg | Sep 2017 | Yes | Yes |
| 3067997 | 100 mg | Oct 2017 | Yes | Yes |
| 3074233 | 100 mg | Oct 2017 | Yes | Yes |

**Table 5:** 29 EU-approved bevacizumab Drug Product Lots Information.

| Drug Product Lot Number | Presentation | Labeled Expiry Date | Used in the Equivalence Test of "% Relative Potency as assessed by Proliferation Inhibition Bioassay"? | Used in the Equivalence Test of "VEGF-A Binding by ELISA"? |
|---|---|---|---|---|
| H0001B01 | 100 mg | Jul 2011 | | |
| B0001B03 | 100 mg | Jul 2011 | | |
| H0114B01 | 400 mg | Aug 2012 | Yes | |
| H0118B02 | 400 mg | Nov 2012 | Yes | |
| H0120B01 | 400 mg | Nov 2012 | Yes | |
| H0121B01 | 400 mg | Jan 2013 | Yes | |
| H0007B23 | 100 mg | Mar 2013 | Yes | |
| H0021B06 | 400 mg | Jun 2013 | Yes | |
| H0111B10 | 100 mg | Aug 2013 | Yes | |
| H0134B01 | 400 mg | Oct 2013 | Yes | |
| H0135B13 | 400 mg | Oct 2013 | Yes | |
| H0138B01 | 400 mg | Oct 2013 | Yes | |
| H0142B04 | 400 mg | Nov 2013 | Yes | |
| H0113B16 | 100 mg | Feb 2014 | Yes | |
| H0150B12 | 400 mg | Apr 2014 | Yes | Yes |
| B7102B10 | 100 mg | Mar 2015 | Yes | |
| B7103B17 | 100 mg | Mar 2015 | Yes | Yes |
| B8006B01 | 400 mg | Mar 2015 | Yes | Yes |
| B7115B10 | 400 mg | Jun 2015 | Yes | Yes |
| B7003B03 | 400 mg | Jul 2015 | Yes | Yes |
| B7108B02 | 100 mg | Oct 2015 | Yes | Yes |
| B7108B22 | 100 mg | Oct 2015 | Yes | |
| B7036B01 | 400 mg | Mar 2016 | Yes | Yes |
| B8500H06 | 400 mg | Jul 2016 | Yes | Yes |
| B8502H30 | 100 mg | Oct 2016 | Yes | Yes |
| B7216H12 | 400 mg | Mar 2017 | Yes | Yes |
| B7219H04 | 400 mg | Apr 2017 | Yes | Yes |
| B8006H24 | 100 mg | Jul 2017 | Yes | Yes |
| B8006H20 | 100 mg | Jul 2017 | Yes | Yes |

The Agency carefully evaluated the data for the % Relative Potency as assessed by Proliferation Inhibition Bioassay and VEGF-A Binding by ELISA provided in the BLA submission. Our comments regarding Amgen, Inc.'s equivalence testing (Tier 1 approach) is provided in Section 3, and our independent statistical equivalence testing analyses are presented in Section 4.

## 3 APPLICANT'S STATISTICAL EQUIVALENCE TESTING

In this submission, Amgen, Inc. conducted Tier 1 statistical equivalence testing with the margin defined as $\left(-1.5\hat{\sigma}_R,\ +1.5\hat{\sigma}_R\right)$ for % Relative Potency as assessed by Proliferation Inhibition Bioassay and VEGF-A Binding by ELISA. Pairwise comparisions were used for the assessment of the Tier 1 quality attributes. Similarity is demonstrated if all the two-sided 90% confidence intervals of the difference between means for ABP 215 vs. US-licensed Avastin, ABP 215 vs. EU-approved bevacizumab, and EU-approved bevacizumab vs. US-licensed Avastin are within the EAC of $\left(-1.5\hat{\sigma}_R,\ +1.5\hat{\sigma}_R\right)$, where R represents the reference product US-licensed Avastin or the comparator product EU-approved bevacizumab in each of the 3 pairwise comparisions. Amgen, Inc. presumed unequal variances for the two-sided 90% confidence interval. FDA CMC statistics reviewer's comments on Amgen, Inc.'s equivalence testing are:

1) Amgen, Inc.'s statistical approach generally followed the agent's current recommendation for Tier 1 analytical similarity assessment.
2) Amgen did not adjust the imbalance sample size between the 27 EU-approved bevacizumab lots, 13 ABP 215 lots and 24 US-licensed Avastin lots, specifically for the tier 1 equivalence testing for relative potency. Amgen did not restrict the degrees of freedom so that no more reference product lots than 1.5 times biosimilar or intended comparision drug product lots are included.

FDA CMC statistical reviewer applied the correct adjustment on the sample size into the FDA CMC Statistical analysis in section 4.

## 4 FDA STATISTICAL ANALYSES

To evaluate analytical similarity, the Agency recommends a tiered approach. That is, product quality attributes are assigned to three tiered based on their criticality. The quality attributes with

potential highest risk in product quality, efficiency, safety and PK/PD are assigned to Tier 1, in which analytical similarity is assessed by statistical equivalence test. Quality attributes with lower impact are 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 (Mean – X*SD, Mean + X*SD) defined by the reference product. Here, the multiplier X should be justified by the scientific knowledge. The quality attributes with the lowest risk are assigned to Tier 3 and their analytical similarity is evaluated by side-by-side comparison using graphic display. This review focuses on the equivalence testing in Tier 1.

### 4.1 Statistical method

Let $\mu_T$ and $\mu_R$ be respectively the population means of the quality attribute for the test product and the population mean of the quality attribute for the US-licensed Avastin product. Let $\sigma_R$ be the standard deviation of the quality attribute of interest for the US-licensed Avastin. In order to conclude the equivalence in the quality attribute of interest between the test product and the US-licensed Avastin product, we aim to reject the null hypothesis of the following null and alternative hypotheses:

$$H_0: \mu_T - \mu_R \leq \theta_1 \quad \text{or} \quad \mu_T - \mu_R \geq \theta_2$$
$$H_1: \theta_1 < \mu_T - \mu_R < \theta_2$$

.

Here $\theta_1 = -1.5\sigma_R$, $\theta_2 = 1.5\sigma_R$ , $\theta_1$ and $\theta_2$ are equivalence margins.

We reject $H_0$ if 90% confidence interval for the mean difference in the quality attribute of interest falls within $(-1.5\sigma_R, 1.5\sigma_R)$. In other words, we conclude that the equivalence in the quality attribute of interest between the test product and the US-licensed Avastin product if 90% confidence interval for the mean difference in the quality attribute 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 US-licensed Avastin 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 $(-1.5\sigma_R, 1.5\sigma_R)$ is 87% if the true mean difference is $0.125\sigma_R$ for a sample size of

10 biosimilar lots and 10 US-licensed Avastin lots. When the number of lots is smaller than 10, the test size may be relaxed somewhat, but agreement on this should be reached in advance with FDA scientists. First we estimate $\sigma_R$ by the sample variability of the US-licensed Avastin product and then in the statistical analysis, $\theta_1$ and $\theta_2$ are treated as a constant, not a random variable.

Let $X_{Tj}$ be the observed value of the quality attribute of interest for Batch j of the test product (the proposed biosimilar product) and $X_{Rj}$ be the observed value of the quality attribute of interest for Batch j of the US-licensed Avastin product. Since the two products are manufactured by two manufacturers, two groups are independent. $\overline{X}_i = \frac{\sum_{j=1}^{n_i} X_{ij}}{n_i}$ and $S_i^2 = \frac{\sum_{j=1}^{n_i} (X_{ij} - \overline{X}_i)}{(n_i - 1)}$, 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 US-licensed Avastin product, the $(1 - 2\alpha) \times 100\%$ confidence interval of the mean difference in the quality attribute of interest can be calculated as:

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

Here $t_\alpha(v)$ is the $(1 - \alpha)$ quantile and v is the degrees of freedom calculated by Satterthwaite's approximation.

If $n_R > 1.5n_T$, the $(1 - 2\alpha) \times 100\%$ confidence interval of the mean difference in the quality attribute of interest can be calculated as:

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

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

If the number of biosimilar lots, $n_T$, is 50% more than the number of reference lots, $n_R$, we can apply a similar approach as above with $n_T^* = \min(n_T, 1.5n_R)$ for the confidence interval calculation. In the following analyses, we use $\alpha = 0.05$.

### 4.2 FDA statistical equivalence testing for Proliferation Inhibition Bioassay

The Proliferation Inhibition Bioassay data distributions of ABP215, US-licensed Avastin and EU-approved bevacizumab are displayed in Figure 1. Thirteen batches of ABP215, 24 batches of US-licensed Avastin, and 27 batches of EU-approved bevacizumab are included in the Proliferation Inhibition Bioassay dataset for statistical equivalence testing. Descriptive statistics for the Proliferation Inhibition Bioassay data of ABP215, US-licensed Avastin, and EU-approved bevacizumab are listed in Table 6.

**Figure 1:** Scatter plots of proliferation Inhibition bioassay for US-licensed Avastin, ABP215, and EU-approved bevacizumab.

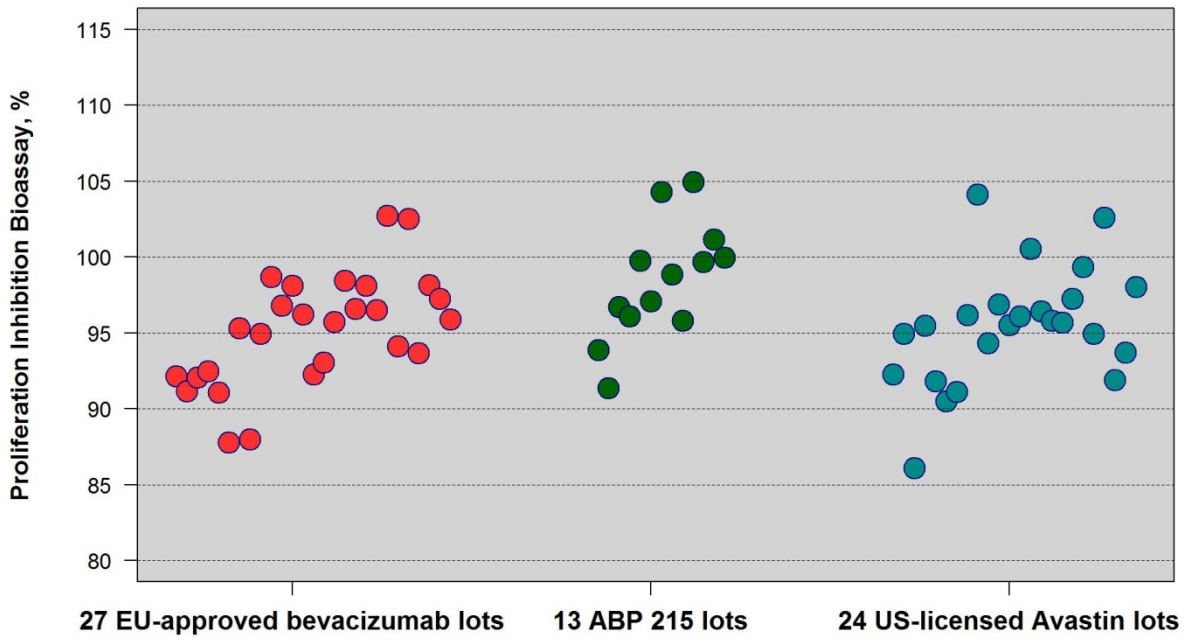


**Table 6**: Descriptive statistics for the proliferation inhibition bioassay data

| Product | Number of lots | Sample mean, % | Sample standard deviation, % | Min, % | Max, % |
|---|---|---|---|---|---|
| ABP 215 | 13 | 98.5 | 3.86 | 91 | 105 |
| US-licensed Avastin | 24 | 95.5 | 3.93 | 86 | 104 |
| EU-approved bevacizumab | 27 | 98.1 | 3.76 | 88 | 103 |

Table 7 shows that the 90% confidence interval for the mean difference in the Proliferation Inhibition Bioassay between ABP215 and US-licensed Avastin is (0.55, 5.29)%. It falls entirely within the equivalence margin (-5.90, +5.90)%. Hence, the results of the Proliferation Inhibition Bioassay for ABP215 are equivalent to those for US-licensed Avastin.

It also shows that the 90% confidence interval for the mean difference in Proliferation Inhibition Bioassay between ABP215 and EU-approved bevacizumab is (0.98, 5.64)%. It falls within the equivalence margin (-5.64, 5.64)%. Therefore, the results of the Proliferation Inhibition Bioassay for ABP215 are equivalent to those for EU-approved bevacizumab.

The 90% confidence interval for the mean difference in Proliferation Inhibition Bioassay between EU-approved bevacizumab and US-licensed Avastin is (-2.21, 1.42)%, which falls entirely within the equivalence margin (-5.90, 5.90)%. Therefore, the results of the Proliferation Inhibition Bioassay for EU-approved bevacizumab are equivalent to those for US-licensed Avastin.

The statistical equivalence analyses support that relative potency as measured by the Proliferation Inhibition Bioassay of ABP215 is similar to that of US-licensed Avastin. The results of all three pairwise comparisons support the analytical portion of the scientific bridge to justify the relevance of the data obtained from clinical studies that compared EU-approved bevacizumab and the ABP215 product to support a demonstration of biosimilarity to US-licensed Avastin.

**Table 7**: Results of equivalence testing for Potency by Bioassay

| Comparison | # of lots | Mean Difference, % | 90% Confidence Interval for Mean Difference, % | Equivalence Margin, % | Pass the Equivalence Testing? |
|---|---|---|---|---|---|
| ABP 215 vs. US | (13, 24) | 2.92 | (0.55, 5.29) | (-5.90, +5.90) | Yes |
| ABP 215 vs. EU | (13, 27) | 3.31 | (0.98, 5.64) | (-5.64, +5.64) | Yes |
| EU vs. US | (27, 24) | -0.39 | (-2.21, 1.42) | (-5.90, +5.90) | Yes |

### 4.3 FDA statistical equivalence testing for VEGF-A Binding by ELISA

Scatter plots of the VEGF-A Binding by ELISA for ABP215, US-licensed Avastin and EU-approved bevacizumab are shown in Figure 2. Thirteen batches of ABP215, 14 batches of US-licensed Avastin, and 13 batches of EU-approved bevacizumab are included in the VEGF-A Binding by ELISA dataset for statistical equivalence testing. Descriptive statistics for the VEGF-A Binding by ELISA data of ABP215, US-licensed Avastin, and EU-approved bevacizumab are listed in Table 8.

**Figure 2:** Scatter plots of VEGF-A binding by ELISA for US-licensed Avastin, ABP215, and EU-approved bevacizumab

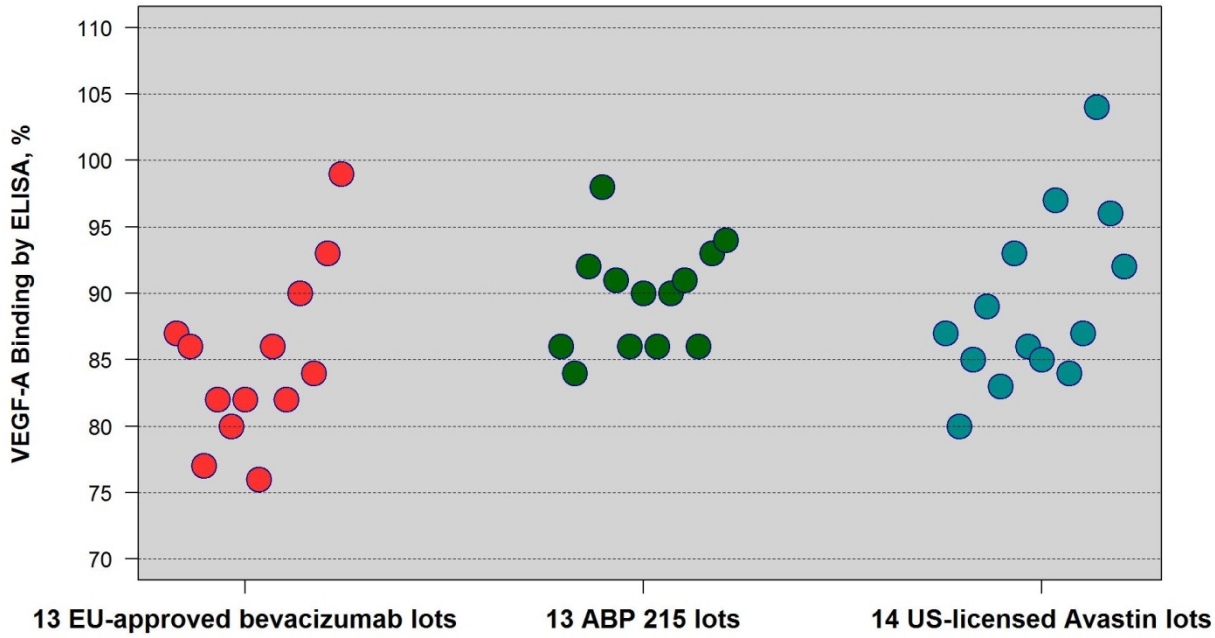

**Table 8**: Descriptive statistics for the VEGF-A binding by ELISA data

| Product | Number of lots | Sample mean, % | Sample standard deviation, % | Min, % | Max, % |
|---|---|---|---|---|---|
| ABP 215 | 13 | 89.8 | 4.02 | 84 | 98 |
| US-licensed Avastin | 14 | 89.1 | 6.53 | 80 | 104 |
| EU-approved bevacizumab | 13 | 84.9 | 6.38 | 76 | 99 |

Table 9 shows that the 90% confidence interval for the mean difference in the VEGF-A Binding by ELISA between ABP215 and US-licensed Avastin is (-2.93, 4.18)%. It falls entirely within the equivalence margin (-9.79, +9.79)%. Hence the VEGF-A binding by ELISA of ABP215 is equivalent to the VEGF-A binding by ELISA of US-licensed Avastin.

It also shows that the 90% confidence interval for the mean difference in the VEGF-A binding by ELISA between ABP215 and EU-approved bevacizumab is (1.24, 8.45)%. It falls within the equivalence margin (-9.57, 9.57)%. Therefore, the VEGF-A binding by ELISA of ABP215 is equivalent to the VEGF-A binding by ELISA of EU-approved bevacizumab.

The 90% confidence interval for the mean difference in VEGF-A binding by ELISA between EU-approved bevacizumab and US-licensed Avastin is (-8.47, 0.03)%, which falls entirely within the equivalence margin (-9.79, 9.79)%. Therefore, the VEGF-A binding by ELISA of EU-approved bevacizumab is equivalent to the VEGF-A binding by ELISA of US-licensed Avastin.

The statistical equivalence analyses support that VEGF-A binding measured by ELISA of ABP215 is similar to that of US-licensed Avastin. The results of all three pairwise comparisons support the analytical portion of the scientific bridge to justify the relevance of the data obtained from clinical studies that compared EU-approved bevacizumab and the ABP215 product to support a demonstration of biosimilarity to US-licensed Avastin.

**Table 9**: Equivalence testing results for the VEGF-A Binding by ELISA

| Comparison | # of lots | Mean Difference, % | 90% Confidence Interval for Mean Difference, % | Equivalence Margin, % | Pass the Equivalence Testing? |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| ABP 215 vs. US | (13, 14) | 0.63 | (-2.93, 4.18) | (-9.79, +9.79) | Yes |
| ABP 215 vs. EU | (13, 13) | 4.85 | (1.23, 8.45) | (-9.57, +9.57) | Yes |
| EU vs. US | (13, 14) | -4.22 | (-8.47, 0.03) | (-9.79, +9.79) | Yes |

# 5 CONCLUSION AND RECOMMENDATION

The statistical equivalence analyses shown above regarding VEGF-A binding and the inhibition of HUVEC proliferation of ABP215 support a demonstration that ABP215 is highly similar to US-licensed Avastin. They also support the analytical portion of the scientific bridge to justify the relevance of EU-approved bevacizumab data from the comparative clinical study.

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/s/

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