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APPLICATION NUMBER:

761028Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	BLA 761028
Supporting document/s:	2
Applicant's letter date:	November 14, 2016
CDER stamp date:	November 14, 2016
Product:	ABP 215
Indication:	Treatment of patients with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen
Applicant:	Amgen Inc.
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 2)
Reviewer:	Alexander H. Putman, PhD
Supervisor:	Whitney S. Helms, PhD
Division Director:	John Leighton, PhD (Patricia Keegan, MD)
Project Manager:	Leah Her

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1 Executive Summary

1.1 Introduction

Amgen has submitted BLA 761028 for ABP 215 under the 351(k) pathway as a biosimilar for Avastin®. ABP 215 is a humanized IgG1 monoclonal antibody directed against vascular endothelial growth factor (VEGF). Studies demonstrating direct binding of ABP 215 to VEGF were reviewed in detail by the product review team as a part of the similarity assessment, but based on data included in the submission, ABP 215 was able to bind VEGF with a similar affinity as US Avastin (K_Ds of 116 and 126 pM, respectively).

1.2 Brief Discussion of Nonclinical Findings

To support the similarity between ABP 215 and bevacizumab (Avastin®), the Applicant compared the activity and safety of ABP 215 and bevacizumab in 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. ABP 215 and bevacizumab resulted in similar tumor growth inhibition and decreased tumor vascularization in mice implanted with human models of epidermoid or colorectal cancer. ABP 215 also inhibited VEGF-induced vascular permeability in mouse skin similarly to bevacizumab. No significant differences were noted in the pharmacokinetics of ABP 215 versus bevacizumab when administered to rats as a single 1 mg/kg dose. As noted in the original pharmacology/toxicology IND review of ABP 215, neither ABP 215 nor bevacizumab demonstrated ADCC activity in in vitro studies. In the comparative toxicity study in cynomolgus monkeys, 50 mg/kg of ABP 215 or bevacizumab were administered twice per week for 1-month. No biologically significant differences in toxicity were noted between ABP 215 and bevacizumab. In addition, the toxicokinetic profiles of ABP 215 and bevacizumab were similar in cynomolgus monkeys.

1.3 Recommendations

1.3.1 Approvability

The non-clinical studies support the similarity of ABP 215 to bevacizumab. From a pharmacology/toxicology perspective, approval of ABP 215 is recommended.

1.3.2 Additional Non-Clinical Recommendations

None. From a pharmacology/toxicology perspective, no additional post-marketing commitments (PMCs) or post-marketing requirements (PMRs) are recommended for this indication.

1.3.3 Labeling

Since ABP 215 is a biosimilar to bevacizumab (Avastin®), sections of the labeling relevant to non-clinical studies are identical to those in the FDA-approved labeling for bevacizumab (Avastin®).

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

216974-75-3

2.1.2 Generic Name

Biosimilar to bevacizumab

2.1.3 Code Name

ABP 215

2.1.4 Chemical Name

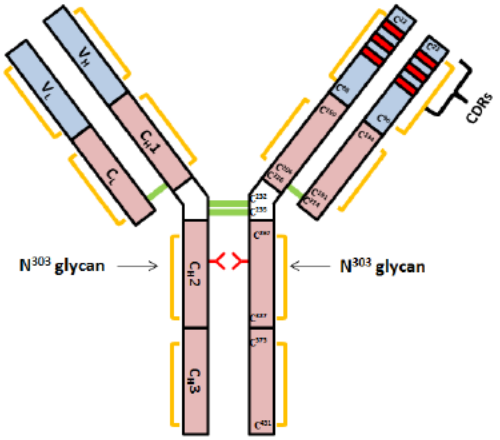
A humanized IgG1 monoclonal antibody directed against vascular endothelial growth factor (VEGF).

2.1.5 Molecular Formula/Molecular Weight

ABP 215 contains 1334 amino acids. The amino acid sequence of ABP 215 is identical to that of bevacizumab (Avastin®), which is a humanized monoclonal immunoglobulin IgG1 directed against VEGF. The heavy chain is composed of 453 amino acids with a molecular mass of about 49,720 Daltons. The light chain is composed of 214 amino acids with a molecular weight of about 23,451 Daltons.

2.1.6 Structure

ABP 215 Structure



(Figure excerpted from Applicant's BLA)

2.1.7 Pharmacologic class

A humanized IgG1 monoclonal antibody directed against vascular endothelial growth factor (VEGF).

2.2 Relevant INDs, NDAs, BLAs, and DMFs

IND 111960 for ABP 215
BLA 125085 for bevacizumab (Avastin®)

2.3 Drug Formulation

Composition of ABP 215

Component	Grade	Function	Quantity	Concentration
ABP 215	In house[a]	Active ingredient	400 mg	25 mg/mL
α,α-trehalose dihydrate	NF, PhEur	(b) (4)	960 mg	60 mg/mL
Polysorbate 20	NF, PhEur		6.4 mg	0.040%(w/v)
Sodium phosphate monobasic, monohydrate	USP, PhEur		92.8 mg	5.8 mg/mL
Sodium phosphate dibasic, anhydrous	USP, PhEur		19.2 mg	1.2 mg/mL
Water for Injection	USP, PhEur, JP		qs to target volume	qs to target volume

qs = quantum sufficit
[a] Tested to internal specifications as described in S.4.1 (Specification).

(Table excerpted from Applicant's BLA)

2.3.3 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Since ABP 215 is a biosimilar to bevacizumab (Avastin®), the indications and dosing regimens for which ABP 215 are recommended are identical to those in the FDA-approved labeling for bevacizumab (Avastin®).

2.7 Regulatory Background

ABP 215 is a biosimilar to bevacizumab (Avastin®). Avastin® was originally FDA-approved on February 26, 2004 under BLA 125085 for the first-line treatment of metastatic colorectal cancer in combination with 5-fluorouracil based chemotherapy.

The original IND submission (IND 111960) for ABP 215 was received by the FDA on 4/20/2012. There were no non-clinical issues to prevent initiation of the proposed clinical trial with ABP 215.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology:

Study #	Study title
R20120192	The Effect of Bevacizumab and ABP 215 Treatment on A431 Tumor Xenograft Growth and CD31 Staining of Vasculature in Female Athymic Nude Mice
R20130020	The Effect of Bevacizumab and ABP 215 Treatment on Colo205 Tumor Xenograft Growth and CD31 Staining of Vasculature in Female Athymic Nude Mice
R20130024	The Effect of ABP 215 Compared to Bevacizumab as an IP Dose Response in Female Athymic Mice in the Vascular Permeability Assay

Pharmacokinetics:

Study #	Study title
114878	PK Study of bevacizumab and High-Mannose Variant ABP 215 Following IV Administration of a Single 1 mg/kg Dose to Male Sprague-Dawley Rats with Cross-Over Satellite Groups

Repeat-dose Toxicity:

Study #	Study title
114831	ABP 215: 1-month Intravenous Toxicology Study in the Cynomolgus Monkey

3.2 Studies Not Reviewed

Pharmacology:

Study #	Study title
R20120191	The Effect of Bevacizumab and ABP 215 Treatment on Tumor Growth in an A431 Tumor Xenograft Model in Female Athymic Nude Mice
R20130003	The Effect of Bevacizumab and ABP 215 Treatment on Tumor Growth in a Colo205 Tumor Xenograft Model in Female Athymic Nude Mice

4 Pharmacology

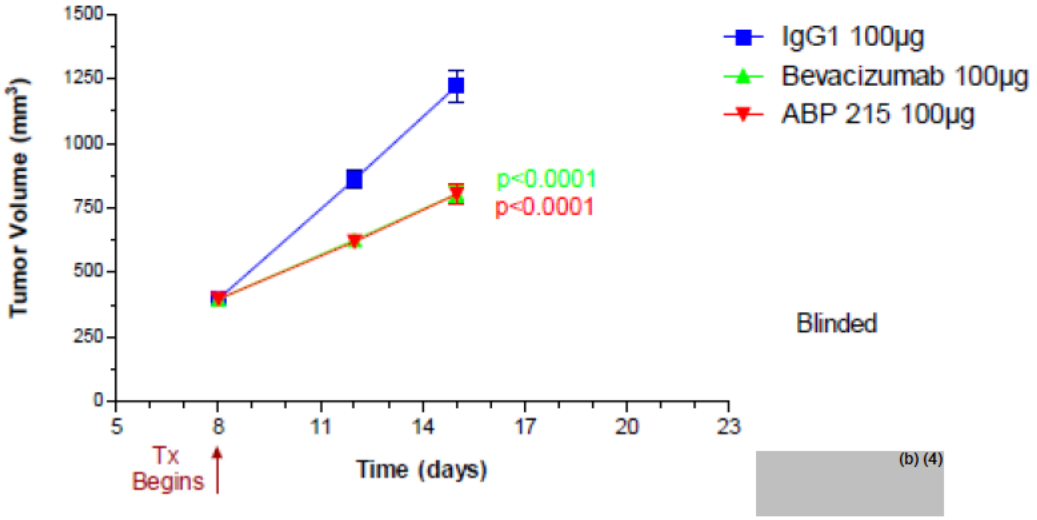
4.1 Primary Pharmacology

Vascular endothelial growth factor (VEGF) is a growth factor that binds to its receptors (R), VEGFR1 and VEGFR2, on vascular endothelial cells. VEGF induces cell proliferation and angiogenesis. ABP 215 is a humanized IgG1 monoclonal antibody that binds VEGF and prevents it from binding to and activating its receptors, resulting in inhibition of vascular endothelial cell proliferation and angiogenesis.

The Applicant utilized two xenograft tumor models in mice to demonstrate that ABP 215 has similar anti-tumor activity to bevacizumab (Avastin®, U.S. formulation). In the first model (Study R20120192), female athymic nude mice (10/group) were subcutaneously injected with epidermoid carcinoma-derived A431 cells at a concentration of 5 $x10^6$ cells per mouse. Treatment began 8 days later when tumors reached approximately 400 mm^3 in size and consisted of 100 µg of either bevacizumab or ABP 215, administered twice per week for 1 week, via intraperitoneal injection. Tumor volume and body weight were measured twice per week. Tumors were collected at sacrifice for CD31 staining and blood vessel area analysis.

As shown in Figure 1, administration of either ABP 215 or bevacizumab resulted in similar A431 tumor growth inhibition compared to the negative control (100 µg IgG1). Neither ABP 215 nor bevacizumab had an effect on body weight loss (data not shown).

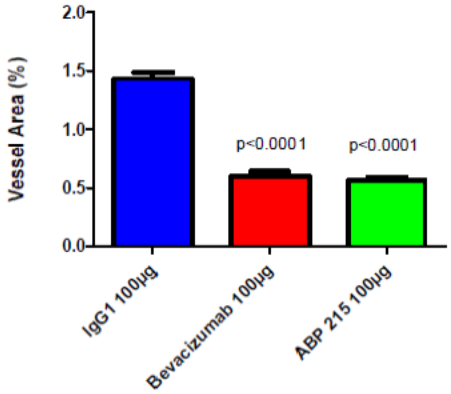
Figure 1: Effect of Bevacizumab or ABP 215 on A431 Tumor Growth



(Figure excerpted from Applicant's BLA)

For blood vessel area analysis, blood vessels were visualized using mid-sagittal sections of formalin fixed paraffin embedded tumors and were stained for CD31. Sections were scanned using an Aperio digital slide scanner and imported into Visiomorph. Pixel counts were recorded for CD31 positive areas and for the tissue areas. Blood vessel area density estimates were expressed as percent blood vessel area of tissue. As shown in Figure 2, administration of ABP 215 or bevacizumab resulted in similar decreases in blood vessel area, compared to the negative control (100 µg IgG1).

Figure 2: Effect of Bevacizumab or ABP 215 on Blood Vessel Area in A431 Tumors



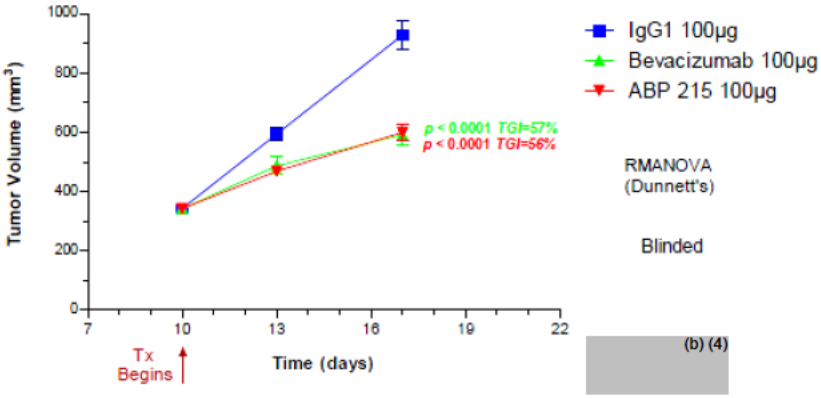
(Figure excerpted from Applicant's BLA)

In the second model (Study R20130020), female athymic nude mice (10/group) were subcutaneously injected with colon-derived Colo205 cells at a concentration of 2 $x10^6$ cells per mouse. Treatment began 10 days later when tumors reached approximately 343 mm^3 in size and consisted of 100 µg of bevacizumab (Avastin ®, U.S. formulation) or ABP 215, administered twice per week for 1 week, via intraperitoneal injection.

Tumor volume and body weight were measured twice per week. Tumors were collected at sacrifice for CD31 staining and blood vessel area analysis.

As shown in Figure 3, administration of ABP 215 or bevacizumab resulted in similar Colo205 tumor growth inhibition, compared to the negative control (100 µg IgG1). ABP 215 and bevacizumab had no effect on body weight loss (data not shown).

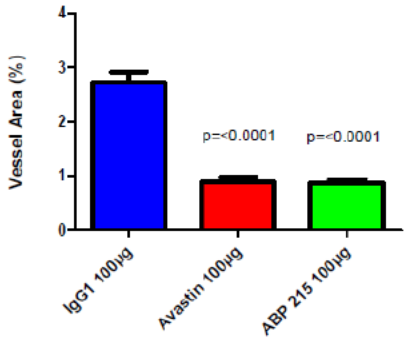
Figure 3: Effect of Bevacizumab or ABP 215 on Colo205 Tumor Growth



(Figure excerpted from Applicant's BLA)

Blood vessel area analysis on Colo205 tumors was conducted as described above. As shown in Figure 4, administration of ABP 215 or bevacizumab resulted in similar decreases in blood vessel area, compared to the negative control (100 µg IgG1).

Figure 4: Effect of Bevacizumab or ABP 215 on Blood Vessel Area in Colo205 Tumors

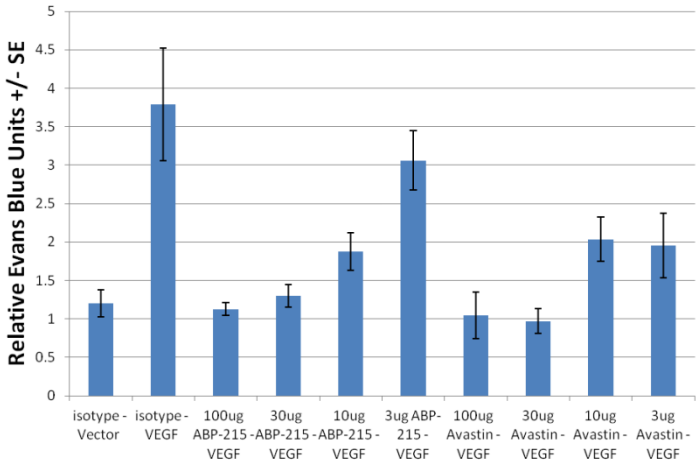


(Figure excerpted from Applicant's BLA)

ABP 215 and bevacizumab also showed similar inhibitory activity in a VEGF-induced vascular permeability assay. On Day 1, female athymic nude mice (5/group) were intraperitoneally injected with up to 100 µg of ABP 215 or bevacizumab (Avastin ®, U.S. formulation), or 100 µg of IgG1 isotype control. On Day 2, one group of mice was subcutaneously injected with $1x10^5$ HEK 293 cells transfected with an empty vector. The remaining groups of mice were subcutaneously injected with $1x10^5$ HEK 293 cells transfected with a vector containing the sequence for human VEGF. On Day 3, all mice were intravenously injected with 100 µL of 1% Evans Blue dye 10 minutes before being

sacrificed to quantify the level of vascular permeability from a skin sample at the injection site via spectrophotometry. As shown in Figure 5, both ABP 215 and bevacizumab inhibited VEGF-induced vascular permeability in mouse skin with similar activity at doses ≥ 10 µg, though at the low dose (3 µg) there was some variability in the activity between the two products.

Figure 5: Inhibition of VEGF-induced Vascular Permeability by ABP 215 and Bevacizumab



Relative Evans Blues Units = % Evans Blue × $10^{4;}$ Data expressed as average ± SE
(Figure excerpted from Applicant's BLA)

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The pharmacokinetics (PK) of ABP 215 and bevacizumab were evaluated in a single-dose study conducted in male Sprague-Dawley rats (Study 114878). On Day 0, 24 rats were assigned to 2 groups of 12 rats and received a single intravenous injection of 1 mg/kg ABP 215 (Group 1) or 1 mg/kg bevacizumab (Group 2; Avastin®, U.S. formulation). On Day 21, 4 rats from Group 1 were crossed over to receive bevacizumab, and 4 rats from Group 2 were crossed over to receive ABP 215. Serum samples were collected from all animals for PK analysis on Days 0 and 21. No significant differences were noted between the pharmacokinetics of ABP 215 and bevacizumab when given as a single 1 mg/kg dose on Day 0 (Table 1). On Day 21 (Table 2), the AUC appeared to differ between animals crossed over to ABP 215 or bevacizumab while the Cmax remained similar. Given the high variability in the rat anti-drug antibody responses to humanized antibodies at this timepoint, the utility of Day 21 pharmacokinetics in crossed over rats for supporting similarity is questionable, particularly given the small number of animals (n=4) assessed.

Table 1: Mean Pharmacokinetics of ABP215 or Bevacizumab in Rats on Day 0

Route	Treatment	N	t_{max} (hr) [1]	C_{max} (ug/mL)	C_0 (ug/mL)	AUC_{0-504} (ug*hr/mL)	CL_{0-504} (mL/hr/kg)
IV	ABP 215	12	0.25 (0.25-1.00)	22.3 (3.68)	23.2 (4.13)	2800 (352)	0.362 (0.0454)
	bevacizumab	12	0.25 (0.25-0.25)	23.9 (2.78)	25.2 (3.11)	3090 (327)	0.327 (0.0330)

(Table excerpted from Applicant's BLA)

Table 2: Mean Pharmacokinetics of ABP215 or Bevacizumab in Rats on Day 21 (Cross-Over Animals)

Route	Treatment	N	t_{max} (hr) [1]	C_{max} (ug/mL)	C_0 (ug/mL)	AUC_{0-504} (ug*hr/mL)	CL_{0-504} (mL/hr/kg)
IV	ABP 215	4	0.25 (0.25-0.25)	30.1 (1.82)	30.6 (1.90)	3410 (1530)	NC
	bevacizumab	4	0.25 (0.25-0.25)	30.0 (8.72)	31.3 (7.96)	1800 (2060)	NC

(Table excerpted from Applicant's BLA)

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study Title: ABP 215: 1-month Intravenous Toxicology Study in the Cynomolgus Monkey

Key Study Findings:

- No biologically significant differences in toxicity or toxicokinetics were noted between ABP 215 and bevacizumab (Avastin®, U.S. formulation).

Study no.:	114831
Study report location:	4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 9, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Drug 1: ABP 215; 0010085282; 98.1% Drug 2: bevacizumab (Avastin®, U.S. formulation); 913149

Methods:

Doses:	50 mg/kg of ABP 215, compared to 50 mg/kg of bevacizumab (Avastin®, U.S. formulation)
Frequency of dosing:	Twice weekly
Route of administration:	IV bolus
Dose volume:	2 mL/kg
Formulation/Vehicle:	51 mM sodium phosphate, 60 mg/mL trehalose dehydrate, 0.04% (w/v) polysorbate 20 at pH 6.2
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	3
Age:	2.6 to 3.4 years
Weight:	2.3 to 2.7 kg – males; 2.4 to 3.2 kg – males

Dose justification: According to the Applicant, doses were selected based on a 1-month toxicology study with bevacizumab in which physeal dysplasia and decreased ovarian and uterine weights were reported. The frequency of dosing was selected to provide continuous exposure.

Observations and Results:

Mortality [observations twice daily]

None

Clinical Signs [daily]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Body Weights [weekly]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Food Consumption [daily]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Ophthalmoscopy [pre-dose; week 4]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Electrocardiography [pre-dose; day 3 and 24]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Urinalysis [pre-dose; day 29]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Hematology [pre-dose; day 2 and 29]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Clinical Chemistry [pre-dose; day 2 and 29]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Coagulation [pre-dose; day 2 and 29]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Organ Weights [at sacrifice]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Gross Pathology [at sacrifice]

Unremarkable; no differences were noted between APB 215 and bevacizumab.

Histopathology [at necropsy]

Adequate Battery: Yes
Peer Review: Yes

No significant differences in histopathological findings were noted between ABP 215 and bevacizumab.

Incidence and grade of selected histopathology at end of dosing period

Tissue and finding	Grade	ABP 215 Males	Bevacizumab Males	ABP 215 Females	Bevacizumab Females
Brain *-infiltrate, mononuclear cell*	1	3/3	3/3	3/3	3/3
Epididymis *-immature*	NA	3/3	3/3	-	-
Injection site *-infiltrate, mononuclear cell*	1	3/3	3/3	2/3	3/3
Mammary glands *-immature*	NA	-	-	2/3	3/3
Stomach *-infiltrate, lymphoplasmacytic, mucosa*	1-3	3/3	2/3	3/3	3/3

Tissue and finding	Grade	ABP 215 Males	Bevacizumab Males	ABP 215 Females	Bevacizumab Females
Skin (back) *-infiltrate, mononuclear cell*	1	3/3	3/3	3/3	3/3
Femur *-dysplasia, physeal*	2	3/3	3/3	3/3	3/3

Grade 1, 2, 3, 4 refers to minimal, mild, moderate, marked, respectively

Immunogenicity - Anti-drug antibodies [pre-dose; days 15 and 29]

No anti-ABP 215 or anti-bevacizumab antibodies were detected.

Toxicokinetics [pre-dose; 0.25, 1, 4, 8, 24, 48, 72, and 96 hours post-dose on day 1 and 25]

As detailed in Table 3, exposure levels (Cmax and AUC) to ABP 215 and bevacizumab were similar in cynomolgus monkeys. Accumulation was noted from Day 1 to Day 25 with ABP 215 and bevacizumab. No significant differences between males and females were noted.

Table 3: Mean Toxicokinetic Parameters in Cynomolgus Monkeys

Route	Test Material	Day	N	t_{max} [1] (hr)	C_{max} (ug/mL)	AUC_{0-72} (ug*hr/mL)	AR_{ratio}
IV	ABP 215	1	6	0.25 (0.25-1.00)	1420 (138)	60400 (7950)	NC
		25	6	1.00 (0.25-1.00)	3750 (547)	196000 (20000)	3.26 (0.131)
	Avastin	1	6	0.25 (0.25-1.00)	1340 (49.7)	53500 (3870)	NC
		25	6	0.62 (0.25-1.00)	3400 (307)	182000 (22000)	3.40 (0.251)

[1] t_{max} (hr) is Median (min - max)
Source Data: 114831 - 114831_Watson GLP Description-ABP 215: 1-Month Intravenous Toxicology Study in the Cynomolgus Monkey
Scenario Source Data: NCA Version- 3 Description- Serum Base Scenario
Date Generated by PK Reporter S-PLUS: Thu Nov 10 12:08:27 PST 2011 User: (b) (4)

(Table excerpted from Applicant's BLA)

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/s/

ALEXANDER H PUTMAN
08/08/2017

WHITNEY S HELMS
08/09/2017

I concur with Dr. Putman's conclusions that the nonclinical data submitted suggest that ABP 215 has similar in vitro activity and in vivo toxicity as bevacizumab and that no further nonclinical data are needed to support this application under the 351(k) pathway. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of this product under the 351(k) pathway.