FDA Briefing Document

Oncologic Drugs Advisory Committee

July 13, 2017

BLA 761028

ABP215, a proposed biosimilar to Avastin (bevacizumab)

Amgen Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the 351(k) BLA for ABP215 with the Applicant's proposed indications to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

Table of Contents

Table of Tables

Table of Figures

1 INTRODUCTION

The Applicant (Amgen) submitted a Biologics License Application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for ABP215[1], a proposed biosimilar to US-licensed Avastin (bevacizumab). BLA #125085 for Avastin was initially licensed by FDA on February 26, 2004, and the BLA license holder is Genentech. The Applicant is seeking licensure of ABP215 for the following indications for which US-licensed Avastin is approved[2]:

- 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.

ABP215 was developed as 100 mg per 4 mL and 400 mg per 16 mL single-use vials to reflect the same strength and presentations approved for US-licensed Avastin. Proposed dosing and administration labeling instructions are the same as those approved for US-licensed Avastin.

1 In this document, FDA generally refers to the Applicant's proposed product by the Applicant descriptor "ABP215". FDA has not yet designated a nonproprietary name for the Applicant's proposed biosimilar product that includes a distinguishing suffix (see Final Guidance on Nonproprietary Naming of Biological Products).

2 US-licensed Avastin's indication for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is platinum-*resistant* in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan is protected by orphan drug exclusivity expiring on November 14, 2021. US-licensed Avastin's indication for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is platinum-*sensitive* in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine is protected by orphan drug exclusivity expiring on December 6, 2023. See the Orphan Drug Designations and Approvals database at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm. The Applicant is not seeking licensure for these indications in their application.

2 BACKGROUND

2.1 Introduction to Regulatory Pathway

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety, purity, and potency of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product specific nonclinical and clinical data.

The PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a "stand-alone" marketing application). The goal of a "stand-alone" development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be structurally and functionally highly similar to a reference product is anticipated to behave like the reference product in clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and

the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data such as nonclinical and/or clinical data, can be tailored to address residual uncertainty(ies).

The 'totality of the evidence' submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and, if applicable, pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the US-licensed reference product. When an applicant's proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant must provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

2.2 The Reference Product

The BPCI Act defines the "reference product" as the single biological product licensed under section 351(a) of the PHS Act against which a proposed biosimilar product is evaluated in a 351(k) application. In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the reference product, in this case, US-licensed Avastin. When an applicant's proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant must provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., the proposed biosimilar product, the reference product, and the non-US-licensed comparator product) and is likely to also include bridging clinical PK or PD study data for all three products.

3 EXECUTIVE SUMMARY

This is a 351(k) BLA submitted by Amgen, Inc. for ABP215, a proposed biosimilar to US-licensed Avastin (bevacizumab). The Applicant is seeking licensure for the

indications approved for US-licensed Avastin listed in the introduction. The application consists of:

- Extensive analytical data intended to support (i) a demonstration that ABP215 and US-licensed Avastin are highly similar; (ii) a demonstration that ABP215 can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet appropriate quality standards; and (iii) a justification of the relevance of the comparative data generated using EU-approved bevacizumab to support a demonstration of biosimilarity of ABP215 to US-licensed Avastin.

- A single-dose pharmacokinetic (PK) study (Study 20110216) providing a three-way comparison of ABP215, US-licensed Avastin, and EU-approved bevacizumab intended to (i) support PK similarity of ABP215 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 ABP215 to US-licensed Avastin.

- A comparative clinical study (Study 20120265) between ABP215 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 ABP215 and US-licensed Avastin. This was a randomized, double-blind, parallel group study conducted in 642 patients with previously untreated NSCLC who were randomized (1:1) to receive carboplatin and paclitaxel with ABP215 or EU-approved bevacizumab (15 mg/kg dose every 3 weeks for up to 6 cycles). The primary endpoint of Study 20120265 was the risk ratio of the overall response rate (ORR). The study met its primary endpoint, as the risk ratio of ORR fell within the pre specified margin. In addition to meeting the primary endpoint, the study showed that cardinal anti-VEGF effects (e.g., hypertension) were similar between arms.

- A scientific justification for extrapolation of data to support biosimilarity in each of the additional indications for which the Applicant is seeking licensure.

The Applicant used a non-US-licensed comparator (EU-approved bevacizumab) in the comparative clinical study intended to support a demonstration of no clinically meaningful differences from US-licensed Avastin. Accordingly, the Applicant provided scientific justification for the relevance of that data by establishing an adequate scientific bridge between EU-approved bevacizumab, US-licensed Avastin, and ABP215. Review of an extensive battery of test results provided by the Applicant confirmed the adequacy of the scientific bridge and hence the relevance of comparative clinical data obtained with EU-approved bevacizumab to support a demonstration of biosimilarity to US-licensed Avastin. This battery of tests included both analytical studies and a comparative PK study in humans.

In considering the totality of the evidence, the data submitted by the Applicant support a demonstration that ABP215 is highly similar to US-licensed Avastin, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between ABP215 and US-licensed Avastin in terms of the safety, purity, and potency of the product.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support biosimilarity to other conditions of use and potential licensure of ABP215 for each of the indications for which US-licensed Avastin is currently licensed and for which the Applicant is eligible for licensure.

4 DRAFT POINTS TO CONSIDER

Discussion Point 1:
Please discuss whether the evidence supports a demonstration that ABP215 is highly similar to US-licensed Avastin, notwithstanding minor differences in clinically inactive components.

Discussion Point 2:
Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between ABP215 and US-licensed Avastin in the studied condition of use.

Discussion Point 3:
Please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications[2].

Voting Point 1:
Does the totality of the evidence support licensure of ABP215 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 as listed below:

- 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.

5 RELEVANT REGULATORY HISTORY

The first interaction with FDA regarding the ABP215 development program occurred during a Biosimilar Biological Product Development (BPD) meeting held on July 12, 2011, with follow-up interactions to discuss product quality, non-clinical, and clinical issues.

During a July 30, 2013, BPD Type 3 meeting, FDA agreed that PK similarity between ABP215 and US-licensed Avastin, between ABP215 and EU-approved bevacizumab, and EU-approved bevacizumab and US-licensed Avastin appeared to have been established based on a preliminary analysis of the data submitted from Study 20110216.

FDA and the Applicant also held a discussion regarding the design of Study 20120265 intended to compare EU-approved bevacizumab with ABP215. FDA agreed that EU-approved bevacizumab could be used in the proposed comparative clinical study if an adequate scientific bridge was established.

On December 12, 2014, FDA issued an advice letter with additional recommendations for the calculation of the similarity (equivalence) margin for Study 20120265. These recommendations were made based on the Agency's current thinking about comparative clinical studies intended to assess clinically meaningful differences between ABP215 and US-licensed Avastin. During a subsequent January 21, 2015, BPD Type 1 meeting, the Applicant clarified that the study had completed enrollment and FDA acknowledged that due to the regulatory timelines associated with gaining approval and implementing a global protocol amendment, requirement for new contracts with study sites, Contract Research Organizations and laboratories; FDA's advice to increase the Study 20120265 sample size based on FDA's recommended similarity margin could not be implemented. FDA stated that the Applicant's lower equivalence margin for Study 20120265 would be considered in the context of the totality of the evidence and recommended that the Applicant submit the rationale for their margin selection in the BLA.

FDA and the Applicant held meetings on May 20, 2015, and February 5, 2016, to discuss the proposed format and contents of the BLA.

6 CMC

Executive Summary
The Applicant utilized an array of analytical methods to assess the primary and higher order structure, physicochemical properties, and biological functions of ABP215 in comparison to US-licensed Avastin and EU-approved bevacizumab. The comparison to

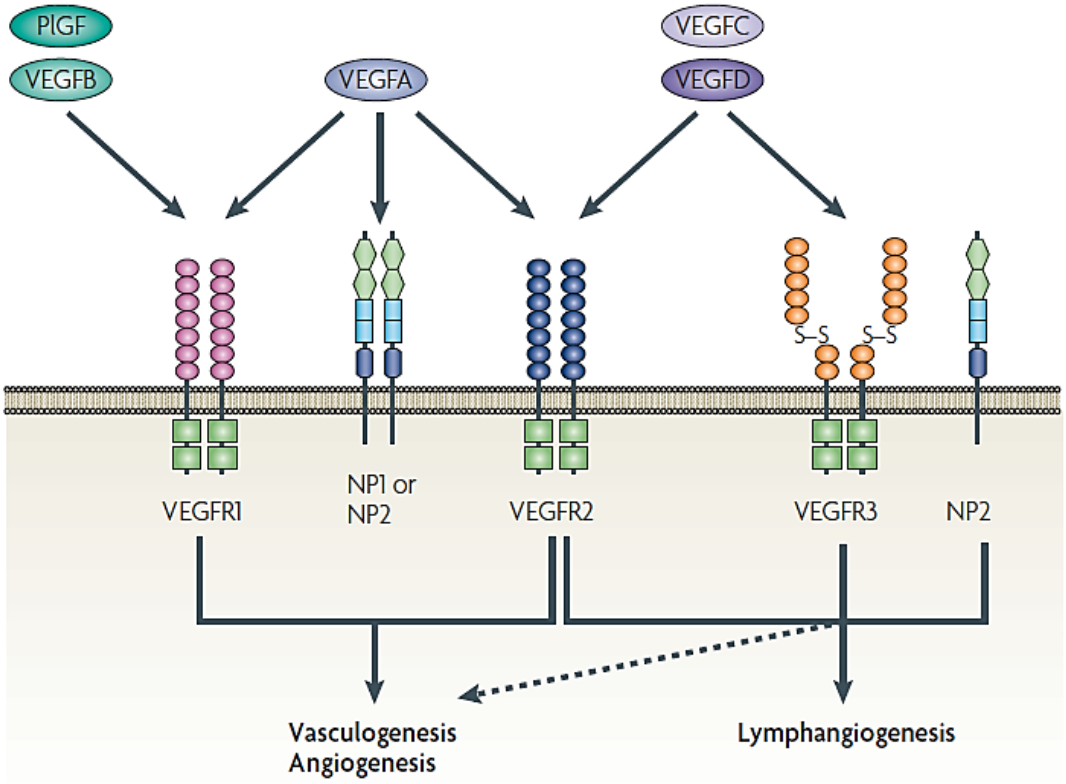
EU-approved bevacizumab was performed to provide the analytical portion of the scientific bridge to justify the use of clinical data generated using EU-approved bevacizumab as the comparator. The results of the analytical similarity assessment showed that each pairwise comparison between products met the pre-specified acceptance criteria for analytical similarity that also included statistical equivalency criteria for the potency bioassay (inhibition of endothelial cell proliferation assay) and for binding to the target antigen, vascular endothelial growth factor A. These results support a demonstration that ABP215 is highly similar to US-licensed Avastin. Minor differences in glycosylation profile, charge variant profile, levels of aggregates, levels of fragments and FcγRIIIa (158V) binding were observed. In each case, the differences did not preclude a demonstration that ABP215 is highly similar to US-licensed Avastin, as the differences were evaluated and not found to have clinical impact.

The results of the analytical similarity assessment which consisted of three pair-wise analytical comparisons of ABP215 to US-licensed Avastin, ABP215 to EU-approved bevacizumab, and EU-approved bevacizumab to US-licensed Avastin, provide an adequate analytical portion of the scientific bridge between EU-approved bevacizumab, US-licensed Avastin, and ABP215 to justify the relevance of the comparative clinical data generated using EU-approved bevacizumab.

6.1 Pathophysiologic Role of VEGF and Mechanism of Action of Avastin

Vascular endothelial growth factor family members, A (VEGFA), B, C, D, and placental growth factor, belong to a superfamily of proteins that are classified as cysteine knot growth factors based on structure (Muller Y. e., 1997) and are responsible for regulating vasculogenesis, angiogenesis, and lymphangiogenesis under both normal (e.g., developmental and wound repair functions) and pathophysiological (e.g., tumor growth and intraocular neovascularization) conditions. VEGFA provides several functions that are important for angiogenesis and include induction of endothelial cell proliferation and survival, increase in vascular permeability, and chemotaxis and homing of bone marrow cells for hematopoiesis (Ferrara, Vascular Endothelial Growth Factor: Basic Science and Clinical Progress, 2004). The main receptors that bind VEGFA and mediate vasculogenesis/angiogenesis and chemotaxis/hematopoiesis are VEGF receptor 2 (VEGFR2 also known as KDR or Flk-1(mouse)) and receptor 1 (VEGFR1 also known as Flt-1), respectively (Ferrara, Vascular Endothelial Growth Factor: Basic Science and Clinical Progress, 2004).

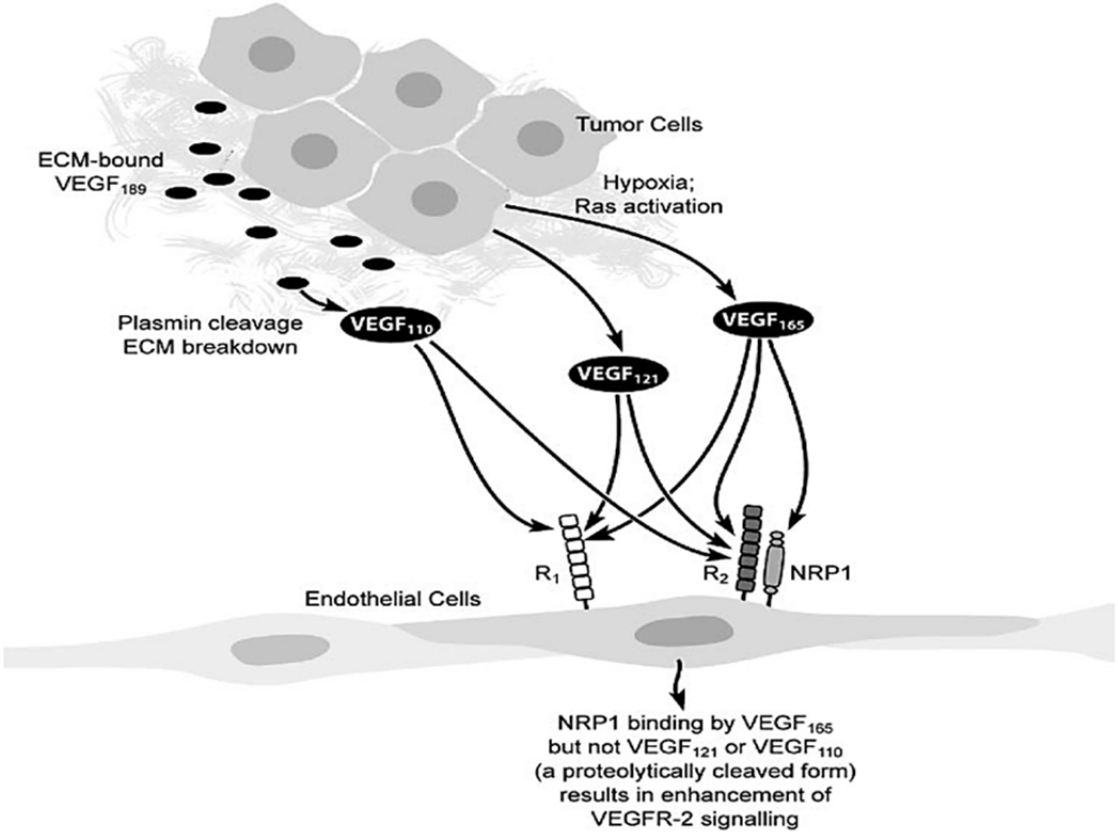
Figure 1 - Vascular endothelial growth factor family members and receptors



Source (Ellis, 2008)

VEGFA can exist in several isoforms and exert local as well as distal signaling events (Ferrara, 2010). The VEGFA isoforms are the result of alternative splicing of eight exons (Arcondeguy, 2013). The most commonly expressed VEGFA isoforms are 165, 121, 189, and 206 (numbers represent the amino acid lengths following cleavage of 26 N-terminal residues of the signal peptide). The longer VEGFA isoforms 165, 189, and 206 can bind to extracellular matrix through heparan sulfate proteoglycans and are cell-surface associated, whereas VEGFA 121 isoform exists as a completely soluble form and is thus freely diffusible. VEGFA 165 has also been shown to exist in a soluble form and to have intermediate properties, i.e., exist both as cell-surface bound and freely soluble (Houck, 1991).

Figure 2 - VEGF isoforms and their interaction with VEGFRs



Source (Ferrara, 2004)

ABP215 is a recombinant humanized IgG1 monoclonal antibody that targets human VEGFA and prevents the interaction of VEGFA to its receptors. The targeting of VEGFA by ABP215 results in the inhibition of the known functional activities of VEGFA, including tumor angiogenesis and progression (Goel, 2013). The VEGFA isoform expression in tumor types for the indications for which US-licensed Avastin is approved is predominantly the VEGFA 121 isoform, with the exception of colorectal cancer type, which expresses both VEGFA 121 as well as 165 isoforms (Vempati, 2014). As discussed in the biological function section of the analytical similarity assessment, all three products bind to these different isoforms similarly.

As an IgG1 monoclonal antibody, ABP215 retains the theoretical ability to carry out Fc-mediated effector functions (e.g., antibody-dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC)). Of note, ADCC and CDC have not been demonstrated to be mechanisms of action for bevacizumab (Wang, 2004). Nevertheless, as VEGFA isoforms exist as cell-surface bound (in addition to a soluble form), ADCC and CDC activities were evaluated as part of the similarity assessment with cell lines that express cell surface VEGFA as well as soluble VEGFA (see Analytical Similarity Assessment section).

6.2 ABP215 Manufacturing

ABP215 is manufactured using recombinant DNA technology and is expressed and purified from a mammalian cell culture system. The upstream and downstream manufacturing process steps were optimized to obtain a relatively pure product with low residual levels of process-related impurities such as host cell proteins and host cell DNA. The drug product is available in two strengths: a 100 mg/vial and a 400 mg/vial solution of ABP215. The formulation buffer for ABP215 contains the same excipients as the US-licensed Avastin and EU-approved bevacizumab products and consists of α,α-trehalose dehydrate, sodium phosphate, and polysorbate 20, pH 6.2.

The manufacturing process for the drug substance included one site change early during development, whereas the drug product manufacturing process included a site change for the manufacture of the commercial drug product. Comparability studies were performed to demonstrate product comparability after the site changes for both the drug substance and drug product. In addition, drug substance and drug product lots manufactured at the new sites were also included in the similarity assessment.

The ABP215 drug substance and drug product process validation studies are complete and demonstrate consistency of manufacture and adequate control over the manufacturing process. An assessment of the manufacturing facilities took place from May 8, 2017 to May 16, 2017 for the drug substance, by a group of Agency inspectors. The commercial drug product manufacturing facility was waived based on a number of reasons including acceptable inspectional history and drug product process and experience.

6.3 Analytical Similarity Assessment

The analytical similarity assessment for the proposed biosimilar product ABP215 consisted of a comparison of ABP215 to US-licensed Avastin for the purpose of demonstrating that ABP215 is “highly similar” to the US-licensed Avastin notwithstanding minor differences in clinically inactive components. Pairwise comparisons of ABP215 to EU-approved bevacizumab and EU-approved bevacizumab to US-licensed Avastin were performed for the purpose of establishing the analytical portion of the scientific bridge necessary to support the use of the data derived from the clinical studies that used the EU-approved bevacizumab as the comparator.

The FDA performed confirmatory statistical analyses of the submitted data. A total of 19 ABP215, 27 US-licensed Avastin, and 29 EU-approved bevacizumab lots were used in the analytical similarity assessment. Not all lots were used, however, to measure each product quality attribute; the number of lots used to evaluate each quality attribute was determined by the Applicant and based on their assessment of the variability of the analytical method and availability of US-licensed Avastin and EU-approved bevacizumab. Both the 100 mg/vial and 400 mg/vial strengths were used in the analytical similarity assessment. For the most critical quality attributes, e.g., attributes related to the mechanism of action such as binding to VEGFA and inhibition of

endothelial cell proliferation, the Applicant used 13 lots of ABP215, 24 lots of US-licensed Avastin, and 27 lots of EU-approved bevacizumab. US-licensed Avastin and EU-approved bevacizumab drug product lots were collected over a period of six years and covered a shelf-life span of 3 months to 27 months to expiry.

Methods used in the Analytical Similarity Assessment

The methods selected to perform the analytical similarity exercise were selected by the Applicant based on product knowledge regarding the structure, function, heterogeneity, and stability of US-licensed Avastin. The analytical similarity assessment was grouped into eight categories that evaluated biological activity, primary structure, higher order structure, particles and aggregates, product-related substances and impurities, thermal stability and forced degradation, general properties, and process-related impurities (see Table 1 for the list of methods). The analytical methods used were appropriately validated or qualified and deemed suitable for intended use.

Table 1 - Quality attributes and methods used to evaluate analytical similarity of ABP215, US-licensed Avastin, and EU-approved bevacizumab

Quality Attribute	Methods
Primary Structure	• Intact Molecular Mass by electrospray ionization time-of-flight mass spectrometry (ESI-TOF-MS) • Reduced and Deglycosylated Molecular Mass of Heavy and Light Chains (ESI-TOF-MS) • Amino Acid Analysis by reduced peptide Mapping with ultraviolet (UV) and liquid chromatography (LC)-MS/MS • Disulfide structure using non-reduced and reduced peptide mapping LC-MS
Protein Content	• Concentration by UV280 absorbance
Higher Order Structure	• FTIR Spectroscopy • Near UV Circular Dichroism • Differential Scanning Calorimetry
Size Variants/ Aggregates	• Size Exclusion Chromatography (SE-HPLC) (UV detection) • SE-HPLC-Static Light Scattering (SE-HPLC-SLS) • Dynamic Light Scattering (DLS) • Field Flow Fractionation (FFF) • Analytical Ultracentrifugation Sedimentation Velocity (AUC-SV) • Capillary Electrophoresis (CE)-SDS (reduced and non-reduced)
Charge	• Capillary Isoelectric Focusing (cIEF) • Cation Exchange Chromatography (CEX-HPLC)

Quality Attribute	Methods
Glycosylation	• Afucosylation • Galactosylation • High mannose • Sialic Acid
Potency	• Inhibition of Human Umbilical Vein Endothelial Cell (HUVEC) Proliferation Bioassay
Binding Assay-VEGFA 165	• ELISA
Binding Assay and Kinetics (VEGFA 111, 121, and 165)	• Surface Plasmon Resonance (SPR)
Binding Assay-Fc	• FcRn (Alpha Screen) • FcγRIa (AlphaLISA) • FcγRIIa H type (SPR) • FcγRIIb (SPR) • FcγRIIIa V type and F type (AlphaLISA) • FcγRIIIb (SPR) • C1q (ELISA)
Bioassay/ Specificity and Cell-surface associated VEGFA effects	• Specificity for VEGFA (VEGFR2 autophosphorylation in HUVEC) • Absence of ADCC (cancer cell lines that secrete soluble VEGFA isoform with natural killer cell line) • Absence of ADCC (cancer cell line that produce cell-surface associated VEGFA isoform with peripheral mononuclear cells) • Absence of CDC (cancer cell lines that secrete both soluble and cell-surface associated VEGFA isoforms)
Sub-visible Particles	• Light Obscuration • Micro Fluid Imaging
Thermal Degradation	• SE-HPLC • rCE-SDS • CEX-HPLC • Potency
General Properties	• Deliverable Volume • Osmolality • pH • Appearance • Color • Clarity

Primary Structure
As a proposed biosimilar product to US-licensed Avastin, the amino acid sequence of ABP215 was designed to match US-licensed Avastin. The Applicant ensured that ABP215 will have the same amino acid sequence as US-licensed Avastin by sequencing the expression construct for ABP215 to confirm that the expected nucleotide sequence was present to express the correct amino acid sequence and by sequencing ABP215 protein purified from the cell culture to confirm that ABP215 has the same amino acid sequence as US-licensed Avastin.

As part of the analytical similarity assessment, the Applicant used several direct and orthogonal methods to determine the primary structure of ABP215, US-licensed Avastin, and EU-approved bevacizumab. The peptide maps were generated from samples treated with trypsin followed by reduction. All samples were analyzed using RP-HPLC followed by MS/MS for peptide identification. The RP-HPLC chromatograms and the mass difference between the observed and theoretical mass were evaluated and found to be similar. All observed peptides were similar to the theoretical masses and within the mass accuracy of the methods used. However, one new peak slightly above the noise level was observed for ABP215 only. The new peak represents a sequence variant due to a point mutation, specifically, amino acid 121 serine (S) residue to alanine (A) switch. The variant is stable and exists at <1% of the total ABP215 protein. The location of the S to A switch occurs in a loop region of the VL domain and is not part of the complementarity determining region. In addition, the switch to alanine will not perturb the structure because the switch was from a small amino acid to a small amino acid (like for like). The variant is not expected to have a clinical impact based on the location and amount of the sequence variant in ABP215. Therefore, the presence of this variant does not preclude a finding that the products are highly similar notwithstanding minor differences in clinically inactive components.

The observed intact molecular mass of the three products was compared against the theoretical mass. The theoretical mass was determined from the expected amino acid sequence of US-licensed Avastin and with expected post-translational modifications such as the cleavage of the C-terminal lysine residue. The mass of all three products and the deconvoluted intact molecular mass profiles for all three products were similar. The analyses of the reduced and deglycosylated mass of the heavy chain (HC) and the light chain (LC) were also found to be similar. Lastly, all 16 disulfide (four intrachain and 12 interchain) linkages were confirmed in all three products by comparing the non-reduced condition peptide map data with the reduced peptide map data.

Protein Content
As part of the general properties evaluation of ABP215, protein concentration was evaluated for similarity to US-licensed Avastin and EU-approved bevacizumab lots due to its impact on dosing and efficacy. Thirteen ABP215 lots, 24 US-licensed Avastin, and 26 EU-approved bevacizumab lots were measured for protein concentration using ultraviolet spectrophotometer absorbance at 280 nm. The extinction coefficient used was 1.7 mL mg-1cm-1 and was both theoretically and experimentally determined. The

data confirm that total protein amounts in the ABP215 drug product and US-licensed Avastin met the pre-specified acceptance criterion.

Higher Order Structure

Higher order structures were determined as part of the analytical similarity assessment to ensure that the products have similar three-dimensional structures that are necessary for biological functions. Three different methods were used to determine the secondary and tertiary structures of ABP215, US-licensed Avastin, and EU-approved bevacizumab: Fourier transform infrared (FTIR) spectroscopy, near ultraviolet circular dichroism (CD), and differential scanning calorimetry (DSC). The results from the FTIR, CD, and DSC demonstrated that all three products had similar secondary and tertiary structures.

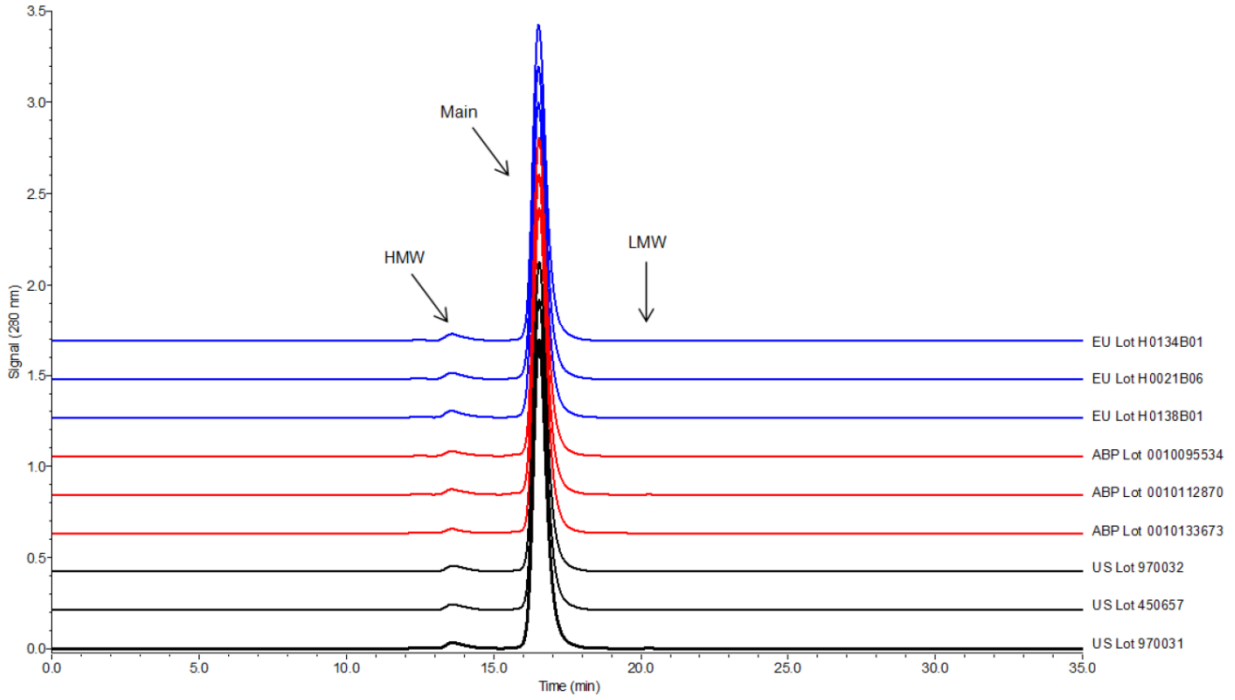
Aggregates

Aggregates are important quality attributes of therapeutic proteins because they could impact product efficacy and immunogenicity (Rosenberg A. , 2006) (Moussa, 2016). Therefore, aggregate levels in all three products were quantified using SE-HPLC as percent high molecular weight (HMW) species and further characterized by additional orthogonal methods such as FFF, DLS, SE-HPLC-SLS, and AUC-SV methods. Data derived from the SE-HPLC method for 13 lots of ABP215, 24 US-licensed Avastin lots, and 26 EU-approved bevacizumab lots were evaluated against a quantitative analytical similarity acceptance criterion.

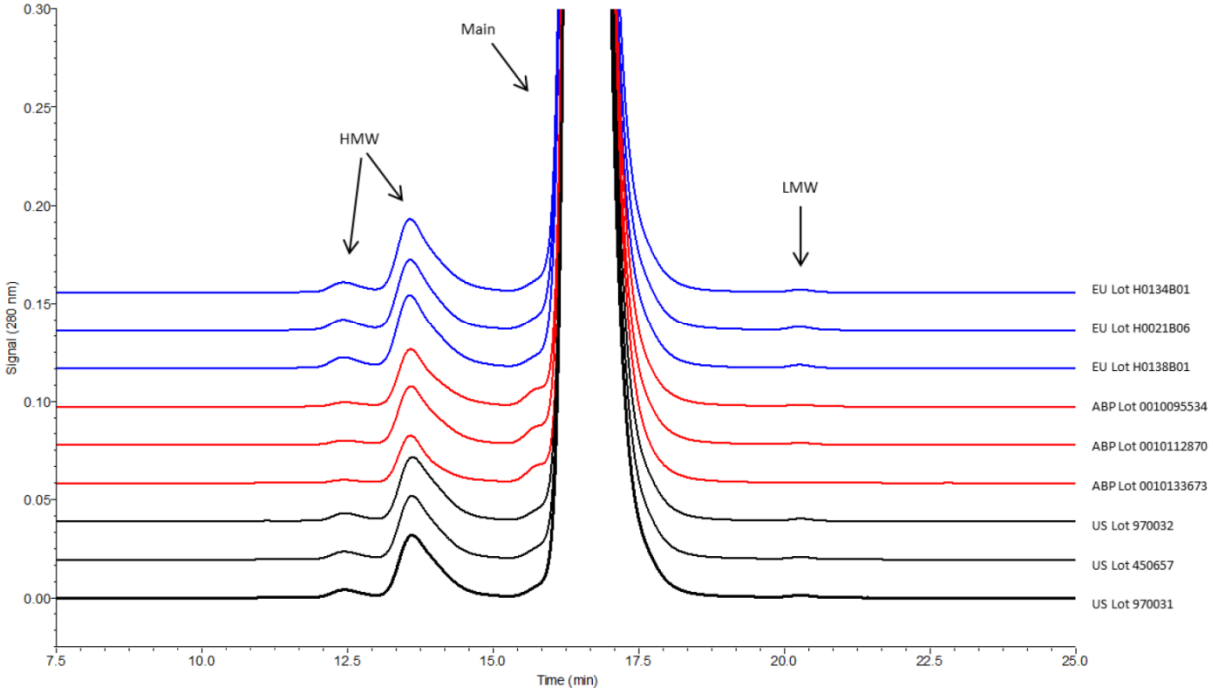
The results showed lower aggregate levels for ABP215 and all three products showed similar peak profiles (see Figure 3). The average value and the range of aggregate values are shown in Table 2.

Figure 3 - Chromatographic comparison of SE-HPLC peak profile for ABP215, US-licensed Avastin and EU-approved bevacizumab

Full View



Expanded View



Source: Figure excerpted from the Applicant's 351(k) BLA submission

Table 2 - High molecular weight (HMW) levels in ABP215, US-licensed Avastin, and EU-approved bevacizumab

Product	Mean (%) HMW Species	Min/Max Range HMW Species
ABP215	1.72	1.3 to 2.3
US-licensed Avastin	2.72	2.4 to 3.3
EU-approved bevacizumab	2.95	2.3 to 3.4

Source: Mean and range derived from initial time point data from the Applicant's 351(k) submission

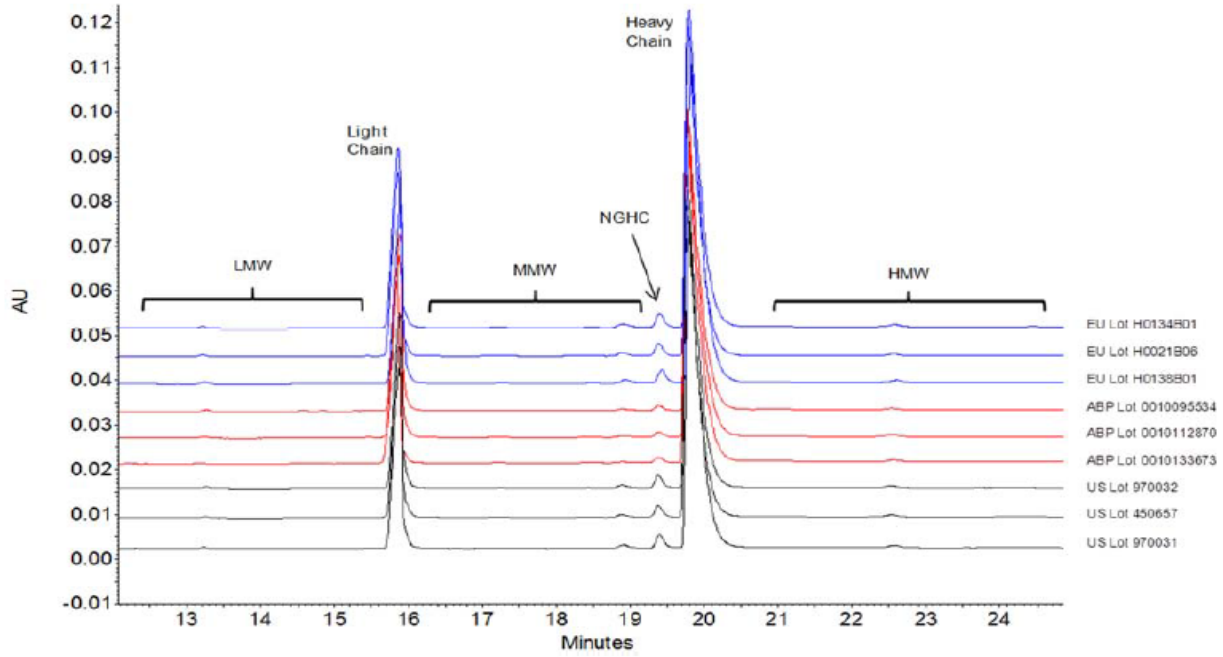
ABP215 contains slightly lower levels of aggregates relative to US-licensed Avastin and EU-approved bevacizumab. As aggregates may potentially increase slightly during the course of storage, the Applicant monitored changes in US-licensed Avastin and EU-approved bevacizumab over the duration of its shelf life. The analysis demonstrated slight increases in aggregates under the long-term storage condition. Therefore, differences in product age are partially responsible for differences in levels of aggregates. However, subsequent characterization of the aggregate species (by FFF, DLS, SE-HPLC-SLS, and AUC-SV methods) demonstrated that aggregates from ABP215, US-licensed Avastin and EU-approved bevacizumab are similar in profile and are likely dimeric species. Taken together, the slight difference in the aggregate amount does not preclude a finding that the products are highly similar notwithstanding minor differences in clinically inactive components.

Size Variants

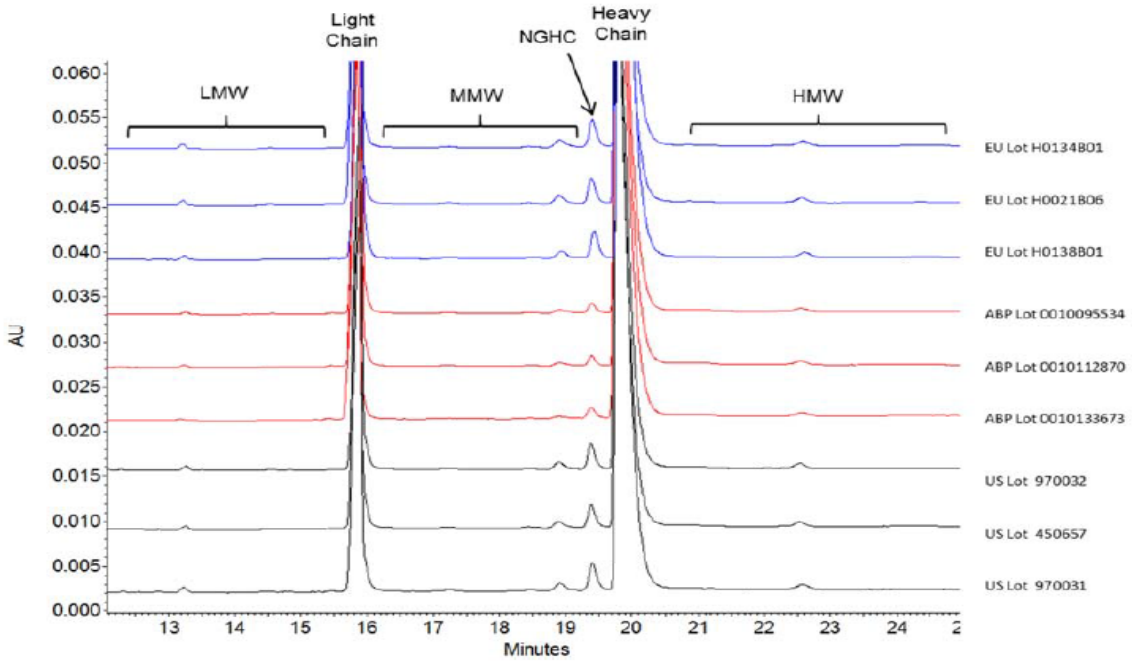
The purity and size heterogeneity of monoclonal antibodies can result from the cell culture system and the manufacturing process. The resultant product-related size variants can have the potential to affect product potency. The different types of size variants were analyzed using both reduced and non-reduced capillary electrophoresis (rCE-SDS and nrCE-SDS) and quantified as %LC + HC, percent non-glycosylated HC (% NGHC), and percent low molecular weight and middle molecular weight fragments (%LMW + MMW) by the rCE-SDS method and % main peak and % pre-peaks by the nrCE-SDS method. Note that HMW species were not quantified using rCE-SDS because the data were captured using the SE-HPLC method and discussed under the Aggregates section above. Data derived from rCE-SDS and nrCE-SDS methods were evaluated against quantitative analytical similarity acceptance criteria. Sample chromatographic overlays of ABP215, US-licensed Avastin, and EU-approved bevacizumab are shown in Figure 4 and Figure 5 for rCE-SDS and nrCE-SDS, respectively.

Figure 4 - rCE-SDS chromatographic comparison of size variant profiles for ABP215, US-licensed Avastin, and EU-approved bevacizumab

Full View

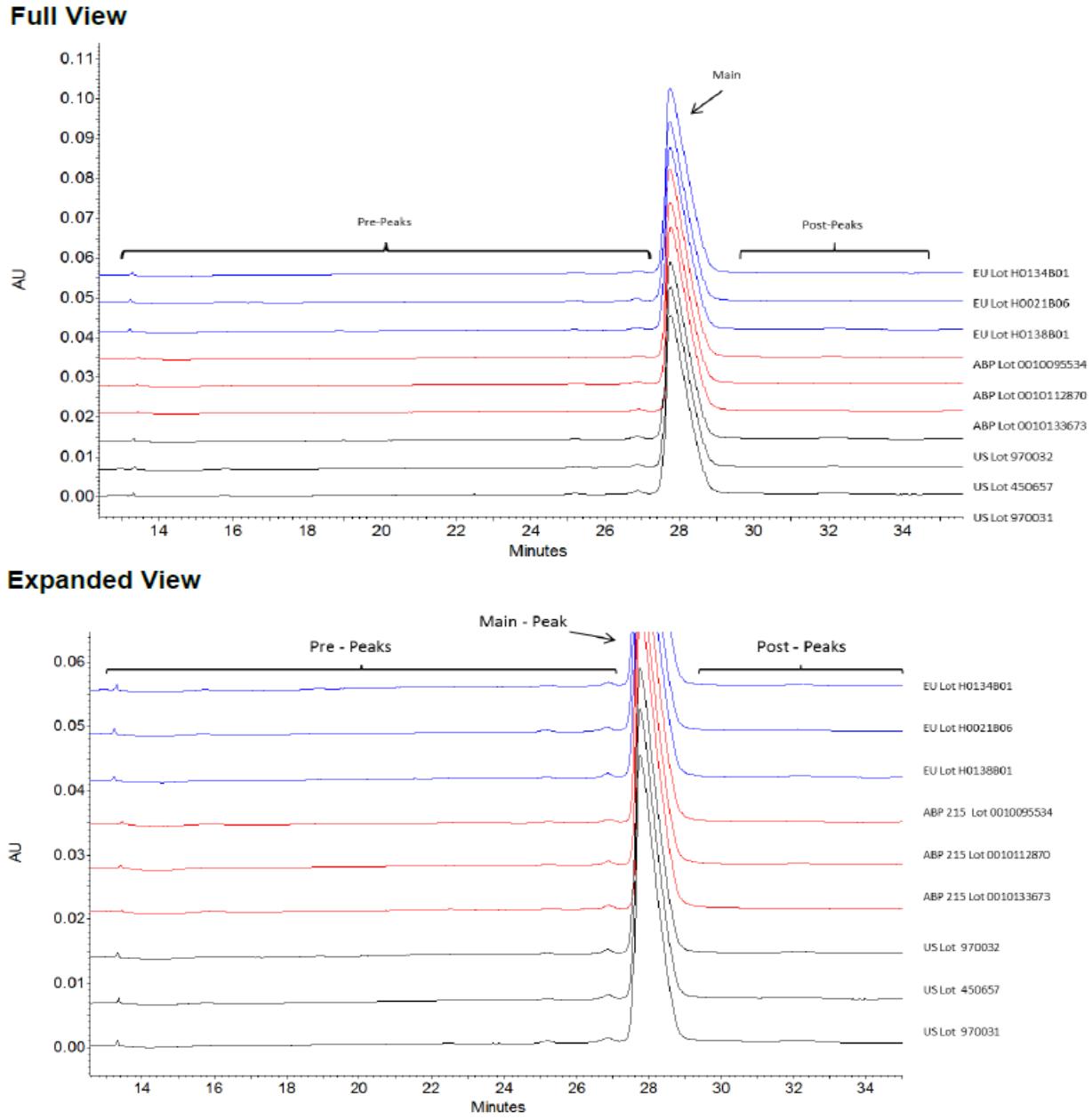


Expanded View



Source: Figure excerpted from the Applicant's 351(k) BLA submission

Figure 5 - nrCE-SDS chromatographic comparison of size variant profiles for ABP215, US-licensed Avastin, and EU-approved bevacizumab



Source: Figure excerpted from the Applicant's 351(k) BLA submission

The results showed lower levels of LMW and MMW fragments, %NGHC, and %pre-peaks in ABP215. The average value and the range of size variants are shown in Table 3.

Table 3 - Size variants detected by rCE-SDS and nrCE-SDS in ABP215, US-licensed Avastin, and EU-approved bevacizumab

Product	Mean (%) HC + LC	Min/Max Range % HC +LC
ABP215	98.19	97.9 to 98.4
US-licensed Avastin	96.13	95.4 to 96.6
EU-approved bevacizumab	95.94	95.2 to 96.3
Product	**Mean (%) NGHC**	**Min/Max Range % NGHC**
ABP215	0.78	0.6 to 0.9
US-licensed Avastin	1.83	1.7 to 2.1
EU-approved bevacizumab	1.87	1.6 to 2.1
Product	**Mean (%) LMW+MMW**	**Min/Max Range % LMW+HMW**
ABP215	0.68	0.5 to 0.9
US-licensed Avastin	1.54	1.2 to 2.3
EU-approved bevacizumab	1.69	1.4 to 2.0
Product	**Mean (%) Main Peak**	**Min/Max Range % Main Peak**
ABP215	98.05	96.7 to 98.4
US-licensed Avastin	97.58	96.9 to 97.9
EU-approved bevacizumab	97.42	96.3 to 98.2
Product	**Mean (%) Pre-Peak**	**Min/Max Range % Pre-Peak**
ABP215	1.75	1.5 to 2.9
US-licensed Avastin	2.10	1.8 to 2.6
EU-approved bevacizumab	2.20	1.8 to 3.0

Source: Mean and range derived from initial time point data from the Applicant's 351(k) submission

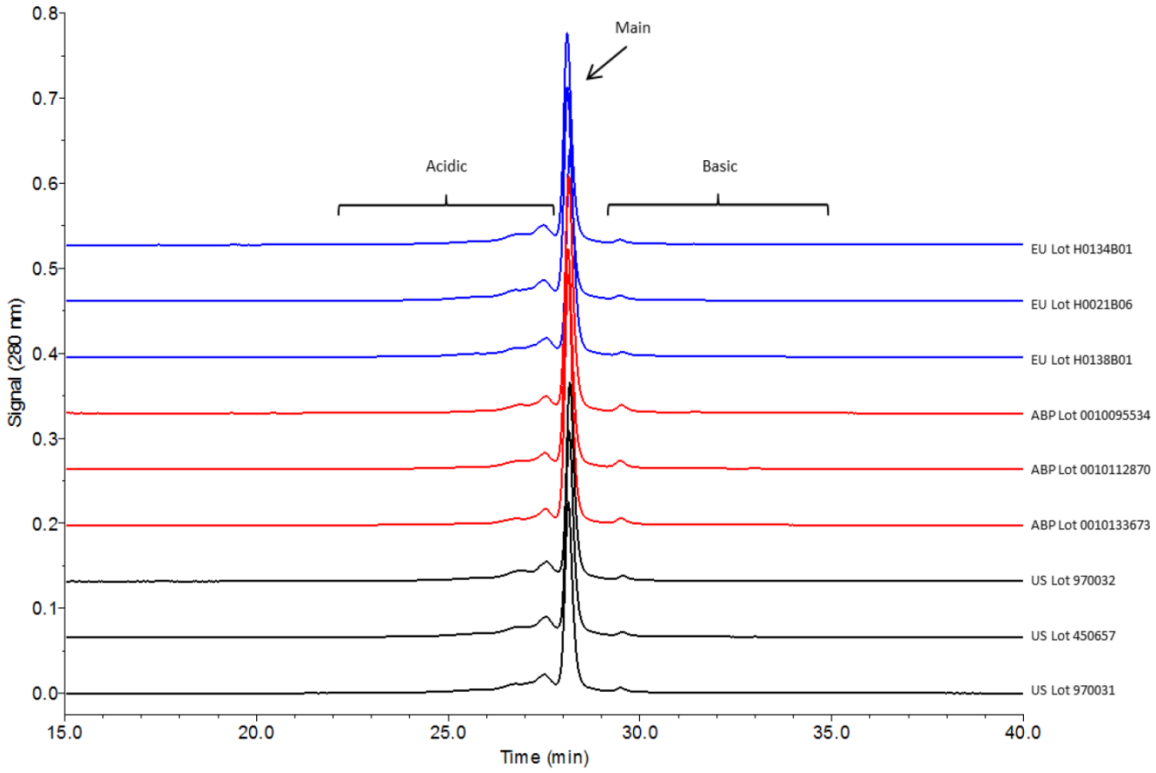
As with aggregates, product age at the time of analysis may slightly influence the levels of size variants that are observed. However, the high purity of the product coupled with results from the two Tier 1 assays (Inhibition of HUVEC Proliferation Bioassay and Binding to VEGFA165) demonstrate the differences in size variants to be negligible. Therefore, these differences do not preclude a finding that the products are highly similar notwithstanding minor differences in clinically inactive components.

Charge

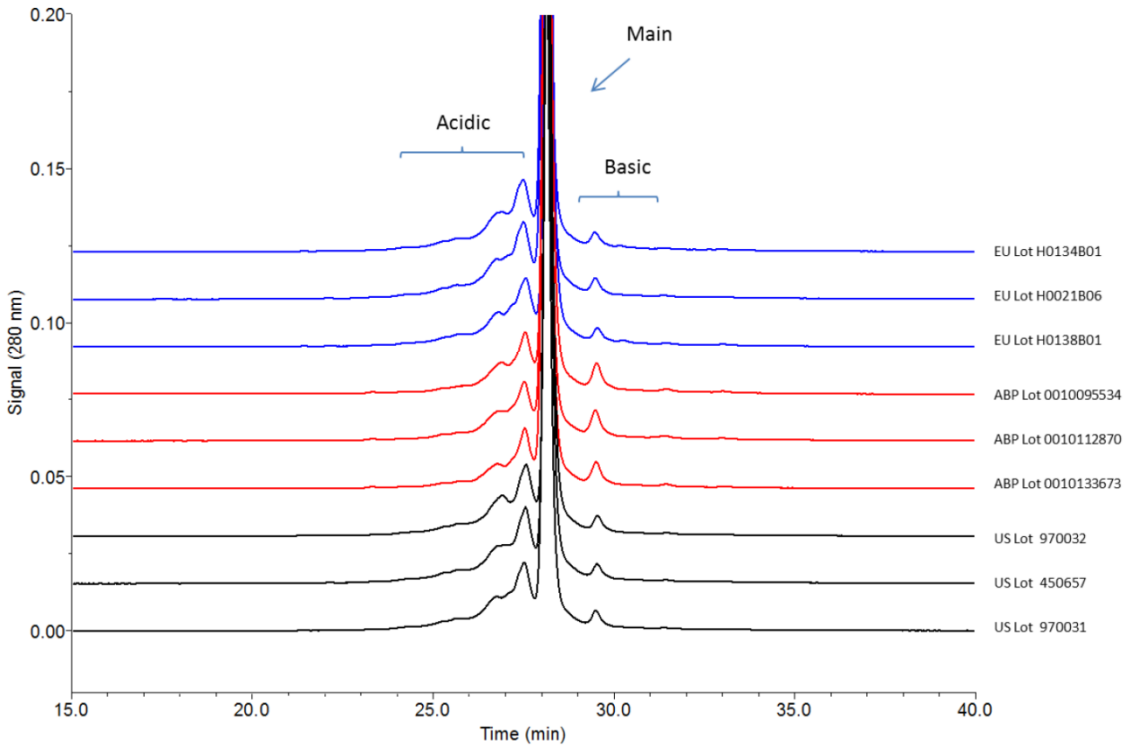
Charge heterogeneity in protein products is inherent to the protein molecule and the manufacturing process. The typical modifications observed on monoclonal antibodies that results in charge differences can be glycosylation, glycation, deamidation, oxidation, and C-terminal lysine residue. The charge profile for ABP215, US-licensed Avastin and EU-approved bevacizumab show three distinct regions, labeled as acidic peaks, main peak, and basic peaks. A sample chromatographic overlay of ABP215, US-licensed Avastin, and EU-approved bevacizumab is shown in Figure 6.

Figure 6 - Chromatographic comparison of charge variant profile for ABP215, US-licensed Avastin, and EU-approved bevacizumab

Full View



Expanded View



Source: Figure excerpted from the Applicant's 351(k) BLA submission

The results from the analytical similarity analysis showed lower levels of acidic peaks and higher levels of the main and basic peaks in ABP215. The average value and the range of acidic, main, and basic peaks in ABP215, US-licensed Avastin, and EU-approved bevacizumab are shown in Table 4.

Table 4 - Average CEX-HPLC acidic, main, and basic peak levels in ABP215, US-licensed Avastin and EU-approved bevacizumab

Product	Mean (%) Acidic	Min/Max Range % Acidic
ABP215	19.06	17.5 to 20.1
US-licensed Avastin	27.21	24.2 to 29.5
EU-approved bevacizumab	27.32	25.7 to 30.7
Product	**Mean (%) Main**	**Min/Max Range % Main**
ABP215	72.38	69.1 to 75.2
US-licensed Avastin	66.73	64.6 to 70.1
EU-approved bevacizumab	66.47	62.8 to 68.3
Product	**Mean (%) Basic**	**Min/Max Range % Basic**
ABP215	8.56	6.6 to 11.5
US-licensed Avastin	6.07	5.4 to 7.2
EU-approved bevacizumab	6.18	5.0 to 7.4

Source: Mean and range derived from initial time point data from the Applicant's 351(k) submission

In order to elucidate the differences observed in the acidic, main, and basic peaks, the Applicant further characterized the three products to determine the constituents within the acidic, main, and basic regions. Specifically, the Applicant treated all three products with carboxypeptidase B prior to CEX-HPLC analysis, and purified the CEX-HPLC acidic, main, and basic peaks to determine activity and variant content by peptide map (LC/MS) analysis.

The peptide map (LC/MS) analysis of the purified CEX-HPLC peaks showed that in all three products the acidic peak had enriched amounts of deamidated variants in the non-complementarity determining region and cyclization of the N-terminal glutamate residue (pyroglutamate). The basic peaks showed enriched levels of C-terminal lysine variant as well as C-terminal proline amidation in all three products. In a separate analysis using carboxypeptidase B treatment, which clips C-terminal lysine residues, the Applicant confirmed that the ~2% higher levels of basic peaks in ABP215 are due to the presence of C-terminal lysine variant (see data below).

Table 5 - CEX-HPLC results of carboxypeptidase B digested ABP215, US-licensed Avastin, and EU-approved bevacizumab

	Before Digestion			After Digestion		
Sample	% Acidic Peaks	% Main Peak	% Basic Peaks	% Acidic Peaks	% Main Peak	% Basic Peaks
EU Lot H0134B01	28.8	65.8	5.4	29.3	65.5	5.2
ABP Lot 0010095534	20.3	72.3	7.3	21.3	73.6	5.0
US Lot 970032	29.2	65.4	5.5	30.4	65.3	4.3

Source: Table excerpted from the Applicant's 351(k) BLA submission

Potency data of the purified peaks showed that the acidic and basic peaks retained up to 80% activity when compared to the purified main peak. The overall effect of the differences in acidic and basic peaks was shown to have minimal impact on binding to VEGFA or potency.

The modifications leading to charge variants in all three products were evaluated by the Applicant and found to consist of similar types of modifications, e.g. product variant with C-terminal lysine, deamidation, and pyroglutamate variant. Numerous publications have shown that modifications such as pyroglutamate formation or the presence or the absence of C-terminal lysine residues on monoclonal antibodies have no effect on antibody structure, antigen binding, and fragment crystalizable (Fc)-mediated functions, e.g., neonatal Fc receptor (FcRN) binding (Liu, 2014).

In addition to the variants found in the acidic and basic peaks that do not impact product activity, degradants such as deamidated species were observed in all three products. The levels of degradants observed in ABP215 were lower compared to US-licensed Avastin and EU-approved bevacizumab lots and this difference is likely caused by the relative age of the products at the time of the analytical similarity assessment, as was discussed above for aggregate levels. The stability data of ABP215 also supports the conclusion that the higher levels of acidic and basic peaks are due to age as these peaks also increased in ABP215 over time. Therefore, the differences observed in charge variants do not preclude a finding that the products are highly similar notwithstanding minor differences in clinically inactive components.

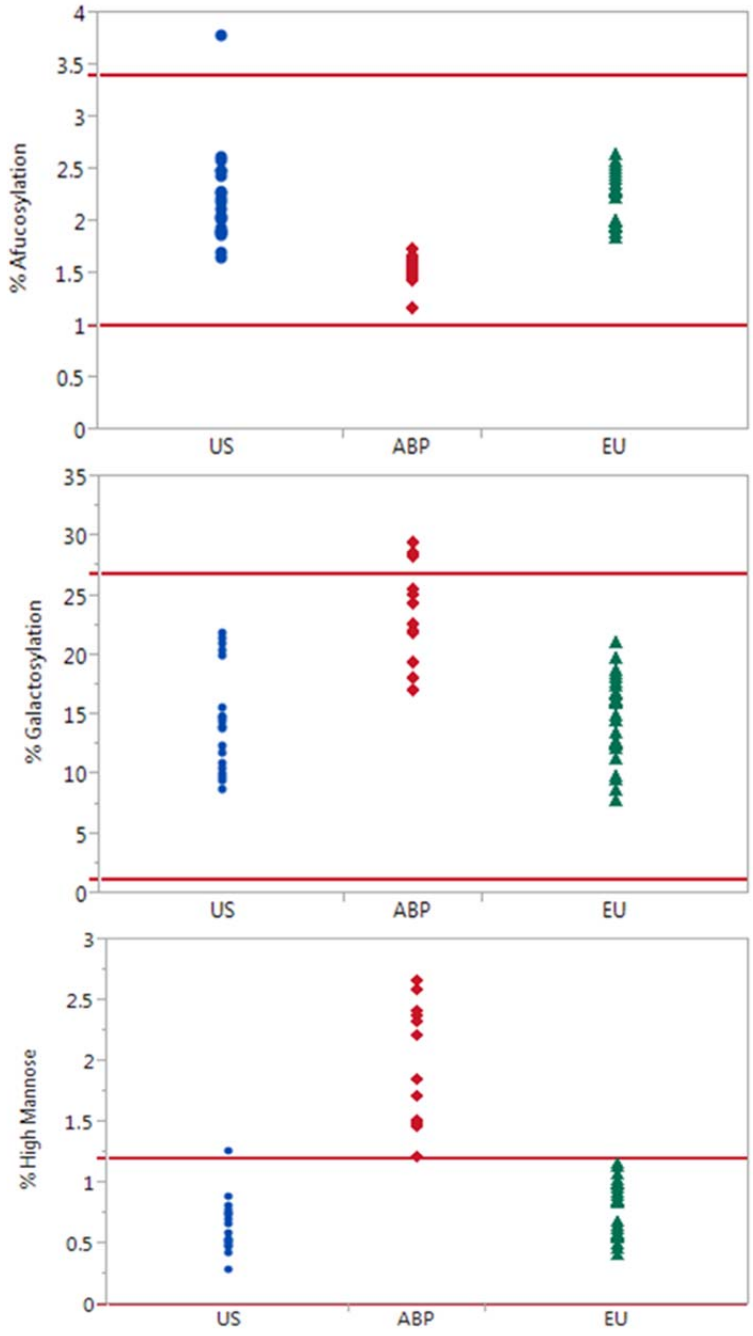
Glycosylation

Glycosylation of monoclonal antibodies is known to occur on the constant region of the heavy chain, specifically to asparagine (N) residue within a consensus sequence that is recognized by the host cellular glycosylation machinery. There are three N-glycan types, high mannose, complex, and hybrid that are commonly found on monoclonal antibodies. Different glycan structures can modify product activity. For example, the presence of fucose residue on a complex or hybrid N-glycan chain can reduce the interaction with Fcγ receptor IIIa (FcγRIIIa) on effector cells and reduce antibody-dependent cell-mediated cytotoxicity (ADCC). Glycan structures can also affect pharmacokinetics, in that high mannose glycans can increase the clearance rate of a product (Higel, 2016). Therefore, the Applicant evaluated the glycosylation content of ABP215, US-licensed Avastin, and EU-approved bevacizumab using a hydrophilic interaction liquid chromatography method with fluorescence and on-line MS as part of the analytical similarity assessment.

For the glycan analysis, the Applicant calculated the total percent afucosylation from the addition of all complex and hybrid glycan structures without core fucose residue, total percent galactosylation from the addition of all complex and hybrid glycan structures with at least one terminal galactose, and the percent high mannose from the addition of all high mannose glycans, M5 to M8. Figure 7 below shows the glycan levels in all three

products and the red bars are the US-licensed Avastin quality range analysis generated by the Applicant.

Figure 7 - Comparison of glycan profile for ABP215, US-licensed Avastin, and EU-approved bevacizumab



Source: FDA analysis of the Applicant's 351(k) BLA submission

The results of the glycan analysis showed that ABP215 contained higher amounts of high mannose and galactose content compared to US-licensed Avastin and EU-approved bevacizumab. US-licensed Avastin and EU-approved bevacizumab contained higher levels of afucosylated glycans compared to ABP215. Sialic acid content was also analyzed and found to have similarly low levels in all three products (data not shown). The differences in the glycan levels are unlikely to have a clinical impact based on the knowledge that ABP215, US-licensed Avastin, and EU-approved bevacizumab have a predominantly soluble target, i.e. the potential effects of lower afucosylation and higher galactosylation to affect ADCC or CDC activities are low and these activities are also not observed experimentally (see Biological Assay section on cell-surface associated VEGFA interaction). In addition, as shown by the similar PK profiles (see Clinical Pharmacology section below) for ABP215, US-licensed Avastin, and EU-approved bevacizumab, the difference in high mannose content did not have an observed clinical impact. Therefore, these slight differences do not preclude a finding that the products are highly similar and are not expected to have a clinical impact.

Biological Activity

Several bioassays to elucidate the biological activities of ABP215, US-licensed Avastin, and EU-approved bevacizumab were employed in the analytical similarity assessment and included VEGFA target binding and inhibition of VEGFA induced endothelial cell proliferation as the most critical product quality attributes. In addition, the binding kinetics, binding specificity to VEGFA versus other VEGF family members, and Fc binding activities were evaluated in the analytical similarity assessment. The Applicant conducted a 3-way similarity assessment of comparing ABP215, EU-approved bevacizumab and US-licensed Avastin.

VEGFA binding analyzed by ELISA and the inhibition of proliferation of human umbilical vein endothelial cells (HUVEC) that express the VEGF receptors, VEGFR1, VEGFR2, and VEGFR3 as well as VEGF co-receptors, Neuropilin 1 and 2, represent the assays designed to evaluate the similarity of the mechanism of action for ABP215, US-licensed Avastin, and EU-approved bevacizumab.

Two assays were analyzed as Tier 1 quality attributes (QAs): the Proliferation Inhibition Bioassay (% Relative Potency) and the VEGF-A Binding by ELISA. These two Tier 1 QAs are subjected to statistical equivalence testing with the equivalence margins of $\pm 1.5\sigma_R$ where σ_R represents the US-licensed Avastin product variability and is estimated by the US-licensed Avastin lot values generated by the Applicant. The data were reported as a percentage relative to the Applicant's in-house ABP215 reference standard.

Proliferation Inhibition Bioassay

The Proliferation Inhibition Bioassay data distributions of ABP215, US-licensed Avastin and EU-approved bevacizumab are displayed in Figure 8. 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 8 - Scatter plots of proliferation Inhibition bioassay for US-licensed Avastin, ABP215, and EU-approved bevacizumab.

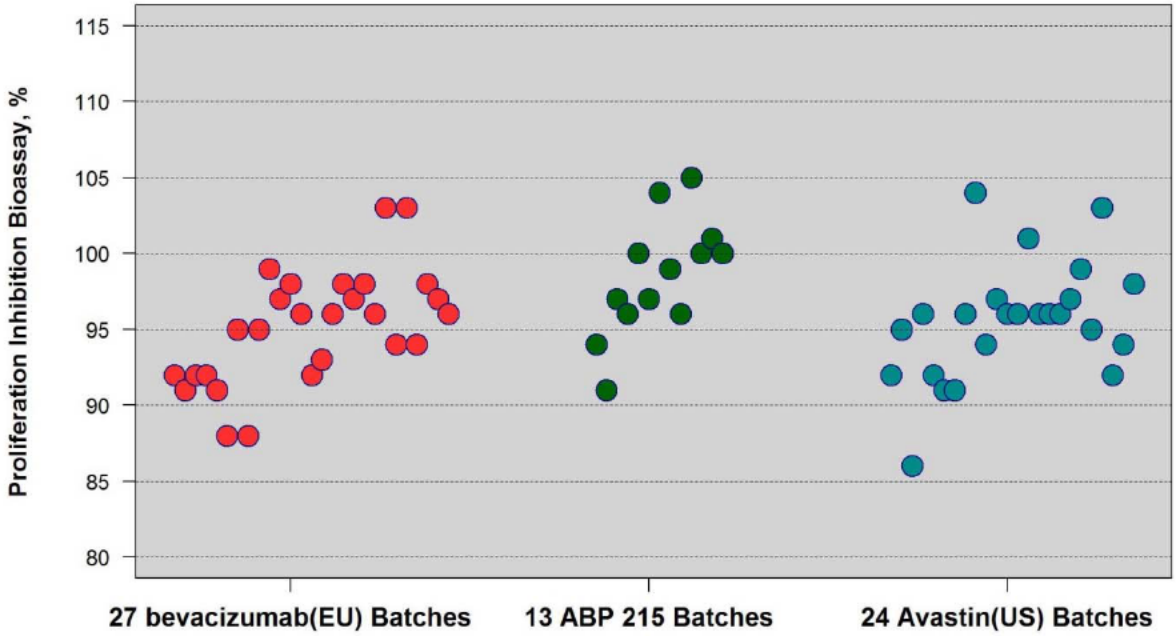


Table 6 - Descriptive statistics for the proliferation inhibition bioassay data

Product	Number of Batches	Sample Mean, %	Sample Standard Deviation, %	Min, %	Max, %
ABP215	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 - Equivalence testing results for the proliferation inhibition bioassay

Comparison	# of Batches	Mean difference, %	90% confidence interval, %	Equivalence margin, %	Equivalent
ABP215 vs. US	(13, 24)	2.92	(0.55, 5.29)	(-5.90, +5.90)	Yes
ABP215 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

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 9. 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 9 - Scatter plots of VEGF-A binding by ELISA for US-licensed Avastin, ABP215, and EU-approved bevacizumab

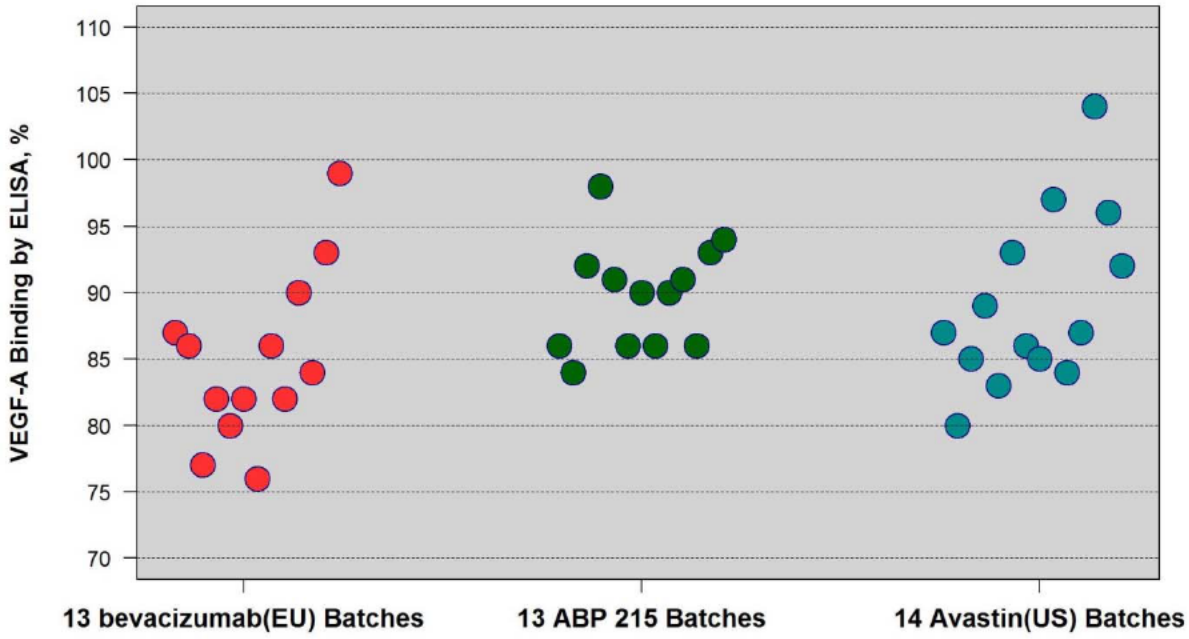


Table 8 - Descriptive statistics for the VEGF-A binding by ELISA data

Product	Number of batches	Sample mean, %	Sample Standard deviation, %	Min, %	Max, %
ABP215	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, %	Equivalence margin, %	Equivalent
ABP215 vs. US	(13, 14)	0.63	(-2.93, 4.18)	(-9.79, +9.79)	Yes
ABP215 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

The statistical equivalence analyses shown above regarding VEGFA binding and the inhibition of HUVEC proliferation of ABP215 support a demonstration that ABP215 is highly similar to US-licensed Avastin.

The binding kinetics of ABP215, US-licensed Avastin, and EU-approved bevacizumab to three isoforms of VEGFA (165, 121, and 111) and the specificity for VEGFA as compared to other VEGF family members was assessed. All three products demonstrated similar binding kinetics and specificity to VEGFA. It is possible that different VEGFA isoforms could be preferentially expressed by a particular tumor, e.g., non-small cell lung cancers predominantly express the VEGFA 121 isoform (Vempati, 2014). However, all known variants to date contain exon 3 and exon 4 that participate in VEGF R1 (Wiesmann, 1997) and R2 (Muller Y. e., 1997) binding and contain the target binding site of US-licensed Avastin (Muller Y. e., 1998).

Taken together, these analyses support the demonstration of similarity in binding to the VEGFA targets as well as the analytical portion of the scientific bridge between US-licensed Avastin, EU-approved bevacizumab, and ABP215 to justify the relevance of the comparative data generated from clinical studies that used EU-approved bevacizumab as the comparator.

Other biological activity assays examined in the analytical similarity assessment included binding activities of the Fc portion of ABP215, US-licensed Avastin, and EU-approved bevacizumab to Fc receptors such as the neonatal Fc receptor, FcRn, and to the complement cascade component protein, C1q. Binding activities to FcRn, FcγRIIIa, and C1q were evaluated because of their potential impact to PK and safety; the latter due to unwanted effector functions leading to ADCC and CDC activities.

The binding to FcRn and FcγRs, specifically FcγRI, II, and III were evaluated and the results showed similar binding activities for C1q and all the receptors except for FcγRIIIa (158 V), which is known as the high affinity FcγRIIIa receptor that mediates ADCC activity. ABP215 binding was slightly higher for FcγRIIIa (158 V) and could be attributed to the higher levels of high mannose content, which is also known to have increased affinity to FcγRIIIa (Yu, 2012). However, given that the target antigen is predominantly soluble and no ADCC activity was observed (see cell-based ADCC assay results below), the slight difference in binding to the FcγRIIIa receptor is not likely to have a clinical impact.

Biological Assays to Address Effect of Cell-Surface Associated VEGFA Interaction

As previously described in section 6.1, VEGFA can exist in multiple isoforms due to alternative splicing of the mRNA. Both soluble and cell-surface associated forms of VEGFA exist in both normal and tumor tissues. Specifically, the VEGFA isoforms that contain exons 6 and 7 can bind to heparan sulfate on the extracellular matrix (Ferrara, 2010). Therefore, the ability of ABP215, US-licensed Avastin, and EU-approved bevacizumab to bind to FcγRIIIa on effector cells to mediate cell death or activate the complement system in cancer cell lines that secrete as well as express cell-surface associated VEGFA were assessed as part of the analytical similarity assessment.

Three cell lines, SKOV3 (ovarian carcinoma), DLD-1 (adenocarcinoma), and Calu-6 (lung epithelial carcinoma) were used to evaluate immune effector functions of the Fc portion of ABP215, US-licensed Avastin, and EU-approved bevacizumab. The SKOV3 cell line was chosen by the Applicant to demonstrate a lack of ADCC activity in cells that have been shown in literature (Salvador et al, 2008; ref provided by the Applicant) to produce both soluble as well as cell-surface associated isoforms of VEGFA, e.g., VEGF 165. The effector cells used with SKOV3 cells were peripheral blood mononuclear cells. As a positive control for the ADCC assay, the Applicant used trastuzumab, which binds to HER2 expressed on SKOV3 cells. For the DLD-1 and Calu-6 cells, an NK cell line, NK-92M1/CD16, was used as the effector cells. The results from the cell-based ADCC assay showed a lack of ADCC activity by all three products in all three cell lines tested (data not shown).

Likewise, the same three cell lines were used to evaluate the ability of ABP215, US-licensed Avastin, and EU-approved bevacizumab to activate the complement system. Rabbit complement was used in the CDC activity assay. The results from the CDC activity assay also showed a lack of CDC activity by all three products in all three cell lines tested (data not shown).

The results from the additional biological functional assays support a demonstration that ABP215 is highly similar to US-licensed Avastin and provide evidence that the observed differences in glycan content as well as FcγRIIIa will not have a clinical impact.

Sub-Visible Particles

Sub-visible particles in the range of 2 to 25 µm were evaluated in the analytical similarity assessment because of their potential to affect immunogenicity (Carpenter, 2009) (Rosenberg A. e., 2012) of ABP215. The USP <788> method was used to measure sub-visible particles that are greater than 10 and 25 µm using a light obscuration method (HIAC). The same method was also used along with micro-flow-imaging method (MFI) to evaluate particles that were less than 10 µm.

The HIAC method was used in 19 ABP215 lots, 14 lots of US-licensed Avastin, and 15 lots of EU-approved bevacizumab. The MFI method was used in 19 ABP215 lots, 11 US-licensed Avastin lots, and 12 EU-approved bevacizumab lots. The results for both the HIAC and MFI methods demonstrated that all three products have low levels of sub-visible particles and therefore have low risk to adversely impact immunogenicity and safety.

Comparative Stability Studies

The Applicant evaluated temperature stress on ABP215, US-licensed Avastin, and EU-approved bevacizumab to delineate and compare the similarity of the degradation pathways using four methods: SE-HPLC, rCE-SDS, CEX-HPLC, and potency by the HUVEC proliferation inhibition assay. The three temperatures chosen for the stress studies were 50°C, 40°C, and 25°C.

Six lots each of ABP215, US-licensed Avastin, and EU-approved bevacizumab were analyzed side-by-side. The results of each thermal stress condition study showed that the degradation profiles are similar for all three products, which indicates that the three products are similar in structure (Figure 10 shows an example of CEX-HPLC thermal degradation profile and Figure 11 shows the CEX peak changes over time at 50°C).

Figure 10 - CEX-HPLC chromatogram overlays for ABP215, US-licensed Avastin, and EU-approved bevacizumab at 50°C

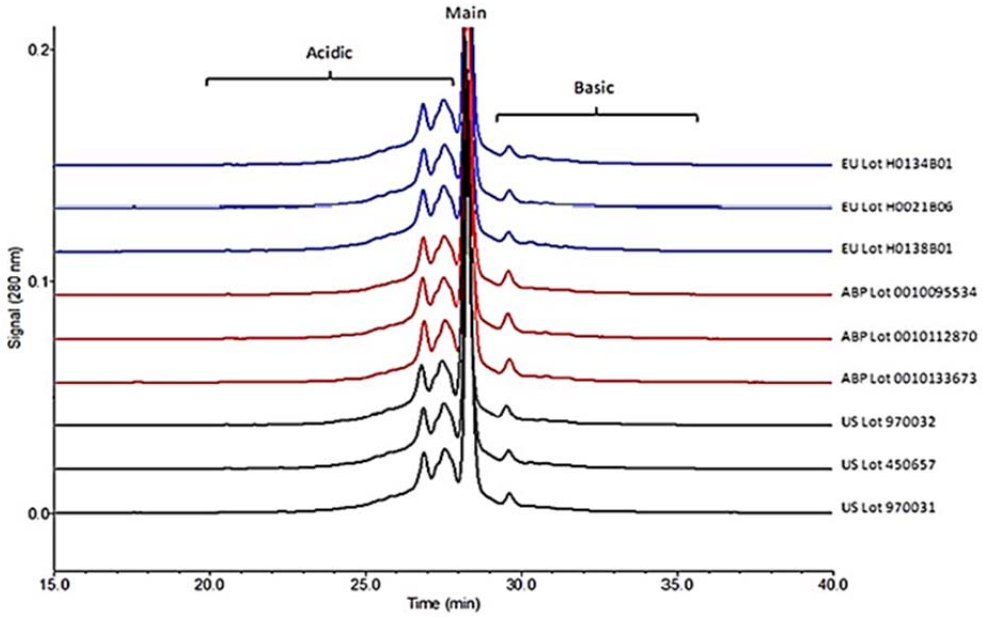
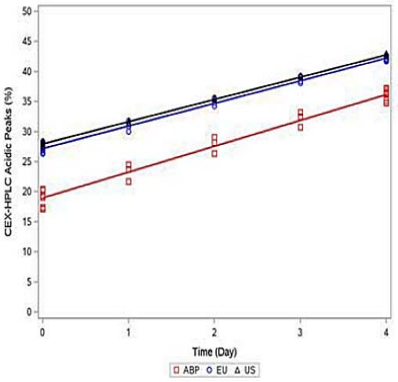
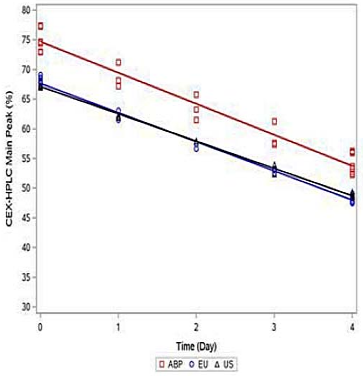
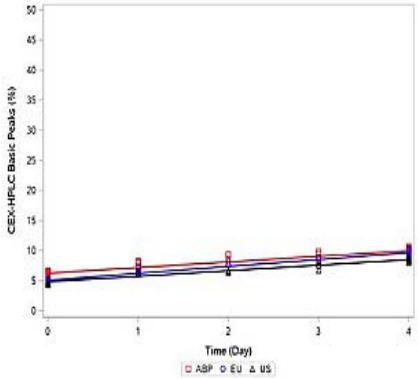


Figure 11 - CEX-HPLC acidic, main, and basic peak degradation rates for ABP215, US-licensed Avastin, and EU-approved bevacizumab at 50°C

Acidic Peaks	Main Peak	Basic Peaks
		

Source: Figures excerpted from the Applicant's 351(k) BLA submission

Process-Related Impurities

The similarity in the levels of process-related impurities such as host cell protein (HCP), host cell DNA, and protein-A were evaluated for any significant differences between ABP215, US-licensed Avastin and EU-approved bevacizumab that could impact product safety. All three products showed similar levels of process-related impurities that further supports the overall analytical similarity of the three products.

General Properties

The general properties for ABP215 include pH, osmolality, appearance, color, and clarity. These product quality attributes were also evaluated in ABP215, US-licensed

Avastin and EU-approved bevacizumab in the analytical similarity assessment and used compendia methods. The results indicate that all three products were similar in their general properties.

Summary of Analytical Similarity Assessment
The Applicant employed numerous analytical methods that compared the primary and higher order structures, product-related variants such as aggregate levels and charge variants, process-related components such as host cell DNA, and biological functions to support a demonstration that ABP215 is highly similar to US-licensed Avastin. In addition, the Applicant supported the analytical portion of the scientific bridge to justify the relevance of data obtained from the use of EU-approved bevacizumab as the comparator product in clinical studies.

The analytical data submitted supports a demonstration that ABP215 is highly similar to US-licensed Avastin. All three products demonstrated similar binding affinities to VEGFA and similar potency, which are product quality attributes associated with the mechanism of action for ABP215 and US-licensed Avastin. Lastly, the higher order structure determinations showed the presence of similar secondary and tertiary structures and further support the binding and potency results. The impurity profiles also demonstrated that ABP215 has acceptably low levels of impurities that are similar to US-licensed Avastin.

Some quality attributes were found to be slightly different between products but unlikely to have clinical impact and do not preclude a demonstration that ABP215 is highly similar to US-licensed Avastin. For example, the differences in charge variants for ABP215 were due to lower levels of the product variants in US-licensed Avastin and are likely due to the age difference between ABP215 and US-licensed Avastin at the time of the analytical similarity assessment. Furthermore, the differences in the glycan species were shown to not affect PK in clinical studies and no effector functions were observed in vitro that could be impacted by differences in the level of glycoforms.

The analytical similarity data comparing ABP215, EU-approved bevacizumab and US-licensed Avastin supported the relevance of clinical data derived from using EU-approved bevacizumab as the comparator to support a demonstration of biosimilarity of ABP215 to US-licensed Avastin.

7 PHARMACOLOGY/TOXICOLOGY

To support the initial clinical study with ABP215, the Applicant submitted a comparative toxicity study in which monkeys received ABP215 or US-licensed Avastin, twice per week, for 1 month. No biologically significant differences in toxicity or toxicokinetics were noted between ABP215 and US-licensed Avastin. Additional pharmacology studies and a single-dose pharmacokinetic study in rats further support the similarity between ABP215 and US-licensed Avastin. These studies were not designed to demonstrate statistical significance for similarity.

8 CLINICAL PHARMACOLOGY

Executive Summary

The objective of the clinical pharmacology program is to evaluate the pharmacokinetic similarity between ABP215 and US-licensed Avastin and to support the scientific bridge between ABP215, US-licensed Avastin and EU-approved bevacizumab.

The Applicant submitted Study 20110216, which evaluated the pharmacokinetic similarities of ABP215, US-licensed Avastin, and EU-approved bevacizumab. Study 20110216 was a randomized, single-blind, single-dose, 3-arm, parallel group study in 202 healthy male subjects designed to determine the pharmacokinetic (PK) similarity of ABP215, US-licensed Avastin, and EU-approved bevacizumab following a single 3 mg/kg intravenous (IV) dose. The 90% confidence intervals (CI) for all three pairwise comparisons of $AUC_{0-\infty}$, $AUC_{0-t,}$ and C_{Max} were within the pre-specified limits of 80-125%. The results of the study established the PK similarity between ABP215 and US-licensed Avastin and provided the PK element of the scientific bridge to justify the relevance of the comparative data generated using EU-approved bevacizumab in Study 20120265 to support a demonstration of biosimilarity to US-licensed Avastin. Additional considerations on the use of data generated using the non-US-approved comparator product, are provided in Section 2 (under “The Reference Product”) above.

Study 20120265 was a randomized, double-blind, multicenter study comparing ABP215 to EU-approved bevacizumab (15 mg/kg IV every three weeks) in 642 patients with advanced non-small cell lung cancer (NSCLC). Trough concentrations of ABP215 or EU-approved bevacizumab were collected on Cycle 1 through Cycle 4, and Cycle 6 pre-dose.

Overall, Study 20110216 supports a demonstration of PK similarity between ABP215 and US-licensed Avastin, as well as the scientific bridge between ABP215, US-licensed Avastin and EU-approved bevacizumab.

8.1 Description of Relevant Clinical Pharmacology Studies

The PK of ABP215 following IV administration has been characterized in a study using US-licensed Avastin and EU-approved bevacizumab as the comparator products. A summary of the pivotal PK study, including PK endpoints is provided below.

Study 20110216 was a 3-arm, randomized (1:1:1), single-blind, parallel-group PK study designed to compare the pharmacokinetic profiles of ABP215 (n=68), US-licensed Avastin (n=67), and EU-approved bevacizumab (n=67) administered as a 3 mg/kg IV infusion to healthy male subjects (N=202). The predefined primary endpoints were C_{Max}, AUC_{0-Inf}, and AUC_{0-t}.

Based on the Guidance for Industry entitled, “Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product,” a single-dose, parallel group

design is appropriate because US-licensed Avastin has a long half-life (around 20 days) and avoids repeated exposures that can lead to immune responses or affect the PK similarity assessments. A study in healthy male subjects is considered safe and more sensitive compared with that in patients with potentially confounding factors such as underlying malignancy or concomitant medications. Lastly, the selected dose of 3 mg/kg is appropriate as it is in the linear part of the bevacizumab dose-exposure curve.

8.2 Results of Clinical Pharmacology Studies

Study 20110216
Pharmacokinetic Results

In Study 20110216, the 90% CIs for the ratios of the geometric mean of $AUC_{0-\infty}$, AUC_{0-t} and C_{Max} in pairwise comparisons between ABP215, US-licensed Avastin, and EU-approved bevacizumab were within the pre-specified limits of 80% to 125% for PK similarity, as summarized in Table 10 and depicted in Figure 12.

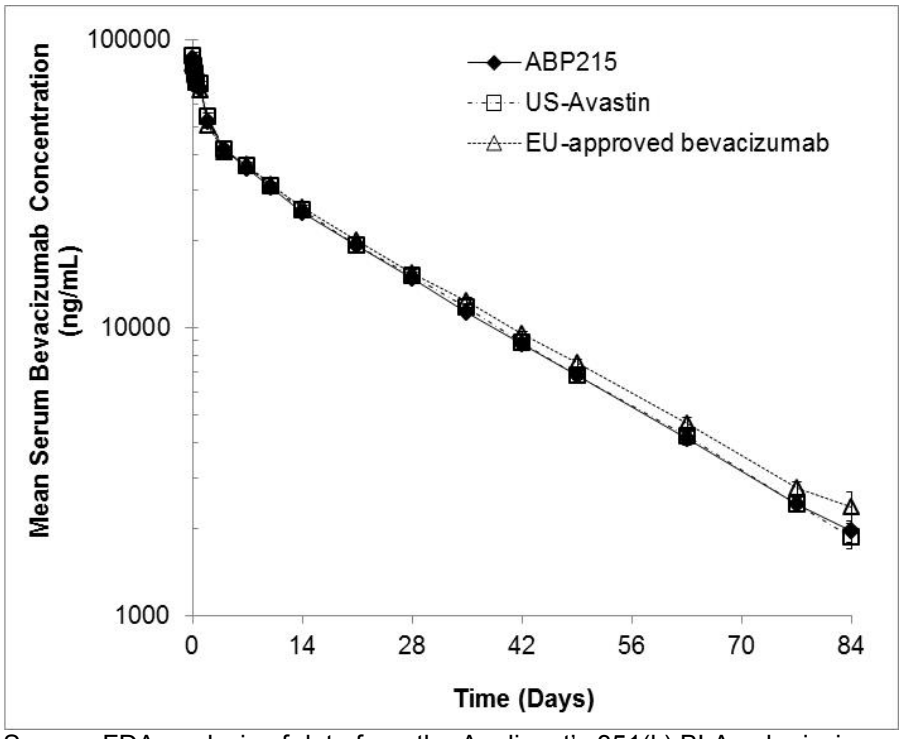
These data establish the PK similarity between ABP215 and US-licensed Avastin. The data also establish the PK component of the scientific bridge to justify the relevance of the comparative clinical data generated using EU-approved bevacizumab (Study 20120265) to support a demonstration of the biosimilarity of ABP215 to US-licensed Avastin.

Table 10 - Statistical analyses of pharmacokinetic parameters in Study 20110216

Comparison	Geometric Mean Ratio (90% CI)		
	C_{Max}	AUC_{0-t}	AUC_{0-Inf}
ABP215 vs US-Avastin	98.1 (93.7-102.8)	98.3 (94.0-102.9)	98.3 (94.0-102.9)
ABP215 vs EU-bevacizumab	102.9 (98.2-107.8)	95.6 (91.3-100.0)	95.6 (91.3-100.0)
US-Avastin vs EU-bevacizumab	104.9 (100.1-109.9)	97.2 (92.8-101.7)	97.2 (92.8-101.7)

Source: FDA analysis of data from the Applicant's 351(k) BLA submission

Figure 12 - Pharmacokinetic profiles following 3 mg/kg single intravenous dose of ABP215, US-licensed Avastin, and EU-approved bevacizumab in healthy subjects in Study 20110216



Source: FDA analysis of data from the Applicant's 351(k) BLA submission

8.3 PK Results for ABP215 and EU-Approved Bevacizumab in Comparative Clinical Study 20120265

As part of Study 20120265, trough serum concentrations (C_{trough}) were collected on Cycle 1 through Cycle 4, and Cycle 6 pre-dose in order to describe the PK of ABP215 and EU-approved bevacizumab. Study 20120265 was a randomized, double-blind study comparing ABP215 and EU-approved bevacizumab (15 mg/kg IV every three weeks) in patients with advanced non-small cell lung cancer (NSCLC). The study was not intended to evaluate the PK similarity of ABP215 to EU-approved bevacizumab; however, C_{trough} and inter-subject variability were comparable to that observed for EU-approved bevacizumab following single and multiple dosing (Table 11).

Table 11 - Mean bevacizumab trough serum concentration (µg/mL) comparison in patients with NSCLC in Study 20120265

Treatment Day	ABP215		EU-approved bevacizumab	
	N	Mean (CV%)	N	Mean (CV%)
After 1st dose (pre-Week 4)	286	64.2 (57.3%)	279	73.2 (75.5%)
After 2nd dose (pre-Week 7)	255	101.4 (57.7%)	261	108.6 (62.1%)
After 4th dose (pre-Week 13)	208	128.7 (45.2%)	212	138.5 (50.7%)
After 6th dose (pre-Week 19)	251	120.6 (49.8%)	248	123.5 (47.8%)

Source: FDA analysis of data from the Applicant's 351(k) BLA submission

8.4 Clinical Pharmacology Summary

Overall, the submitted clinical pharmacology study adequately supports a demonstration of PK similarity between ABP215 and US-licensed Avastin, as well as the scientific bridge between ABP215, US-licensed Avastin and EU-approved bevacizumab. The demonstration of PK similarity supports a finding of biosimilarity between ABP215 and US-licensed Avastin.

9 IMMUNOGENICITY

Executive Summary

The incidence of immunogenicity for ABP215 and EU-approved bevacizumab was compared in a multiple-dose, parallel-arm study in patients with non-small cell lung cancer (NSCLC) (Study 20120265). The results indicate similar rates of anti-drug antibodies (ADA) for both products. No apparent impact of ADA on safety, activity, or pharmacokinetic endpoints was observed. Therefore, the data indicate that there is no increase in immunogenicity risk for ABP215 as compared to EU-approved bevacizumab, and supports the demonstration that there are no clinically meaningful differences between ABP215 and US-licensed Avastin.

Discussion

Background. Immune responses against therapeutic biological products can negatively impact the safety, efficacy, and pharmacokinetics of these products. Often, immune responses to therapeutic biologics are measurable in the form of anti-drug antibodies (ADA) that can be detected in serum following exposure to the drug. Therefore, immunogenicity assessments for therapeutic biological products focus on measuring ADA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of ADA (including neutralizing antibodies, NAb) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of ADA in the studies described below with the incidence of ADA in other studies or to other products may be misleading.

The Applicant established an adequate scientific bridge between ABP215, EU-approved bevacizumab and US-licensed Avastin, to justify the relevance of immunogenicity data obtained using EU-approved bevacizumab to support a demonstration of no clinically meaningful differences between ABP215 and US-licensed Avastin.

Methods. The development of anti-drug antibodies was monitored in Study 20120265, a multiple-dose, parallel arm design that allowed for a comparative assessment of immunogenicity between ABP215 and EU-approved bevacizumab. The study design, patient population, treatment, and immunogenicity sampling schedule of the study is summarized in Table 12.

Table 12 - Immunogenicity sampling in Study 20120265

Study ID	Design	Route	Treatment	Population	Dose/ Schedule	Sampling
20120265	Parallel	Intra-venous	ABP215 or EU-approved bevacizumab	non-small cell lung cancer (NSCLC)	15 mg/kg every 3 weeks	Baseline and pre-dose at Week 4, 7, 13, 19, and Follow up

Source: Summary based on information from the Applicant's 351(k) BLA submission

Serum samples were tested for ADA using a tiered strategy as recommended by FDA. A screening assay was used to test all samples. Samples deemed positive in the screening assay were then tested in a confirmatory assay to confirm that the binding was specific for the product.

FDA determined that based on the Applicant's ADA assessment, which included the specific assay capabilities for detection of ADA, the results observed from Study 20120265, and what is publicly known about the incidence and nature of both ADA and neutralizing ADA to bevacizumab, that an evaluation of neutralizing ADA was not necessary to further inform on the immunogenicity assessment of ABP215.

Results. The results of the multiple-dose, parallel-arm comparative clinical study 20120265 are summarized in Table 13 below.

Table 13 - Immunogenicity results for Study 20120265

Product	N	ADA	
		Baseline	Treatment-Induced
ABP215	294	0%	1.4%
EU-approved bevacizumab	284	1.0%	2.5%

Source: FDA analysis of data from the Applicant's 351(k) BLA submission

There was no impact of immunogenicity on PK parameters from Study 20120265 (data not shown).

Immunogenicity Conclusion
Similar immunogenicity results were observed in Study 20120265 for ABP215 and EU-approved bevacizumab. The data support a determination of no clinically meaningful differences in immunogenicity risk between ABP215 and US-licensed Avastin. Of note, a scientific bridge was established between ABP215, EU-approved bevacizumab and US-approved Avastin, supporting the relevance of comparative data, including immunogenicity data, generated using EU-approved bevacizumab to support a demonstration of no clinically meaningful differences between ABP215 and US-licensed Avastin.

10 CLINICAL OUTCOMES

Executive Summary
The Applicant submitted one PK bridging study to support the PK element of the scientific bridge between ABP215, EU-approved bevacizumab and US-licensed Avastin. The Applicant submitted one comparative clinical study which was multicenter, randomized, double-blinded, parallel group design to assess the activity and safety of ABP215 compared to EU-approved bevacizumab. The FDA review of the data from this study, including data regarding both anti-tumor effects and data regarding cardinal anti-VEGF effects, supports the Applicant's conclusion that there are no differences in efficacy and safety between ABP215 and EU-approved bevacizumab, and hence supports the demonstration of no clinically meaningful differences between ABP215 and US-licensed Avastin.

10.1 Comparative Clinical Study in NSCLC

Study design
Based on the Applicant's conclusion that an adequate scientific bridge had been established between US-licensed Avastin, EU-approved bevacizumab and ABP215, the Applicant conducted Study 20120265 in order to further assess for clinically meaningful differences between ABP215 and EU-approved bevacizumab. Study 20120265 was a randomized, double-blind, comparative clinical study of ABP215 and EU-approved bevacizumab in patients with metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC) receiving first-line therapy with carboplatin and paclitaxel. Patients were randomly allocated (1:1) to receive ABP215 or EU-approved bevacizumab at a dose of 15 mg/kg administered as an IV infusion every three weeks in combination with chemotherapy (carboplatin 6 AUC and paclitaxel 200 mg/m^2) for 6 cycles. Randomization was stratified by geographic region, ECOG performance status (0 vs 1), and sex.

The primary objective was demonstration that the overall response rate (ORR) as assessed by an independent blinded review committee (IRC) per RECIST v 1.1 (Einsenhauer, 2009) was within the pre-specified similarity margin. Secondary

objectives were assessment of the duration of response in each arm and assessment of progression-free survival.

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. Toxicities were assessed for severity according to the CTCAE Version 4. Dose modifications/delays followed the standard of care for bevacizumab treatment and the backbone chemotherapy regimen.

The sample size of 620 patients (310 subjects per arm) was calculated to achieve greater than 95% power to show "equivalence" between ABP 215 and EU-approved bevacizumab on the primary efficacy endpoint of ORR as determined by whether the 90% confidence interval of the ORR risk ratio falls within the equivalence margin of 0.67 to 1.5, assuming an ORR of approximately 38% in both arms. The "equivalence" margin was calculated based on the Botrel meta-analysis (Botrel TE et al, 2011), which included the same four clinical studies as in FDA's meta-analysis for derivation of the similarity margin, described below. Inferential analyses were planned only for the primary endpoint. Secondary endpoints were the duration of response, progression-free survival (PFS), and risk difference of ORR; these analyses are descriptive.

In December 2014 letter, FDA informed the Applicant that FDA did not agree with the similarity margin described above. FDA recommended that the Applicant use the similarity margin calculated by FDA which would rule out that there is no clinically meaningful difference between ABP215 and the EU-approved bevacizumab. FDA's advice to increase the Study 20120265 sample size based on FDA's recommended similarity margin could not be implemented. FDA stated that the Applicant's lower equivalence margin for Study 20120265 would be considered in the context of the totality of the evidence and recommended that the Applicant submit the rationale for their margin selection in the BLA.

ORR as the primary endpoint and the margin selection

The objective of the comparative clinical study is to support a demonstration of no clinically meaningful differences between ABP215 and US-licensed Avastin. This determination is not made by independently establishing the safety and effectiveness of ABP215.

ORR is a measurement of anti-tumor activity due to treatment. It was accepted by FDA as the primary endpoint for the comparative clinical study in this clinical setting because it is a consistent measure of the treatment effect in this setting and is not altered by subsequent therapy, as may be the case for overall survival. Progression-free survival was not preferred because it may be influenced by differences across studies in the timing of tumor assessments or other factors.

FDA chose to use the ratio of the ORR relative risk (RR) to characterize the difference between ABP215 and EU-approved bevacizumab. In FDA's determination of the

similarity margin to be used for the ratio of RR, data from the published results of four randomized studies were included in a meta-analysis to evaluate the treatment effect of bevacizumab in combination with platinum-doublet chemotherapy in the first-line treatment of patients with NSCLC to derive the similarity margin. These four studies were Study E4599 (Sandler et al., 2006), Study JO19907 (Niho 2012), Study AVF0757 (Johnson 2004), and the AVAiL study (Reck 2010). The control arm in three of the studies was paclitaxel plus carboplatin. Cisplatin plus gemcitabine was used in the AVAiL study. As shown below in Table 14, despite the use of a different backbone chemotherapy regimen in AVAiL, the magnitude of the bevacizumab treatment effect observed (as measured by the ORR risk ratio) was comparable to that observed in the other three studies; therefore the AVAiL results were considered appropriate for inclusion in the calculation of the similarity margin.

As shown Table 14, there was a consistent bevacizumab treatment effect on ORR risk ratio, ranging from 0.43 to 0.63 in all four studies, which justified the selection of this population (first-line NSCLC) as adequately sensitive to support a demonstration of no clinically meaningful differences between ABP215 and US-licensed Avastin. In contrast, randomized studies in patients with metastatic colorectal cancer have not yielded consistent evidence of a treatment effect on ORR. For example, while there was evidence of an effect on ORR in some trials, there was no evidence of an effect on ORR when bevacizumab was added to oxaliplatin-containing therapy in patients with metastatic colorectal cancer in a large randomized trial (Saltz et al., 2007).

Table 14 – FDA's meta-analysis

Study	N (CT/BCT)*	CT	BCT	Risk ratio	70% CI
AVF0757	32/34	18.8%	32.4%	0.58	(0.37; 0.92)
JO19907	59/121	33.9%	56.2%	0.60	(0.49; 0.74)
AVAiL	327/329	21.7%	34.7%	0.63	(0.55; 0.72)
E4599	392/381	15.1%	34.9%	0.43	(0.37; 0.50)
Meta-analysis	810/865	19.3%	37.7%	0.53	(0.49; 0.58)

* N: ITT population; CT: chemotherapy; BCT: bevacizumab with chemotherapy

FDA's meta-analysis of the four clinical studies described above (Table 14) yields a RR of 0.53 and an ORR for bevacizumab with chemotherapy of 38%. Based on these assumptions, and assuming a 10% drop-out rate using a symmetrical similarity margin in the comparative clinical study, the sample sizes needed for a comparative clinical study were calculated with 80%, 85%, or 90% power using range of 70% to 95% CI for the observed ORR in the meta-analysis (Table 15) .

Table 15 – FDA's ORR sample size calculation based on the meta-analysis of NSCLC studies

CI of RR		Similarity Margin	Sample Size		
			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

The confidence intervals in the second column of the table above consider the variability of the bevacizumab treatment effect from the meta-analysis. Since a proposed biosimilar product should be highly similar to the reference product based on analytical and pharmacokinetic data, using a 70% CI of the estimated treatment effect on ORR is sufficient to support a demonstration that no clinically meaningful differences exist and the corresponding sample size is also feasible.

10.2 Study Results

Demographics and disease characteristics

The treatment arms in Study 20120265 were similar with respect to demographic and baseline prognostic characteristics. With the exception of race, the population enrolled in Study 20120265 was similar to that enrolled in the randomized studies included in the meta-analysis described in Table 14. Study 20120265 was conducted in Europe, North America, and Asia. Nine percent of patients were enrolled in the U.S.

A total of 642 patients were enrolled and randomized, 328 to ABP215 and 314 to EU-approved bevacizumab. Table 16 summarizes baseline demographic and prognostic characteristics.

Table 16 - Study 20120265: Demographic and disease characteristics (ITT)

Demographic/ Prognostic Factors	ABP215 (n:328) N; (%)	EU-bevacizumab (n:314) N; (%)
Race White	 313 (95)	 300 (96)
Sex - Male - Female	 196 (60) 132 (40)	 188 (60) 126 (40)
Age (years) - Median (range) - Mean (SD) - ≥ 65 y.o.	 62 (30 – 79) 61.60 (9.08) 129 (39)	 63 (29.80) 61.56 (8.82) 123 (39)

Demographic/ Prognostic Factors	ABP215 (n:328) N; (%)	EU-bevacizumab (n:314) N; (%)
ECOG PS 0 ECOG PS 1	127 (39) 201 (61)	117 (37) 197 (63)
Weight loss - ≤ 5% - > 5-10%	 289 (88) 39 (12)	 276 (88) 37 (12)
Smoking status Current smoker Former smoker Never smoked	 100 (30) 163 (50) 65 (20)	 80 (26) 158 (50) 76 (24)
Disease Status - Untreated Stage IV - Recurrent disease	 309 (94) 19 (6)	 290 (92) 24 (8)

The majority of patients (55% in each arm) were not tested for EGFR and ALK mutations. Of note, when tested, 3% and 1% of patients were positive for EGFR mutations or ALK rearrangements, respectively.

Disposition

The majority of patients received at least one dose of study treatment (99% in each arm). Table 17 summarizes the reasons for treatment discontinuation (this table excludes 11 patients listed in Table 16 above who did not receive treatment).

Table 17 - Study 265: Reasons for treatment discontinuation

	ABP215 (n:324) N; (%)	EU-bevacizumab (n:309) N; (%)
Reason for ending combination regimen		
Death	13 (4)	11 (4)
Disease progression	45 (14)	33 (11)
Reason for ending bevacizumab		
Completed all planned doses	192 (59)	202 (65)
Adverse event	40 (12)	37 (12)
Reason for ending carboplatin		
Completed all planned doses	178 (56)	191(62)
Adverse event	48 (15)	41 (13)
Reason for ending paclitaxel		
Completed all planned doses	177 (55)	190 (62)
Adverse event	53 (16)	43 (14)

Although more patients completed combination treatment in the EU-approved bevacizumab arm, the incidence of discontinuation for adverse events was similar in both arms. There were no differences in the median number of cycles between arms (4.8 vs. 5 in the ABP215 and EU-approved bevacizumab arms respectively).

Although there are some differences between arms, particularly with regard to the proportion of patients who discontinued protocol-specified bevacizumab the majority of these patients completed 4 to 6 cycles of treatment before discontinuing study and there were no differences between arms in the proportion of patients who discontinued treatment because of toxicity.

The mean follow-up time from randomization was 4.7 (SD 3.04) and 5.0 (SD 3.17) months for ABP215 and EU-approved bevacizumab, respectively.

Study conduct
The Applicant adequately monitored the conduct of the study. Most of the protocol violations and deviations were considered minor and reflected an intensive monitoring of clinical sites. Important protocol violations were described in 12 patients (4%) and 6 patients (2%) in the ABP215 and EU-approved bevacizumab arms, respectively, and were mostly related to violations of the eligibility criteria or an incorrect dose of chemotherapy and/or IP. FDA inspection at one clinical site that enrolled 36 patients found protocol violations in regards to the investigator's assessment of response rate (secondary endpoint). The results of the primary analysis, which was based on IRC assessment, were not affected. FDA conducted multiple sensitivity analyses to assess the potential impact of these protocol violations. Sensitivity analyses excluding data from this site for the primary endpoint were conducted and the results were comparable to that of the primary analysis.

FDA's analysis
In Study 20120265, the 90% confidence intervals of the ORR relative risk ratio remained within the Applicant's pre-specified "equivalence" margin (0.67, 1.5) as well as the similarity margin identified by FDA (0.73, 1.36).

Among the ITT population, the IRC determined that 32 (10%) and 26 (8%) patients in the ABP215 and EU-approved bevacizumab arms, respectively, were not evaluable for response and the IRC categorized these patients as "non-responders." The most common reasons that patients were considered not evaluable for response were: never received investigational treatment; no measurable disease at baseline; and withdrawal from the study before assessments were conducted.

Table 18 summarizes the IRC analysis of the ORR in the ITT population.

Table 18 -Study 265: ORR IRC analysis (ITT)

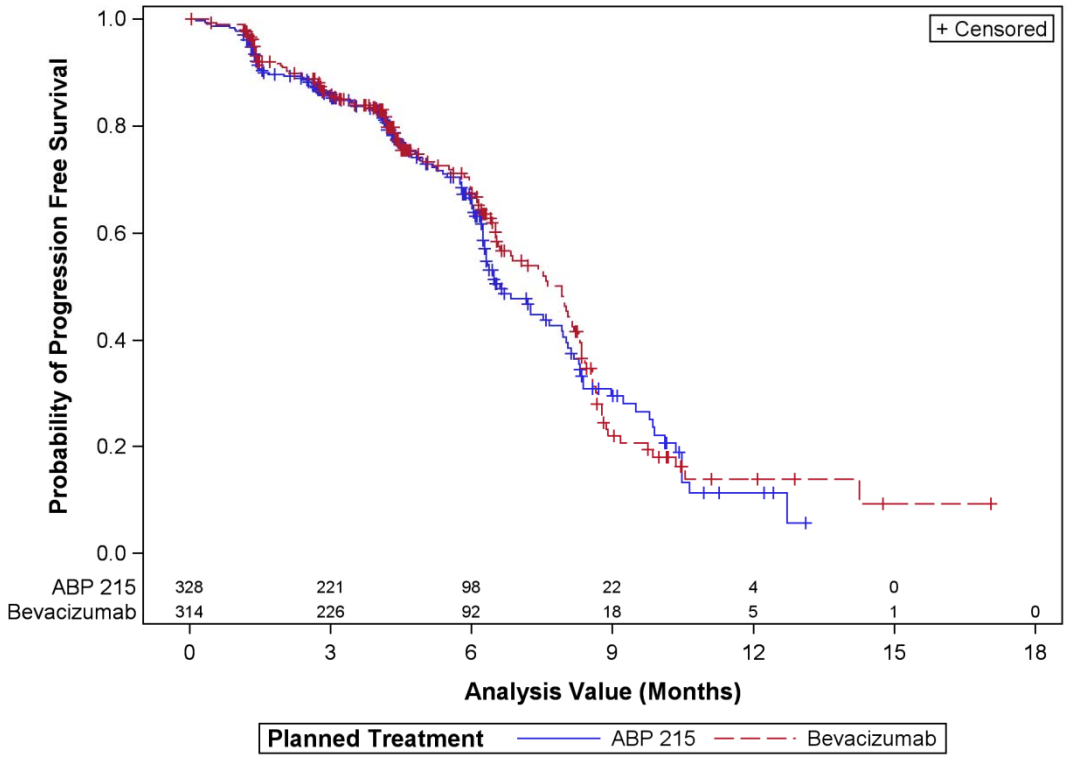
Response	ABP215 (n:328) N (%)	EU-Bevacizumab (n:314) N (%)
ORR	128 (39.0%)	131 (41.7%)
Risk ratio (90% CI)	0.93 (0.80, 1.09)	
Best response		
CR	2 (0.6)	2 (0.6)
PR	126 (38.4)	129 (41.1)
SD	144 (43.9)	137 (43.6)
PD	21 (6.4)	18 (5.7)
Not evaluable	35 (10.7)	28 (8.9)

These results are supported by sensitivity analyses which show similar findings. For example, in the per-protocol population (555 patients), the risk ratio for IRC-assessed ORR is 0.94 (90% CI: 0.80, 1.10) and in the tumor response subpopulation (defined as all randomized subjects treated with ABP215 or bevacizumab with IRC-determined measurable disease at screening (n=622)), the risk ratio for IRC-determined ORR is 0.93 (90% CI: 0.80, 1.09), both are within (0.73, 1.36). Additionally, the risk ratio for ORR as assessed by the investigators was a sensitivity analysis to assess robustness of the results. The ORR is 48% in both arms with a risk ratio of 1.1 (90% CI 0.88; 1.16). This analysis is unlikely to be affected by bias due to “unmasking” in this double-blinded study with an active control of EU-approved bevacizumab.

Duration of response per IRC assessment is a key secondary endpoint. The median duration of response is 5.8 months (95% CI 4.9; 7.7) in the ABP215 arm and 5.6 months (95% CI 5.1; 6.3) in the EU-approved bevacizumab arm.

Progression-free survival assessed by the IRC in the ITT population is displayed in Figure 13. In both arms, 40% of patients (131 and 125 patients in the ABP215 and EU-bevacizumab arms, respectively) had a PFS event by the data-cutoff date. The HR for PFS was 1.03 (95% CI: 0.80, 1.34) and the median PFS is 6.6 months (95% CI: 6.3, 7.9) in the ABP215 arm and 7.9 months (95% CI: 6.6, 8.2) in the EU-approved bevacizumab arm. Interpretation of the PFS analysis should be viewed with caution as this analysis was not designed to demonstrate similarity of PFS within a specified margin.

Figure 13 - Study 20120265: PFS by IRC assessment in the ITT population



Summary

The analyses of ORR, including sensitivity analyses, and PFS, in combination with the safety analyses below and the PK analyses, support the demonstration that there are no clinically meaningful differences between ABP215 and US-licensed Avastin. In general, the study was well conducted with minimal violations to the eligibility criteria, good treatment adherence, and minimal missing data; therefore, any potential concern about bias towards equivalence is mitigated. The 90% confidence intervals of 0.80 to 1.09 around the observed risk ratio of 0.93 fell well within the pre-specified similarity margins of 0.73 to 1.36 as derived from the meta-analysis conducted. The observed ORR for both the ABP215 and EU-approved bevacizumab arms were similar to that observed in the studies included in the meta-analysis, thus the constancy assumption does not appear to have been violated. The totality of the available information supports the assay sensitivity of Study 20120265 to rule out clinically meaningful differences.

FDA inspection at one clinical site that enrolled 36 patients found protocol violations in regards to the investigator's assessment of response rate (secondary endpoint). The results of the primary analysis, which was based on IRC assessment, were not affected. FDA conducted multiple sensitivity analyses to assess the potential impact of these protocol violations. Sensitivity analyses excluding data from this site for the primary endpoint were conducted and the results were comparable to that of the primary analysis.

Safety analysis
No new safety signals were identified in the ABP215 arm compared to the known toxicity profile of US-licensed Avastin. Overall, there were no meaningful differences in adverse events (AEs), serious adverse events (SAEs), deaths up to 30-days after the last treatment dose, or treatment discontinuations.

The mean (SD) number of doses of ABP215 and EU-approved bevacizumab administered was 4.8 (1.76) and 5.0 (1.61), respectively. ABP215 and EU-approved bevacizumab doses were delayed in 22% and 23% patients respectively, primarily because of adverse events. In both arms, the median number of doses of paclitaxel was 5 and the mean was 4.5 (std 1.69) and 4.7 (std 1.56) in the ABP215 and EU-approved bevacizumab arms, respectively. Similarly, in both arms the median number of doses of carboplatin was 5 and the mean was 4.6 (std 1.67) and 4.7 (std 1.57) in the ABP215 and EU-approved bevacizumab arms, respectively.

Grade 3-4 AEs were reported in 42% and 44% of patients in the ABP215 and EU-approved bevacizumab arms, respectively. These severe adverse events were balanced between arms and consistent with the known adverse event profile of carboplatin, paclitaxel, and bevacizumab. There was no event (Grade 3 or 4 in severity) with a >2% difference in incidence rate. SAEs were reported in 26% and 23% patients in the ABP215 and EU-approved bevacizumab arms, respectively. The incidence rate of deaths considered possibly related to an AE was 4% in both arms. The most frequent cause of death in this population was hemorrhage as a category (6 patients in the ABP215 arm and 4 patients in the EU-approved bevacizumab arm) and hemoptysis (2 patients per arm) as a specific adverse event.

The datasets were queried for adverse events of special interest related to the known toxicity profile of VEGF inhibitors (Table 19).

Table 19 - Study 20120265: AEs of special interest

	ABP215 (n:324)		EU-bevacizumab (n:309)	
Adverse Event	**All grades**	**Gr 3-4**	**All grades**	**Gr 3-4**
Hypertension	19%	7%	16%	6%
Hemorrhages	22%	2%	21%	1%
VTE	4%	2%	5%	3%
ATE	2%	1%*	1%	1%
Proteinuria	8%	<1%	6%	<1%
GI perforation	1%	1%	1%	1%

* There were two additional fatal events (Grade 5).

Blood pressure was systematically assessed on Day 1 of each cycle. In both arms, most hypertension events (75%) were reported within 55 days after administration of the first dose of ABP215 or EU-approved bevacizumab. As a result of hypertension, ABP215 was temporarily interrupted or delayed in 6 patients, and discontinued in

2 patients. EU-approved bevacizumab was delayed in 8 patients and discontinued in 2 patients. During each cycle, the difference of mean systolic blood pressure between arms was less than 3.2 mm Hg, a finding consistent with random variability and no clinical significance.

There were no meaningful differences between arms in the incidence of infusion related reactions (IRR). IRRs (using the Standard MedDRA Query narrow search) were identified if the adverse event occurred during an infusion or within 24 hours after the infusion. IRRs exclusively related to ABP215 or EU-approved bevacizumab occurred in 14% and 12% patients, respectively. The majority of these events occurring within the first 24 hours (in 12% and 10% patients, respectively) were hypertension or increased blood pressure (90% patients in each arm received dexamethasone as pre-medication).

There were no differences greater than 2% in the incidence of wound complications, non-gastrointestinal fistulas, cardiac failure, or febrile neutropenia.

In conclusion, the rates, severity, and type of toxicities were similar between the treatment groups and consistent with the safety profile described for US-licensed Avastin. These clearly indicate that ABP215 causes anti-VEGF-related pharmacodynamic effects. The submitted safety and immunogenicity data (see section 9) and analyses of data from ABP215 clinical studies are adequate to support the demonstration of no clinically meaningful differences between ABP215 and US-licensed Avastin. The safety database submitted for ABP215 is adequate to provide a reasonable descriptive comparison between the two products.

11 CONSIDERATIONS FOR EXTRAPOLATION OF BIOSIMILARITY

The Applicant seeks licensure for the following indications for which US-licensed Avastin is licensed:

- metastatic colorectal cancer (mCRC), in combination with intravenous (IV) 5-fluorouracil- (5-FU)-based chemotherapy for first- or second-line treatment
- mCRC, in combination with fluoropyrimidine-, irinotecan-, or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab containing regimen
- non-squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent, or metastatic disease
- glioblastoma multiforme (GBM), as a single agent for adult patients with progressive disease following prior therapy
- metastatic renal cell carcinoma (mRCC), in combination with interferon alfa

- cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease

The ABP215 program provided clinical data from a comparative PK study in healthy volunteers and a comparative clinical study in patients with NSCLC. FDA has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use (e.g., indications) for which the reference product is licensed, based on data supporting a demonstration of biosimilarity, including data from clinical study(ies) performed for another condition of use. This concept is known as extrapolation. As described in the Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", if a biological product meets the statutory requirements for licensure as a biosimilar product under Section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for that product to be licensed for one or more additional conditions of use for which the reference product is licensed. The Applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

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

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. Consistent with the principles outlined in the FDA guidance, the Applicant has provided justification for the proposed extrapolation of clinical data in Study 20120265 in NSCLC, as well as clinical pharmacology data from a healthy volunteer study, to each of the other indications approved for US-licensed Avastin for which the Applicant is seeking licensure, as summarized in this section.

As summarized throughout this document, FDA agrees with the Applicant that the extensive analytical characterization data support a demonstration that ABP215 is highly similar to US-licensed Avastin, and that clinical data support a demonstration that there are no clinically meaningful differences between ABP215 and US-licensed Avastin based on similar clinical pharmacokinetics, anti-tumor activity, safety, and immunogenicity.

Further points to consider in the scientific justification for extrapolation of the data in NSCLC to other indications for which the Applicant is seeking licensure include:

- Bevacizumab binds circulating VEGF which prevents the interaction of VEGF to its receptors (Flt-1 [VEGFR-1] and KDR [VEGFR-2]) on the surface of endothelial cells. Neutralizing the biological activity of VEGF results in the regression of tumor vascularization, normalization of remaining tumor vasculature, and inhibition of the formation of new tumor vasculature, thereby inhibiting tumor growth (Avastin USPI).

  In *each* approved indication, the MOA of bevacizumab is to inhibit VEGF-induced angiogenesis and vascular permeability. The Applicant submitted an extensive analysis of the role of VEGF and VEGF inhibition in each one of the indications for which licensure is sought. FDA agrees that there is no evidence to support claims of a unique MOA in specific indications.

- PK profiles of bevacizumab following IV infusions ranging from 0.1 mg/kg to 10 mg/kg have been evaluated in several dose escalation/dose finding studies in solid tumors (Gordon 2001; Margolis 2001, EMA 2006, Herbst 2008, Han 2016). The PK properties of bevacizumab across approved indications appear consistent.

- Overall, FDA considers that Study 20110216 adequately demonstrated pharmacokinetic similarity among ABP215, US-licensed Avastin, and EU-approved bevacizumab. Since PK similarity was demonstrated between ABP215 and US-licensed Avastin, a similar PK profile would be expected for ABP215 in patients across the indications being sought for licensure.

- As summarized in the labeling for US-licensed Avastin, 14 of 2233 evaluable subjects (0.63%) tested positive for treatment-emergent anti-bevacizumab antibodies as detected by an ECL-based assay. Further analysis of these 14 subjects using an ELISA assay concluded that 3 subjects were positive for neutralizing antibodies against bevacizumab. The clinical significance of these ADA responses to bevacizumab is unknown. The analysis of Studies 20110216 and 20120265 indicate that immunogenicity was low and that treatment of subjects with NSCLC with either ABP215, EU-approved bevacizumab, or US-licensed Avastin resulted in similar rates of formation of binding ADAs.

- The expected toxicities of bevacizumab are well characterized and are summarized in the Avastin USPI, as well as multiple meta-analyses of earlier clinical trial data in various solid tumors. The MOA is common to all of the indications of use. While the incidence of specific toxicities may differ across indications (e.g., hypertension is more frequent in patients with RCC while hemoptysis is more frequent in patients with NSCLC), due to the common MOA, the differing toxicities are predictable in each indication for which licensure is

sought for ABP215 in this application. Data from Study 20120265 demonstrated that the type and incidence of treatment-emergent adverse events of special interest were similar for ABP215 and EU-approved bevacizumab and that there were no clinically meaningful differences between arms. No new safety signals were identified that would be indicative of new toxicities for the approved indications for US-licensed Avastin.

Therefore, the evidence indicates that the extrapolation of biosimilarity to the indications for which the Applicant is seeking licensure is scientifically justified.

12 SUMMARY

The comparison of the structural and functional properties of the clinical and commercial product lots of ABP215 and US-licensed Avastin supports a demonstration that they are highly similar, notwithstanding minor differences in clinically inactive components.

The Applicant provided extensive analytical and clinical pharmacology bridging data to scientifically justify the relevance of data obtained using EU-approved bevacizumab in a clinical study to support a demonstration of biosimilarity of ABP215 to US-licensed Avastin.

The submitted clinical pharmacology studies are adequate to (1) support the demonstration of PK similarity between ABP215 and US-licensed Avastin, (2) establish the PK component of the scientific bridge to justify the relevance of the data generated using EU-approved bevacizumab to a demonstration of biosimilarity to US-licensed Avastin, (3) justify the relevance of the PK findings from the ABP215 clinical program to the indications that were not directly studied in the ABP215 clinical program for which US-licensed Avastin is licensed and for which the Applicant is seeking licensure.

The results of the clinical development program indicate that the Applicant's data support a demonstration of "no clinically meaningful differences" between ABP215 and US-licensed Avastin in terms of safety, purity, and potency in the indication studied.

The Applicant has also provided an extensive data package to address the scientific considerations for extrapolation of data to support a demonstration of biosimilarity in other conditions of use to support their request that ABP215 should receive licensure for the indications for which US-licensed Avastin is currently licensed and for which the Applicant is eligible for licensure.

13 REFERENCES

Arcondeguy, T. (2013). VEGF-A mRNA processing, stability and translation: a paradigm for intricate regulation of gene expression at the post-transcriptional level. *Nucleic Acids Res*, 7997-8010.

Avastin USPI
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

Botrel T., Clark O., Clark L., Paladini L., Faleiros E. at al. Efficacy of bevacizumab plus chemotherapy compared to chemotherapy alone in previously untreated locally advanced or metastaic non-small cell lung cancer: systematic review and metanalysis. Lung Ca (2011), 74: 89-97.

Carpenter, J. e. (2009). Overlooking Subvisible Particles in Therapeutic Protein Products: Gaps That May Compromise Product Quality. *J Pharm Sci*, 1201-1205.

Eisenhauer E., Therasse P., Bogaerts J., Schwartz L., Sargent D. et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J of Cancer 45 (2009) 228 – 247.

European Medicines Agency. European Public Assessment Report, Avastin Scientific Discussion, 2006. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000582/WC500029262.pdf

Ellis, L. a. (2008). VEGF-targeted therapy: mechanisms of anti-tumor activity. *Nat Rev Cancer*, 579-591.

Ferrara, N. (2004). Vascular Endothelial Growth Factor: Basic Science and Clinical Progress. *Endocr Rev*, 581-611.

Ferrara, N. (2010). Binding to the Extracellular Matrix and Proteolytic Processing: Two Key Mechanisms Regulating Vascular Endothelial Growth Factor Action. *Mol Biol Cell* , 687-690.

Goel, H. L. (2013). VEGF targets the tumor cell. *Nat Rev Cancer*, 871-882.

Gordon MS, Margolin K, Talpaz M,et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol. 2001;19:843-850.

Guidance for Industry - Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) April

2015. https://www.fda.gov/downloads/drugs/guidances/ucm444661.pdf

Guidance for Industry - Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) December 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

Han K, Peyret T, Marchand M, et al. Population pharmacokinetics of bevacizumab in cancer patients with external validation. *Cancer Chemother Pharmacol*. 2016;78:341-351.

He K., Chen H., Gwise T., Casak S., Lemery S., et al. Statistical Considerations in Evaluating a Biosimilar Product in an Oncology Clinical Study. Clin Cancer Res; 22(20) October 15, 2016.

Herbst RS, Heymach JV, Lippman SM. Lung cancer. *N Engl J Med*. 2008;359:1367-1380.

Higel, F. e. (2016). N-glycosylation heterogeneity and the influence on structure, function and pharmacokinetics of monoclonal antibodies and Fc Fusion proteins. *Eur J Pharm Biopharm*, 94-100.

Houck, K. e. (1991). The Vascular Endothelial Growth Factor Family: Identification of a Fourth Molecular Species and Characterization of Alterhnative Splicing of RNA. *Mol Endocrinol*, 1806-1814.

Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184–91.

Lemery S., Ricci MS, Keegan P., McKee A., and Pazdur R. FDA's Approach to Regulating Biosimilars. Clin Cancer Res; 23(8) April 15, 2017.

Liu, H. e. (2014). In vitro and in vivo modifications of recombinant and human IgG antibodies. *mAbs*, 1145-1154.

Margolin K, Gordon MS, Holmgren E, et al. Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: pharmacologic and long-term safety data. J Clin Oncol. 2001;19:851-856.

Moussa, E. e. (2016). Immunogenicity of Therapeutic Protein Aggregates. *J Pharm Sci*, 416-430.

Muller, Y. e. (1997). Vascular endothelial growth factor: Crystal structure and funcitional mapping of the kinase domain receptor binding site. *Proc Natl Acad Sci USA*, 7192-7197.

Muller, Y. e. (1998). VEGF and the Fab fragment of a humanized neutralizing antibody: crystal structure of the complex at 2.4 Å resolution and mutational analysis of the interface. *Structure*, 1153-1167.

Niho S, Kunitohb H, Nokiharab H, et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer 2012;76:362–7.

Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010;21:1804–9.

Rosenberg, A. (2006). Effects of Protein Aggregates: An Immunoglogic Perspective. *AAPS J*, E501-E507.

Rosenberg, A. e. (2012). Managing Uncertainty: A Perspective on Risk Pertaining to Product Quality Attributes as They Bear on Immunogenicity of Therapeutic Proteins. *J Pharm Sci*, 3560-3567.

Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al.Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.

Vempati, P. e. (2014). Extracellular rgulation of VEGF: Isoforms, proteolysis, and vascular patterning. *Cytokin Growth Factor Rev*, 1-19.

Wang, Y. e. (2004). Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. *Angiogenesis*, 335-345.

Wiesmann, C. e. (1997). Crystal Structure at 1.7Å Resolution of VEGF in Complex with Domain 2 of the FLT-1 Receptor. *Cell*, 695-704.

Yu, M. e. (2012). Production, characterization and pharmacokinetic properties of antibodies with N-linked Mannose-5 glycans. *mAbs*, 475-487.