CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761028Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	September 14, 2017
From	Patricia Keegan
Subject	Division Director Summary Review
BLA #	BLA 761028 submitted under the provisions of 351(k)
Applicant Name	Amgen, Inc.
Date of Submission	November 14, 2016
BsUFA Goal Date	September 14, 2017
Proprietary Name / Nonproprietary Name	Mvasi/ bevacizumab-awwb
Dosage Forms / Strength	Injection, for intravenous use/ 100 mg/4 mL and 400 mg/16 mL (25 mg/mL) single use vials
Proposed Indication(s)	1. ABP215 is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with 5-fluorouracil-based chemotherapy. 2. ABP215, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab product-containing regimen. 3. ABP215 is indicated for the first line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer in combination with carboplatin and paclitaxel. 4. ABP215 is indicated for the treatment of glioblastoma with progressive disease in adult patients following prior therapy as a single agent. 5. ABP215 is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa. 6. ABP215 in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Leah Her
Medical Officer Review	Sandra Casak
Statistical Review	Weishi Yuan
Pharmacology Toxicology Review	Alexander H. Putman
CMC Review	Jee Chung (Drug Substance, Drug Product, Immunogenicity); Tianhua Wang (CMC statistics Drug Substance and Drug Product); Laura Fontan (Facility); Vicky Borders-Hemphill (Labeling); Chana Fuchs (Application Team Lead)
Microbiology Review	Scott Nichols (Drug Substance); Dupeh Palmer (Drug Product)
Clinical Pharmacology Review	Edwin Chow & Sarah J Schrieber
OSI	Lauren Iacono-Connor
OSIS/DNDBE	Angel S Johnson
CDTL Review	Steven Lemery
OSE/DMEPA Labeling Review	Janine A Stewart

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DNDBE=Division of New Drug Bioequivalence Evaluation
OSIS=Office of Study Integrity and Surveillance
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This is a biologics license application (BLA) submitted under the provisions of section 351(k) of the Public Health Service Act (PHS Act) by Amgen, Inc. for bevacizumab-awwb (tradename "Mvasi"), a proposed biosimilar to U.S.-licensed Avastin (bevacizumab). During development, Amgen identified the product as "ABP215." Amgen is seeking licensure of bevacizumab-awwb on the basis of the following:

- Analytical data:
  - Demonstrating that bevacizumab-awwb can be manufactured in a well-controlled and consistent manner, leading to a product that is sufficient to meet required quality standards;
  - Demonstrating that bevacizumab-awwb and US-licensed Avastin are highly similar; and
  - Providing the analytical portion of the scientific bridge to justify the relevance of comparative data that were generated using European Union (EU)-approved bevacizumab to support a demonstration of biosimilarity of bevacizumab-awwb to US-licensed Avastin.
- A clinical pharmacology program for bevacizumab-awwb, comprised of Study 20110216 (Study 216), a single-dose, 3- way pharmacokinetic (PK) study evaluating bevacizumab-awwb, US-licensed Avastin, and EU-approved bevacizumab, and pharmacokinetic data from the comparative clinical study, Study 20120265 (Study 265):
  - Demonstrating the pharmacokinetic (PK) similarity of bevacizumab-awwb and US-licensed Avastin in Study 216;
  - Providing the PK element of the scientific bridge to justify the relevance of comparative data generated using EU-approved bevacizumab to support a demonstration of biosimilarity of bevacizumab-awwb to US-licensed Avastin in Study 216; and
  - Characterizing the PK and immunogenicity of bevacizumab-awwb in the comparative clinical study, Study 265, discussed below.
- A clinical development program for bevacizumab-awwb consisted of a single comparative clinical study. Study 265 was a randomized, double-blind, comparative clinical study conducted in 642 patients with unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) receiving first-line, platinum-based chemotherapy. In addition to planned chemotherapy, patients were randomized (1:1) to receive bevacizumab-awwb or EU-approved bevacizumab at a dose of 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed overall response rate (ORR).
- A scientific justification for extrapolation of biosimilarity to the other indications which were not directly studied in the bevacizumab-awwb development program but for which US-licensed Avastin is licensed and for which Amgen is also seeking licensure, i.e., first-

or second-line treatment of patients with metastatic carcinoma of the colon or rectum (mCRC) in combination with 5-fluorouracil-based chemotherapy; second-line treatment of patients with mCRC who have progressed on a first-line bevacizumab-product containing regimen, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy; treatment of glioblastoma with progressive disease following prior therapy; treatment of metastatic renal cell carcinoma in combination with interferon alfa; and treatment of persistent, recurrent, or metastatic carcinoma of the cervix in combination with paclitaxel and cisplatin or paclitaxel and topotecan. Amgen is not seeking approval for the following approved indications for US-licensed Avastin, which are protected by orphan drug exclusivity:

- In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for treatment of patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

- Either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Avastin as a single agent, for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

2. Background

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.

Section 351(i) of 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" (see section 351(i)(2) of the PHS Act). 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).

The foundation of an abbreviated development program for a biosimilar product is extensive structural and functional characterization of the both the proposed biosimilar product and its reference product to demonstrate that the products are highly similar. Residual uncertainties about the clinical impact of analytical differences between the products may be addressed by

comparative human PK and, if applicable, pharmacodynamic data, clinical immunogenicity, safety, and effectiveness data. However, unlike a stand-alone development program (i.e., BLAs submitted under section 351(a) of the Public Health Service Act), a demonstration of efficacy and safety in each clinical indication is not expected. It is under this pathway that Amgen seeks licensure of bevacizumab-awwb.

Regulatory History

Clinical development for bevacizumab-awwb was conducted under IND 111960. The following pre-submission meetings occurred between the applicant and FDA:

July 12, 2011: A preIND meeting was held to discuss the plan for quality, non-clinical, and clinical studies intended to support a 351(k) biologics license application (BLA) for bevacizumab-awwb. FDA provided advice on justification of the number of lots included in analytical similarity studies, need for assessment of multiple quality attributes, including Fc effector function, and the need to establish a scientific bridge in order to rely on data obtained with EU-approved bevacizumab to support a demonstration of biosimilarity to US-licensed Avastin. Additionally, FDA provided advice on the approach to selection of the non-inferiority margin in the planned comparative clinical study.

March 27, 2012: A preIND, chemistry, manufacturing, and controls (CMC) meeting was held to discuss whether the proposed analytical similarity data package would be adequate to support initiation of the planned pharmacokinetic similarity study to be submitted in the initial IND. While FDA agreed that the data would support the proposed study, FDA stated that additional lots should be evaluated based on adequately justified specifications and statistical analyses for the planned BLA.

July 30, 2013: A BPD Type 3 meeting was held to discuss the design of the comparative clinical study, Study 265. FDA agreed that EU-approved bevacizumab could be used in the proposed comparative clinical study if an adequate scientific bridge was established. FDA further advised that patients with targetable tumor mutations in ALK or EGFR be excluded or informed of the availability of alternative therapy and that Amgen assess the effects of exclusion of such patients on the proposed non-inferiority margins, as such patients were included in the historical studies used to develop the margin. Finally, FDA advised the primary analysis population be the intent-to-treat (all randomized) population.

Dec.3, 2014: FDA issued an advice letter containing comments regarding Amgen's proposed similarity margin and recommendations regarding an acceptable approach to determination of the similarity margin. FDA's approach was based on a meta-analysis of four randomized clinical trials enrolling 1675 patients with NSCLC receiving chemotherapy with or without bevacizumab. FDA stated that assuming symmetrical margins, 50% maintenance of the confidence limit, an ORR of 37.7% with the addition of bevacizumab to chemotherapy, a 10% drop-

out rate, and 70% power, would result in sample sizes similar to that proposed in the ongoing comparative clinical study.

January 21, 2015: A BPD Type 1 meeting was held to discuss FDA's letter of December 3, 2014, regarding FDA's request to revise the selected margin for Study 265. Amgen informed FDA that Study 265 had completed enrollment and that use of FDA's proposed non-inferiority margin would require re-opening of the study to increase the sample size. FDA acknowledged that the FDA's recommended similarity margins would require an increase in sample size that could not be implemented due to logistics (need for global protocol amendment, renegotiation of contracts with study sites, CRO's and laboratories). FDA stated that the applicant's margins for Study 265 would be considered in the context of the totality of the evidence.

May 20, 2015: A BPD Type 2 meeting was held to provide Amgen with general advice on the content and format of the proposed BLA. FDA agreed with Amgen's proposal for the submission of PK, safety and immunogenicity data and analyses, except that FDA requested that only Study 20110216 be submitted as the pivotal study for demonstration of PK similarity and that the results of (b) (4) (b) (4) would not be required.

Feb. 5, 2016: A BPD Type 4 meeting was held to reach agreement on the content and format of the proposed BLA.

3. CMC/Device

Manufacturing and Product Quality Evaluation

Drug substance

Bevacizumab-awwb is a recombinant humanized IgG1 kappa monoclonal antibody produced in CHO cells consisting of two heavy chains (453amino acids each) and two light chains (214 amino acids each). Bevacizumab-awwb binds specifically to human vascular endothelial growth factor A (VEGF A), preventing the interaction of VEGF A with its receptors, VEGF receptor 2 (VEGFR2/ KDR) and VEGF receptor 1 (VEGFR1/Flt-1) and thereby inhibiting the known functional activities of VEGF A. Bevacizumab-awwb binds to multiple Fcγ receptors and to C1q; while bevacizumab-awwb can mediate antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), this is not relevant to its mechanism of action based on binding to VEGF A, a soluble ligand.

The drug substance (DS) manufacturing process, described in the product quality reviews, is well-controlled. The DS is manufactured at Amgen, Inc., Thousand Oaks, California. Submitted data support a dating period for the DS of (b) (4) months when stored at (b) (4)°C.

Drug Product

Bevacizumab-awwb was developed as single-use use vials at the same strengths, dosage forms, and route of administration as approved for US-licensed Avastin. Bevacizumab-awwb will be supplied as a colorless to pale yellow, sterile, solution in 100 mg/4 mL and 400mg /16 mL (25 mg/mL) single-dose vials. The 100 mg strength contains 100 mg drug product (DP) per 4mL formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg strength contains 400 mg DP per 16 mL formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP. The container closure system for both strengths consists of a 6 cc (100 mg) or 20 cc (400 mg) Type I glass vial, elastomeric stopper, and aluminum seal with flip off cap. The DP is manufactured at (b) (4) Submitted data support an expiration dating period of 36 months at 2-8°C.

Microbiology

The microbiology review team has concluded that the DS and DP are recommended for approval from a product quality microbiology perspective.

Facilities Inspections

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination controls strategy were provided in the BLA for Amgen, Inc., Thousand Oaks, California and (b) (4), the proposed DS and DP manufacturing sites, respectively. All proposed manufacturing and testing facilities are acceptable on the basis of their currently acceptable cGMP compliance status and recent inspections. This BLA is considered adequate for approval from a facilities assessment perspective.

Summary

In summary, the review team has determined that the DS and DP manufacturing process is well-controlled and adequate to support approval. Four post-marketing commitments have been agreed-upon between FDA and Amgen, as described in Section 13 of this Summary Review.

Analytical Similary Evaluation

The analytical similarity evaluation included comprehensive methods that assessed the primary structure, post-translation changes (e.g., glycosylation pattern), higher order structure, product-related substances and impurities, particulates, aggregates, biological activity including VEGFA binding and functional activity in a HUVEC cellular proliferation, Fc binding activity and absence of ADCC and CDC, stability, and forced degradation, general properties (protein concentration, volume by content and weight, pH, osmolality and appearance), and process-related impurities. Comparative analytical data were evaluated using multiple lots of bevacizumab-awwb, US-licensed Avastin, and EU-approved bevacizumab to assess the between products. A cell-based anti-proliferation assay using human umbilical vein endothelial cells (HUVEC) that evaluated prevention of VEGF A-ligand binding dependent

proliferation and an evaluation of VEGF A binding using an enzyme-linked immunosorbent assay (ELISA) assessing the binding kinetics to two VEGF A isoforms (121 and 165) were identified as methods to be evaluated by statistical equivalence testing. Three pairwise comparisons of bevacizumab-awwb to US-licensed Avastin, bevacizumab-awwb to EU-approved bevacizumab, and US-licensed Avastin to EU-approved bevacizumab were used to support the analytical component of the scientific bridge to justify the relevance of the comparative data generated using EU-approved bevacizumab in the comparative clinical study, Study 265.

VEGF A Binding Assay Results
The comparison of VEGF A binding (using multiple isoforms of VEGF A) for bevacizumab-awwb and US-licensed Avastin met the pre-specified criteria for statistical equivalence, supporting a demonstration that bevacizumab-awwb is highly similar to US-licensed Avastin. In addition, statistical evaluation of VEGF A binding for the three pairwise comparisons of bevacizumab-awwb, US-licensed Avastin and EU-approved bevacizumab met the criteria for statistical equivalence, which supports the analytical component of the scientific bridge to justify the relevance of data from the comparative clinical study, Study 265, conducted with EU-approved bevacizumab.

HUVEC Assay
The comparison of the HUVEC anti-proliferation assay results for bevacizumab-awwb and US-licensed Avastin met the pre-specified criteria for statistical equivalence, supporting a conclusion that bevacizumab-awwb is highly similar to US-licensed Avastin. In addition, statistical evaluation of VEGF A binding for the three pairwise comparisons of bevacizumab-awwb, US-licensed Avastin, and EU-approved bevacizumab met the criteria for statistical equivalence, which supports the analytical component of the scientific bridge to justify the relevance of data from the comparative clinical study, Study 265, conducted with EU-approved bevacizumab.

Similarity of Other Quality Attributes
The amino acid sequences of bevacizumab-awwb and US-licensed Avastin are identical. Numerous additional quality attributes, including higher order structure, Fc (effector) binding and function, and other structural/functional characteristics were assessed by quality range analysis and by qualitative comparisons. The results of these comparisons also support a demonstration that bevacizumab-awwb is highly similar to US-licensed Avastin, notwithstanding minor differences in clinically inactive components. The following minor differences in structural or functional activity were evaluated to determine if their effects are clinically significant. Differences in binding to FcγRIIIa receptor specific for the 158V isotype of the receptor were determined not to be clinically significant as ADCC mediated through this receptor binding is not important to the mechanism of action of the drug, as confirmed in a biologic assay with VEGF secreting cell lines. Minor differences in galactosylation were determined to have no clinical importance in C1q binding studies and analyses of CDC activity. Minor differences in mannose content did not result in differences in pharmacokinetic profiles. Minor differences in aggregates and fragments were determined not to be clinically significant as assessed by orthogonal methods verifying a low rate of aggregates and fragments between all three products that did not alter pharmacokinetics and were unlikely to alter the

toxicity profile. Finally, minor differences in basic charge variants resulting from differences in C-terminal lysine residues did not alter the functional characteristics or pharmacokinetic profile and were deemed unlikely to affect product safety.

Summary
In summary, FDA reviewers from the Office of Biotechnology Products (OBP) and Office of Biostatistics (OB) have evaluated the analytical similarity of bevacizumab-awwb, US-licensed Avastin, and EU-approved bevacizumab and have determined that bevacizumab-awwb is highly similar to US-licensed Avastin, notwithstanding minor differences in clinically inactive components. Additionally, Amgen provided an adequate analysis for the purpose of establishing the analytic component of the scientific bridge between bevacizumab-awwb, US-licensed Avastin, and EU-approved bevacizumab to justify the relevance of the comparative clinical data generated with EU-approved bevacizumab in Study 265 to support a demonstration of no clinically meaningful differences between bevacizumab-awwb and US-licensed Avastin. Reviewers from OBP and the Office of Compliance have reviewed the product quality and manufacturing aspects of bevacizumab-awwb and determined the submitted data are adequate to support approval from a product quality perspective.

4. Nonclinical Pharmacology/Toxicology

The pharmacology and toxicology studies submitted in support of the BLA included two mouse xenograft models of cancer, a VEGF-induced vascular permeability study, a single-dose pharmacokinetic study in rats, and a toxicity study in monkeys comparing bevacizumab-awwb and US-licensed Avastin. The nonclinical pharmacology, pharmacokinetic, and repeat-dose toxicity data showed comparable exposure and safety between bevacizumab-awwb and US-licensed Avastin. There are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology

The clinical pharmacology program in this application served several purposes:

1) To evaluate the PK similarity between bevacizumab-awwb and US-licensed Avastin (Study 20110216)
2) To provide the PK component of the scientific bridge between bevacizumab-awwb, US-licensed Avastin and EU-approved bevacizumab (Study 20110216)
3) To provide information on PK in Study 20120265 (Study 265) obtained in patients receiving platinum-based chemotherapy for first-line treatment of NSCLC.

Study 20110216 (Study 216), was a randomized, single-blind, single-dose, 3-arm, parallel group study in which 202 healthy male subjects were randomized 1:1:1 to bevacizumab-awwb, US-licensed Avastin, and EU-approved bevacizumab. This study was the pivotal clinical pharmacology study evaluating the PK similarity of bevacizumab-awwb and US-licensed Avastin. The three pairwise comparisons of bevacizumab-awwb with US-licensed Avastin,

bevacizumab-awwb with EU-approved bevacizumab, and US-licensed Avastin with EU-approved bevacizumab met the pre-specified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and Cmax within the interval of 80% to 125%). Therefore these data 1) establish PK similarity of bevacizumab-awwb and US-licensed Avastin and 2) establish the PK component of the scientific bridge to justify the relevance of data generated with EU-approved bevacizumab in Study 265 to support a demonstration of the biosimilarity of bevacizumab-awwb to US-licensed Avastin.

Similar trough concentrations were demonstrated for bevacizumab-awwb and US-licensed Avastin in patients with NSCLC receiving first-line platinum-based chemotherapy (Study 265). The incidence of immunogenicity (anti-bevacizumab drug product antibodies (ADA)) was compared between treatment arms in Study 265. The results indicated that the incidence of ADA was similar in both arms.

Summary
The Office of Clinical Pharmacology determined that an adequate PK bridge has been established between bevacizumab-awwb, US-licensed Avastin, and EU-approved Avastin. Pharmacokinetic similarity was demonstrated between bevacizumab-awwb and US-licensed Avastin; the results from the PK studies support a demonstration that there are no clinically meaningful differences between bevacizumab-awwb and US-licensed Avastin.

6. Clinical Microbiology

Not applicable. Refer to Section 3 of this summary review for product quality microbiology information.

7. Clinical/Statistical-Efficacy

Amgen conducted a single comparative clinical study, Study 20120265 (Study 265). Study 265 was a randomized, double-blind, study comparing the efficacy and safety of bevacizumab-awwb with EU-approved bevacizumab in patients with locally advanced, unresectable or metastatic non-small cell lung cancer receiving first-line platinum-based chemotherapy for metastatic disease. For patients with unresectable, locally advanced disease, adjuvant chemotherapy must have been administered at least 12 months prior to study entry. Randomization was stratified by geographic region (Eastern Europe vs. Western Europe vs. Asia Pacific/Other vs. North America), ECOG performance status (0 vs. 1), and sex (male vs. female). Patients were randomized to receive bevacizumab-awwb or EU-approved bevacizumab at a dose of 15 mg/kg by intravenous infusion on day 1 of each 21-day cycle and every three weeks after completion of chemotherapy until disease progression or intolerable toxicity. The patient and investigator were masked to the treatment assignment. All patients received open-label carboplatin AUC 6 and paclitaxel 200 mg/m^2 intravenously on day 1 of each 21-day cycles for a maximum of 6 cycles. The primary endpoint was the overall response rate (ORR). Secondary endpoints duration of response (DoR), progression free survival (PFS), characterization of population pharmacokinetics based on sparse sampling, assessment of

immunogenicity, and assessment of adverse events, and assessment of the incidence of anti-drug antibody (ADA) in both arms.

The planned sample size of 620 patients was based on the following assumptions: 90% power to demonstrate that the 90% confidence intervals (CI) for the risk ratio of ORR between bevacizumab-awwb and EU-approved bevacizumab fell within the pre-specified similarity margins of 0.67 and 1.5, assuming that the ORR was 38% in both arms. As discussed in Section 2 of this Summary Review, on December 3, 2014, FDA issued a letter requesting modification of the study based on an alternative approach to determining the non-inferiority margin. Although the protocol was not modified, FDA informed Amgen that the non-inferiority margins for Study 265 would be considered in the context of the totality of the evidence.

The sponsor, Amgen Inc., and five clinical sites were selected for audit by the Office of Scientific Investigations. Although protocol eligibility violations and significant discrepancies in data reporting for certain elements were identified at one of the five clinical sites, these data discrepancies did not involve the primary endpoint. Thus, OSI concluded that the data from Study 20120265 submitted to the Agency appeared reliable.

Results
A total of 642 patients were randomized (1:1) with 328 patients randomized to the bevacizumab-awwb arm and 314 patients randomized to the EU-approved bevacizumab arm. The study was initiated on November 11, 2013 and the last patient completed the study on July 23, 2015.

The investigator-assessed ORR was 39.0% (95% CI: 33.7%, 44.5%) in the bevacizumab-awwb and 41.7% (95% CI: 36.2%, 47.4%) in the EU-approved bevacizumab arm. The estimated risk ratio (RR) for ORR was 0.93 (90% CI 0.80 to 1.09), which fell within the similarity margins of 0.67 and 1.5 proposed by Amgen as well as the FDA-proposed similarity margin of 0.73 to 1.36.

Results for the key secondary efficacy endpoints of duration of response and progression-free survival were similar between the bevacizumab-awwb and EU-approved bevacizumab arms. The median duration of response was 5.8 months (95% CI: 4.9; 7.7) in the bevacizumab-awwb arm and 5.6 months (95% CI: 5.1; 6.3) in the EU-approved bevacizumab arm. In an exploratory comparison of duration of response, the hazard ratio was 0.76 (95% CI: 0.48; 1.23). A comparison of PFS, conducted after 40% of patients in both arms progressed, yielded a hazard ratio of 1.03 (95% CI: 0.80, 1.34).

8. Safety

The primary safety data were derived from the single comparative clinical study, Study 265; the relevance of this safety data was based on the scientific bridge established between bevacizumab-awwb, US-licensed Avastin, and EU-approved bevacizumab. In Study 265, a total of 324 patients received bevacizumab-awwb 15 mg/kg every 21 days for up to 6 cycles in

combination with platinum-doublet chemotherapy and 309 patients received EU-approved bevacizumab at the same dose and schedule. This was supported by the results of safety in the pharmacokinetic similarity study, Study 216, in which 68 healthy male volunteers received a single dose of bevacizumab-awwb 3 mg/kg and 134 healthy male volunteers received a single dose of US-licensed Avastin or EU-approved bevacizumab.

Safety Summary
There were no clinically significant differences in the incidence of overall adverse events, serious adverse events (as defined in 21 CFR 312.32), severe or life-threatening adverse events (Grade 3 or 4 adverse events per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)) or adverse events requiring discontinuation of the investigational product (IP) between arms. These results are shown in the table below, abstracted from Dr. Casak's clinical review.

Table 13 - Study 20120265: Summary of major safety results

	bevacizumab-awwb (N=324) N (%)	**EU-approved bevacizumab (N=309) N (%)**
Subjects who experienced an AE	308 (95)	289 (94)
Subjects who experienced a Grade 3-4 AE	135 (42)	135 (44)
Deaths related to an AEs	13 (4)	11 (4)
Subjects who experienced a SAEs	85 (26)	71 (23)
Subjects who discontinued IP due to an AE	61 (19)	53 (17)
Subjects who discontinued carboplatin and/or paclitaxel due to an AE	74 (23)	59 (19)
Subjects who discontinued carboplatin and paclitaxel due to an AE	69 (21)	57 (18)

In addition, there were no clinically significant differences in the types of adverse events by system organ class (SOC) between arms in Study 265, as shown in the table below, from Dr. Casak's review.

Table 14 - Study 20120265: Adverse Events by System Organ Class (SOC)

SOC	bevacizumab-awwb (N=324) N (%)		EU-approved bevacizumab (N=309) N (%)	
	All grades	Grade 3-4	All grades	Grade 3-4
Nervous system disorders	170 (52)	11 (3)	154 (50)	16 (5)
Gastrointestinal disorders	160 (49)	16 (5)	156 (50)	16 (5)
Skin and subcutaneous tissue disorders	157 (48)	4 (1)	154 (50)	2 (1)
Blood and lymphatic system disorders	136 (42)	66 (20)	134 (43)	63 (20)
General disorders and administration site conditions	137 (42)	13 (4)	132 (43)	12 (4)
Respiratory, thoracic and mediastinal disorders	116 (36)	22 (7)	103 (33)	24 (8)
Musculoskeletal and connective tissue disorders	113 (35)	5 (2)	121 (39)	8 (3)
Infections and infestations	86 (27)	15 (5)	68 (22)	19 (6)
Metabolism and nutrition disorders	84 (26)	14 (4)	72 (23)	12 (4)
Vascular disorders	72 (22)	25 (8)	61 (20)	19 (6)
Investigations	56 (17)	11 (3)	53 (17)	9 (3)
Renal and urinary disorders	39 (12)	2 (1)	26 (8)	3 (1)
Psychiatric disorders	27 (8)	1 (<1)	33 (11)	2 (1)
Cardiac disorders	24 (7)	1 (<1)	12 (4)	3 (1)
Injury, poisoning and procedural complications	14 (4)	4 (1)	14 (4)	3 (1)
Ear and labyrinth disorders	12 (4)	0	6 (2)	1 (<1)
Eye disorders	10 (3)	0	7 (2)	0
Neoplasms benign, malignant and unspecified	6 (2)	1 (<1)	5 (2)	1 (<1)
Reproductive system and breast disorders	6 (2)	1 (<1)	6 (2)	0
Immune system disorders	7 (2)	2 (1)	4 (1)	0
Hepatobiliary disorders	2 (1)	1 (<1)	6 (2)	0
Surgical and medical procedures	4 (1)	0	4 (1)	1 (<1)
Endocrine disorders	2 (1)	0	1 (<1)	0
Congenital, familial and genetic disorders	1 (<1)	0	0	0

Immunogenicity Summary

The incidence of immunogenicity for bevacizumab-awwb and EU-approved bevacizumab was primarily assessed in Study 265. The results indicate similar rates of treatment-emergent anti-drug antibodies (ADA) for bevacizumab-awwb (1.4%) and EU-approved bevacizumab (2.5%). There was no apparent impact on safety, activity, or PK observed among the 11 patients with treatment-emergent ADA as compared to the 567 patients without treatment-emergent ADA. Therefore, the data, together with the scientific bridge established to justify the relevance of data from EU-bevacizumab, support a demonstration of no clinically meaningful differences between the bevacizumab-awwb and US-licensed Avastin.

Summary

There were no new safety signals identified with bevacizumab-awwb and there were no clinically significant differences in the adverse reaction profile observed in Study 265 between bevacizumab-awwb and EU-approved bevacizumab; based on the scientific bridge established between bevacizumab-awwb, US-licensed Avastin, and EU-approved bevacizumab, there are no clinically significant differences in the safety profile of bevacizumab-awwb and US-licensed Avastin.

9. Advisory Committee Meeting

This application was referred for review to the Oncologic Drugs Advisory Committee (ODAC), which met on July 13, 2017. This meeting included experts in product quality assessment, clinical pharmacology, and medical oncology, as well as patient, consumer, and industry representatives. The Committee discussed the analytical data for bevacizumab-awwb and agreed that bevacizumab-awwb was highly similar to US-licensed Avastin, notwithstanding minor differences in clinically inactive components. The Committee also discussed the clinical data with bevacizumab-awwb in healthy subjects enrolled in clinical pharmacology studies and in patients with metastatic non-small cell lung cancer (NSCLC). Based on the totality of the data, the Committee agreed there were no clinically meaningful differences between bevacizumab-awwb and US-licensed Avastin in the studied conditions of use.

The Committee also discussed the scientific justification for extrapolating the conclusion of no clinically meaningful differences between bevacizumab-awwb and US-licensed Avastin to other indications for which US-licensed Avastin is approved: mCRC, recurrent glioblastoma, metastatic renal cell carcinoma, and cervical cancer. Panel members agreed that this extrapolation was justified. For the voting question, panelists were asked whether, based on the totality of the evidence, bevacizumab-awwb should receive licensure as a biosimilar product to US-licensed Avastin for each of the proposed indications for which US-licensed Avastin is currently licensed and for which Amgen is seeking licensure listed above. The Committee voted 17 to 0 in favor of licensure of bevacizumab-awwb for the proposed indications.

10. Pediatrics

As a proposed biosimilar, bevacizumab-awwb triggers the requirements of the Pediatric Research Equity Act (PREA) for all of the proposed indications. The initial pediatric study plan was discussed at the Pediatric Review Committee (PeRC) meeting of July 27, 2016. In addition, the application contained a request for a full waiver from the requirements of PREA for all proposed indications, which was discussed by the Pediatric Review Committee (PeRC) on January 25, 2017. PeRC agreed with the applicant's request for full waivers from the requirements of PREA for metastatic colorectal cancer, non-squamous, non-small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, and cervical cancer.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Proprietary name: FDA found the proposed proprietary name, MVASI, to be conditionally acceptable. Amgen was informed of this determination in a letter dated February 9, 2017.

Non-proprietary name: On August 18, 2017, Amgen submitted a list of suffixes, in order of preference, to be used in the nonproprietary name of their product. FDA found the third proposed non-proprietary name, bevacizumab-awwb, conditionally acceptable. Amgen was informed of this determination in a letter dated August 31, 2017. Alternative proposed non-proprietary names of (b) (4) were found to be unacceptable (b) (4) and were inconsistent with the requirement that the suffix be devoid of meaning format described in FDA's final guidance, titled Guidance for Industry: Nonproprietary Naming of Biological Products.[1]

Product Labeling: Product labeling was modified for consistency with the FDA-approved package insert for US-licensed Avastin except for product-specific descriptions of Mvasi (bevacizumab-awwb).

Carton and Container Labeling: Modifications were incorporated to increase prominence of required elements and minimize the risks of medication errors.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: The action on this biologics license application will be approval.

- Assessment of Biosimilarity

  Section 351(i) of 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" (see section 351(i)(2) of the PHS Act).

  Multiple quality attributes, including primary and higher order structure, Fc (effector) function, and other structural/functional characteristics were assessed by quality range analysis and by qualitative comparisons. Some of these assessments employed testing with orthogonal methods. Comparative assessment of VEGF A binding and inhibition

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

of cell-based proliferation in a HUVEC assay for bevacizumab-awwb and US-licensed Avastin met statistical equivalence criteria. These comparative assessments of quality attributes support a finding that bevacizumab-awwb is highly similar to US-licensed Avastin, notwithstanding minor differences in clinically inactive components.

In Study 216, the comparison of pharmacokinetic data between bevacizumab-awwb and US-licensed Avastin met the acceptance criteria for PK similarity (90% confidence intervals for the ratios of geometric mean of AUC_{inf}, AUC_{last}, and C_{max} within the interval of 80% to 125%). The incidence of immunogenicity for bevacizumab-awwb and EU-approved bevacizumab was primarily assessed in Study 265. The results indicate similar rates of treatment-emergent anti-drug antibodies (ADA) for bevacizumab-awwb (1.4%) and EU-approved bevacizumab (2.5%) and there was no apparent impact on safety, activity, or PK observed among the 11 patients with treatment-emergent ADA.

Comparative assessment of analytical similarity data and pharmacokinetic similarity data between bevacizumab-awwb and US-licensed Avastin, bevacizumab-awwb and EU-approved bevacizumab, and US-licensed Avastin and EU- approved bevacizumab provided an adequate scientific bridge which justified the relevance of comparative data generated with EU-approved bevacizumab in Study 265 to support a demonstration of no clinically meaningful differences to US-licensed Avastin. Therefore the comparative assessments of clinical efficacy, safety, and immunogenicity data from Study 265 in patients with NSCLC randomized to either bevacizumab-awwb or EU-approved bevacizumab in combination with first-line chemotherapy support a finding that there are no clinically meaningful differences between bevacizumab-awwb and US-licensed Avastin in terms of the safety, purity and potency.

Extrapolation
Amgen sought licensure for multiple indications for which US-licensed Avastin is approved (mCRC, NSCLC, glioblastoma, mRCC, and cervical cancer) based on a development program that included data from a comparative clinical study in patients with NSCLC. Amgen is not seeking approval for approved indications for US-licensed Avastin that are protected by orphan drug exclusivity. Amgen provided a scientific justification to support extrapolation of the finding of biosimilarity to other conditions of use.

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.

The primary mechanism of action (MOA) of bevacizumab is through inhibition of the binding of soluble VEGF A ligand to Flt-1 [VEGFR-1] and KDR [VEGFR-2]) receptors on endothelial cells, inhibiting signal transduction and resulting in regression of tumor vascularization, normalization of remaining tumor vasculature, and inhibition of the formation of new tumor vasculature, thereby inhibiting tumor growth. Amgen submitted an extensive analysis of the role of VEGF A and VEGFR1/2 inhibition in each one of the indications for which licensure is sought. FDA agrees that there is no evidence to support claims of differences in MOA across the indications for which licensure is sought.

The PK profile of bevacizumab across doses ranging from 0.1 mg/kg to 10 mg/kg has been assessed in multiple dose escalation/dose finding studies conducted in patients with various solid tumors (Gordon 2001; Margolis 2001, EMA 2006, Herbst 2008, Han 2016). The PK properties of US-licensed Avastin across approved indications appear similar. Additionally, FDA considers that Study 20110216 adequately demonstrated pharmacokinetic similarity among bevacizumab-awwb, US-licensed Avastin, and EU-approved bevacizumab. Since PK similarity was demonstrated between bevacizumab-awwb and US-licensed Avastin, a similar PK profile would be expected for bevacizumab-awwb in patients across the indications being sought for licensure.

Factors affecting the immunogenicity of US-licensed Avastin have not been evaluated, however as with other immunogenic proteins, the incidence of immunogenicity is most likely to be affected by the use of concomitant therapy, such as myelosuppressive chemotherapeutic agents and extent of prior therapy. The immunogenicity of US-licensed Avastin as reported in product labeling (i. is 0.6% in a population (i.e., individuals receiving adjuvant chemotherapy following surgical resection of colorectal cancer) with less immunosuppression than that for

the approved indications for US-licensed Avastin or the indications being sought by Amgen for bevacizumab-awwb,. The immunogenicity observed with bevacizumab-awwb in Study 265 was also relatively low and similar to that observed with EU-approved bevacizumab.

The expected adverse reactions of bevacizumab are well characterized and summarized in product labeling for US-licensed Avastin. The variation in the incidence of specific adverse reactions across indications as reported in product labeling for US-licensed Avastin result from differential risks based on the underlying disease (e.g., the incidence of hypertension is higher in patients with RCC; the incidence of hemoptysis is higher in patients with NSCLC) since the PK profile appears to be similar across indications. In Study 265, the type and incidence of treatment-emergent adverse reactions of bevacizumab were similar for bevacizumab-awwb and EU-approved bevacizumab and no new safety signals were identified with bevacizumab-awwb . When taken together, these data indicate that in terms of the safety profile, no clinically significant differences are predicted between bevacizumab-awwb and US-licensed Avastin for the indications for which licensure is sought.

Based on the information summarized above, the data provided in the application support extrapolation of a determination of biosimilarity for all of the indications sought.

Conclusion
The information submitted by Amgen demonstrates that bevacizumab-awwb is biosimilar to US-licensed Avastin.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  None.

- Recommendation for other Postmarketing Requirements and Commitments
  The following agreed-upon post-marketing commitments will be conducted by Amgen, Inc.

  3261-1 Re-evaluate the bevacizumab-awwb drug substance (DS) stability acceptance criteria for stability samples held at the (b) (4)°C condition after data from 5 DS lots stored at (b) (4)°C are available. The final report should include the corresponding data, the analysis, and statistical plan used to evaluate the results and acceptance criteria and any proposed changes to the approved criteria.

  3261-2 Perform method validation studies in support of the introduction of the glycan mapping method into the drug substance manufacturing control strategy.

  3261-3 Perform method validation studies in support of the introduction of the host cell protein detection method into the drug substance manufacturing control strategy.

3261-4 Develop and implement a validated endotoxin detection method not subject to low endotoxin recovery for use in the release of the drug product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
09/14/2017