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APPLICATION NUMBER:

761099Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

351(k) Biosimilar Review

351(k) BLA Number	761099
Applicant	Pfizer Inc.
Submission Date	06/29/2018
Submission Type	<i>Standard review</i>
Link to EDR	\\cdsesub1\evsprod\BLA761099
Proprietary (Proposed) / Nonproprietary Names	(b) (4) PF-06439535 ¹ , bevacizumab-bvzr]
Dosage Form and Strength	100 or 400 mg in a single-use 5 or 20 mL vial with 4 or 16 mL nominal fill respectively
Route of Administration	Intravenous infusion
Proposed Indication(s)	<ul style="list-style-type: none"> • 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 bevacizumab product 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
Associated IND	117038
Reference Product Information (U.S.-licensed)	
Proprietary (Non-Proprietary) Name	US-licensed Avastin (bevacizumab)
Dosage Form and Strength	100 or 400 mg sterile preservative-free solution in a vial to deliver 4 or 16 mL for intravenous infusion
OCP Review Team Signers	
OCP Review Team	Theingi Thway, Ph.D. and Olanrewaju Okusanya, Pharm.D., MS
OCP Final Signatory	Brian Booth, Ph.D

¹In this document, we generally refer to the applicant's proposed product by the applicant-provided descriptor "PF-06439535", which was the name used to refer to this product during development. Subsequently, the nonproprietary name for this proposed product has been conditionally accepted to be "bevacizumab-bvzr" .

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1. EXECUTIVE SUMMARY

This Biologic License Application (BLA) for PF-06439535 has been submitted under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for PF-06439535 as a proposed biosimilar to US-licensed Avastin licensed under BLA 125085 by Genentech. The applicant submitted pharmacokinetic (PK) similarity data and a comparative clinical study to support a demonstration of no clinically meaningful difference between PF-06439535 and US-licensed Avastin.

Two clinical studies were conducted to support the application which includes a single-dose PK similarity study in healthy male subjects (B7391001) and a multinational multi-dose safety and efficacy study in patients with advanced non-small cell lung cancer (NSCLC) (B7391003). Study B7391001 was a randomized, double-blind, single-dose, 3-arm, parallel group study and designed to fulfil two goals; first to determine the PK similarity between PF-06439535 and US-licensed Avastin, and second to provide data to support the PK portion of the scientific bridge between PF-06439535, EU-approved Avastin, and US-licensed Avastin following a single 5 mg/kg intravenous (IV) dose. The results of the study established PK similarity between PF-06439535 and US-licensed Avastin based on the primary PK endpoints of AUC_{0-inf} and AUC_{last} . The study also established the PK portion of the scientific bridge between PF-06439535, US-licensed Avastin and EU-approved Avastin to support the use of EU-approved Avastin in the comparative clinical Study B7391003. The 90% confidence intervals (CI) of geometric mean ratio (GMR) for all three pairwise comparisons of the pre-specified PK endpoints were within the pre-specified limits of 0.8 to 1.25% in this study.

The immunogenicity results from Study B7391003 indicated that similar incidence of anti-drug antibody (ADAs) formation was observed between PF-06439535 and EU-approved Avastin in NSCLC subjects. The data indicates that there is a similar immunogenicity risk between PF-06439535 and EU-approved Avastin.

In conclusion, the PK and immunogenicity results support a demonstration of no clinically meaningful differences between PF-06439535 and US-licensed Avastin, and add to the totality of the evidence to support a demonstration of biosimilarity of PF-06439535 and US-licensed Avastin.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided in the submission for BLA 761099 and we recommend approval of PF-06439535 from a clinical pharmacology perspective.

Review Summary	Recommendations and Comments
Pivotal evidence of PK similarity and bridging	PK similarity was demonstrated between PF-06439535 and US-licensed Avastin. This study also established the scientific bridge between PF-06439535, US-licensed Avastin, and EU-approved Avastin. The 90% CI of the GMR in each pairwise comparison of the primary PK endpoints (AUC_{0-inf} and AUC_{last}) were within the pre-specified limits of 0.8 to 1.25.
Evidence of immunogenicity comparability	Similar incidence of ADAs was observed between PF-06439535, and EU-approved Avastin in study B7391003.

1.2 Post-Marketing Requirements and Commitments -None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Clinical Pharmacology and Pharmacokinetics

PF-06439535 is a proposed biosimilar product to US-licensed Avastin (bevacizumab). US-licensed Avastin is a recombinant humanized monoclonal IgG1 antibody produced in a mammalian cell line (Chinese Hamster Ovary). Bevacizumab has an approximate molecular weight of 149 kDa and inhibits the biologic activity of human vascular endothelial growth factor (VEGF-A) *in vivo*.

The results of the PK similarity and bridging assessment in Study B7391001 are provided in [Table 1](#). The 90% CIs for the GMRs of the primary PK endpoints of AUC_{0-inf} and AUC_{last} , and secondary endpoint of C_{max} within the pre-defined limits of 0.80 to 1.25 in the pairwise comparisons between PF-06439535, US-licensed Avastin, and EU- approved Avastin.

Table 1. Statistical analyses in PK similarity assessment in study B7391001 (FDA reviewer’s analysis).

Pairwise Comparison	Geometric Mean Ratio (90% CI)		
	AUC_{0-inf}	AUC_{last}	C_{max}
PF-06439535 (N=33) vs US-licensed Avastin (N=33)	1.03 (0.97-1.10)	1.04 (0.98-1.11)	1.10 (1.04-1.16)
PF-06439535 (N=33) vs EU-approved Avastin (N=35)	0.99 (0.92-1.06)	1.00 (0.93-1.07)	1.04 (0.98-1.11)
EU-approved Avastin (N=35) vs US- licensed Avastin (N=33)	1.05 (0.98-1.12)	1.05 (0.99-1.11)	1.05 (0.99-1.12)

The incidence of treatment-induced binding ADAs for PF-06439535 and EU-approved Avastin in a multiple-dose study was 7.4% and 6.0%, respectively in patients with NSCLC (Study B7391003). The results indicate similar immunogenicity risk between these two products.

Overall, the clinical pharmacology study is adequate to demonstrate PK similarity between PF-06439535, US-licensed Avastin, and EU-approved Avastin. The PK results support a demonstration of no clinically meaningful differences between PF-06439535 and US-licensed Avastin and add to the totality of the evidence to support the biosimilarity demonstration of PF-06439535 and US-licensed Avastin.

2.2 OSIS status

Office of Study Integrity and Surveillance inspected the bioanalytical portion of studies B7391001 and B7391003 at (b) (4) and concluded that data were reliable to support a regulatory decision. See OSIS inspector’s review for additional details.

2.3 Outstanding Issues

None.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Regulatory Background

3.1.1 *If applicable, describe (in tabular format) relevant regulatory history for the review of this 351(k) BLA.*

PF-06439535 is a proposed biosimilar product to US-licensed Avastin. The applicant is seeking licensure for the same indications for which US-licensed Avastin is currently approved.

3.2 Clinical Pharmacology Review Questions

3.2.1 *Are the design features of the clinical pharmacology and/or clinical studies to support biosimilarity acceptable?*

The relevant clinical studies to support the determination of biosimilarity between PF-06439535 and US-licensed Avastin are described in [Table 2](#) below.

Table 2. Summary of relevant clinical studies

Protocol	Title	Subjects	Objectives	Route/Dose/Duration
PK Similarity Study				
B7391001	Randomized, Double Blind, , Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-06439535 and Bevacizumab Sourced From US and EU Administered to Healthy Male Volunteers	Healthy (N=101)	PK similarity	IV/ single dose of 5 mg/kg/ 90 min infusion
Comparative Clinical Study				
B7391003	Randomized, Double-Blind Study of PF-06439535 Plus Paclitaxel-Carboplatin and Bevacizumab Plus Paclitaxel-Carboplatin for the First-Line Treatment of Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer	Advanced NSCLC (N=710)	Efficacy, safety, immunogenicity	IV/15 mg/kg for at least 4 cycles (every 3 weeks/cycle) up to 6 cycles/ 90 minutes infusion

PK, pharmacokinetics; NSCLC: non-small cell lung cancer

The study design of B7391001 study is considered adequate to demonstrate PK similarity because:

1. A single IV dose of bevacizumab can be safely administered to healthy subjects who are likely to have less PK variability due to population homogeneity, including less variability in VEGF levels and absence of tumor burden which could affect PK of bevacizumab.
2. A parallel group study design is recommended for PK similarity of products with long half-lives. The half life of bevacizumab is 20 days.
3. Considering PK method sensitivity, dose-exposure linearity, and tolerability, a single IV dose of 5 mg/kg bevacizumab was considered appropriate for a PK similarity study.

Study B7391003 is considered adequate to assess the immunogenicity risk between PF-06439535, and EU-approved Avastin. This study was conducted after the demonstration of a scientific bridge between PF-06439535, US-licensed Avastin and EU-approved Avastin to support the use of EU-approved Avastin

in this study. Refer to the clinical review for additional details.

3.2.2 Are the endpoints in the clinical pharmacology and/or clinical studies to support biosimilarity acceptable?

Yes. In study B7391001, the pre-specified PK endpoints were AUC_{0-inf} , AUC_{last} , and C_{max} . PK similarity and bridging were concluded if the 90% CI of the GMRs between each product pairwise comparison were within the pre-specified limits of 0.8 to 1.25.

The PK sample collection schedules were adequate and were obtained 1 hour prior to dose administration on Day 1 and 5 minutes prior to end of infusion, and 4, 24, 48, 96, 168, 336, 504, 672, 1008, 1344, 1512, 1680, and 2376 hours after start of infusion.

3.2.3 Are the pharmacologically active moieties of the proposed biosimilar and the reference product in plasma (or other biological matrix) appropriately identified and measured to assess the PK parameters?

Yes. See [Appendix 4.1.1](#) for details.

3.2.4 Is PK similarity met?

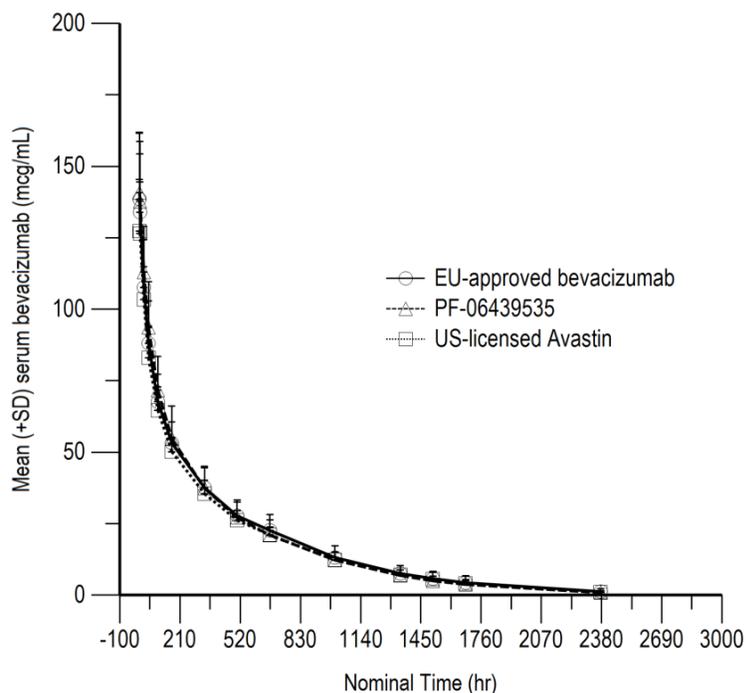
Yes. The 90% CI of geometric mean ratios of the pre-specified PK endpoints in pairwise comparison were contained within pre-defined criteria of 0.8 to 1.25 ([Table 1](#)). Geometric mean serum concentration-time profiles and a summary of PK parameters are also shown in [Table 3](#) and [Figure 1](#), respectively.

Table 3. Summary of PK parameters from study B7391001 (FDA reviewer's analysis).

PK parameters	Geometric mean values (% CV)		
	PF-06439535 (N=33)	US-licensed Avastin (n=33)	EU-approved Avastin (n=35)
C_{max} (mcg/mL)	142 (15%)	129 (13%)	138 (17%)
AUC_{last} (mcg /mL·hr)	41928 (17%)	40393 (12%)	41359 (26%)
AUC_{0-inf} (mcg/mL·hr)	42784 (17%)	41762 (13%)	43923 (25%)
CL (L/day)	0.198 (18%)	0.202 (13%)	0.197 (21%)
V_c (L)	4.12 (25%)	4.49 (18%)	4.21 (18%)

PK data between PF-06439535 and EU-approved Avastin in study B7391003 was also reviewed.

Figure 1. Geometric mean (+SD) concentration vs. time in linear scale (Study B7391001) (Source: FDA reviewer's analysis).



Immunogenicity

3.2.6 What is the ability of the immunogenicity method(s) to detect the anti-drug antibodies (ADA) in the presence of concentration of product in the study samples?

The sensitivities of the binding ADA methods were 0.175 mcg/mL (bevacizumab ADA method) and 0.164 mcg/mL (PF-06439535 ADA method) using affinity purified rabbit polyclonal antibodies (pAbs). The ADA methods can detect 1 mcg/mL of pAbs in the presence of bevacizumab concentration up to 100 mcg/mL. At Day 100, the trough concentration of bevacizumab is expected to be less than 5 mcg/mL thus ADA methods are considered drug tolerant. The presence of VEGF interference was not detected up to 1 ng/mL (i.e 0.001 mcg/mL) of recombinant VEGF tested *in vitro* with 1 mcg/mL of pAbs.

The binding ADA and Nab assays were suitable for determining immunogenicity. Refer to the immunogenicity review by the Office of Biotechnology Products for details regarding the ADA methods.

3.2.7 Is the sampling plan adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of anti-drug antibodies (ADA) formation?

Yes. Sampling plans in the studies were appropriate to minimize interference from the presence of drugs in the samples.

In study B7391003, serum for ADA testing was collected at predose of cycles 1, 2, 3, 4, and 6 (Days 1, 22, 43, 64, and 106) of monotherapy and end of treatment.

3.2.8 What is the incidence of anti-drug antibodies (ADA) and neutralizing antibody (Nab) and how do the findings compare between products?

The incidence of baseline and treatment-induced ADAs observed in study B7391003 is shown in [Table 4](#). These data indicate that there is a similar immunogenicity risk between PF-06439535 and EU-approved Avastin, and supports the demonstration that there are no clinically meaningful differences between PF-06439535 and EU-approved Avastin.

Of note, a scientific bridge was established between PF-06439535, US-licensed Avastin, and EU-approved Avastin, supporting the relevance of the comparative data, including immunogenicity data, generated using EU-approved Avastin to support a demonstration of no clinically meaningful differences between PF-06439535 and US-licensed Avastin.

Table 4. Immunogenicity results for binding ADAs and Nab in study B7391003 (Applicant data from response to information request dated 02/20/19 and from summary of clinical pharmacology studies)

Product	N ^a	Incidence of binding ADAs ^b		Incidence of Nab ^c	
		Baseline	Treatment-induced	Baseline	Treatment-induced
PF-06439535	352	2/352 (0.6%)	25/339 (7.4%)	1/352 (0.3%)	0/339 (0.0%)
EU-approved Avastin	353	4/353 (1.1%)	21/350 (6.0%)	0/353 (0.0%)	3/350 (0.9%)

^aNumber of subjects with predose data

^bBased on 1% false positive rate

^cNab data based on 0.1% false positive rate of binding ADAs which corresponded to 5 subjects per treatment.

3.2.9 What is the impact of ADA and Nab on the PK, PD, safety, and efficacy of the therapeutic protein and how do the findings compare between products?

ADAs did not appear to impact the PK of PF-06439535 or EU-approved Avastin.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 Pharmacokinetics

For the PK similarity study (Study B7391001), serum bevacizumab concentrations were measured using a validated ELISA method #15-1387 (Method validation report B7399002), which was suitable for the assessment of PK similarity. Lipemia impacted the accurate measurement of serum bevacizumab, but no study samples were affected by lipemia. Both the method validation and sample analysis for the study were performed at (b) (4). In this method, 96-well plates coated with recombinant human VEGF was used to capture serum bevacizumab and HRP-labeled mouse anti-human IgG was used to detect the bound analytes. Table 5 shows the summary of method performance in quantification of serum bevacizumab during the method validation and PK similarity study.

Table 5. Summary of the bioanalytical method validation and in-study performance for measurement of serum bevacizumab.

Bioanalytical method review summary	Method validation was adequate to support the study B7391001.		
Materials used for calibration curve & concentration	US-licensed Avastin, Lot:13-110446/548426, nominal concentration of 25 mg/mL		
Validated assay range	250 to 3000 ng/mL		
Material used for QCs & concentration	US-licensed Avastin, Lot:13-110446/548426, nominal concentration of 25 mg/mL EU-approved Avastin, Lot:13-111286/H0151B06 and 13-111567/B7109B09, nominal concentration of 25 mg/mL PF-06439535, Lot: H49500, actual protein concentration of 24.9 mg/mL		
Minimum required dilutions (MRDs)	1/10		
Source & lot of reagents (LBA)	Human VEGF-coated plate (b) (4) Mouse anti-human IgG1-HRP (b) (4), Lot:II4414011 (b) (4), Lot: 1229715 (validation) and 1559940 (study B7391001)		
Regression model & weighting	4-parameter logistic with weighting factor of 1		
Validation parameters	Method validation summary (Method # 15-1387)		Acceptability
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	6	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2% to 3%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4%	Yes
QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 5 QCs & 1 DQC</u> US-licensed Avastin: EU-approved Avastin: PF-06439535:	-5.2 to 6.0% -9.3 to 3.0% -12.7 to -3.1%	Yes
	<u>Inter-batch %CV</u> US-licensed Avastin: EU-approved Avastin: PF-06439535:	≤ 7.6% ≤ 9.9% ≤ 13.5 %	Yes

	<p><u>Percent total error (TE)</u></p> <p>US-licensed Avastin: $\leq 12\%$ EU-approved Avastin : $\leq 19\%$ PF-06439535: $\leq 25\%$</p>	Yes
Selectivity & matrix effect	10 serum lots each from normal and solid tumor individual tested. At least 80% of the lots were within 20% bias in normal serum and 25% bias in solid tumor respectively	Yes
Interference & specificity	Soluble VEGF did not interfere at concentrations tested Monoclonal anti-bevacizumab antibody at 2000 ng/mL decreased the measurement of 3000 ng/mL PF-06439535	Yes
Hemolysis effect	6 serum lots tested and at least 83% of the lots were within 20%.	Yes
Lipemic effect	6 serum lots tested and all lots failed with %bias >29%.	No ^a
Dilution linearity & hook effect	Linear within 5 to 50 fold dilution tested with 150 mcg/mL and within 500 to 2500 fold dilution tested with 1250 mcg/mL No hook effect	Yes
Bench-top/process stability	US-licensed Avastin: up to 24 hrs (b) (4) 42-1201 ^b EU-approved Avastin: up to 24 hrs (b) (4) 15-1387 PF-06439535: up to 16 hrs (b) (4) 15-1387	Yes
Freeze-Thaw stability	US-licensed Avastin: up to 5 cycles (b) (4) 42-1201 ^b EU-approved Avastin: up to 5 cycles (b) (4) 15-1387 PF-06439535: up to 5 cycles (b) (4) 15-1387	Yes
Long-term storage at -20 and -70°C	US-licensed Avastin: up to 1682 days at -70°C (b) (4) 42-1201 ^b EU-approved Avastin: up to 180 days (b) (4) 15-1387 PF-06439535: up to 190 days at -70°C (b) (4) 15-1387	Yes
Parallelism	Demonstrated in B739001	Yes
Carry over	NA	NA
Method performance in study B7391001		
Assay passing rate	<ul style="list-style-type: none"> 98% (60 out of 61) runs including incurred sample reanalysis (ISR) met the method acceptance criteria. 	Yes
Standard curve performance	<ul style="list-style-type: none"> Cumulative bias range: -0.7 to 1.6% Cumulative precision: $\leq 3\%CV$ 	Yes
QC performance	<ul style="list-style-type: none"> Cumulative bias range: -3.3 to -1.8% Cumulative precision: $\leq 6\%CV$ TE: $\leq 8\%$ 	Yes
Method reproducibility	<ul style="list-style-type: none"> ISR was performed in 9% of study samples and 99% of samples met the pre-specified criteria 	Yes
Study sample analysis/stability	Analyzed within 172 days from collection (within established stability days)	

^aNo identified lipemic samples during the sample analysis

(b) (4) 42-1201 was same method as (b) (4) 15-1387 and validated for US-licensed Avastin

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