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MEDICAL & STATISTICAL REVIEWS

CLINICAL AND STATISTICAL REVIEW

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Product Code Name	PF-06439535
Proposed Proper Name	Bevacizumab.bvzr
Proposed Proprietary Name	Zirabev
Pharmacologic Class	Biosimilar to bevacizumab (monoclonal antibody targeting VEGF-A)
Applicant	Pfizer
Applicant Proposed Indication(s)	- Metastatic colorectal cancer, - In combination with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment. - 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. <u>Limitation of Use:</u> not indicated for adjuvant treatment - Non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel, for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease. - Recurrent glioblastoma in adults. - Metastatic renal cell carcinoma, in combination with interferon alfa. - Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan.
Recommendation on Regulatory Action	Approval

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Clinical and Statistical Review

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Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
ALK	Anaplastic lymphoma kinase gene
AUC	Area under the curve
BLA	Biologics License Application
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CCS	Comparative clinical study
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
Cmax	Maximum serum concentration
CMC	Chemistry, Manufacturing, and Controls
CR	Complete response
CRF	Case Report Form
CRO	Contract Research Organization
CRF	Case report form
CRP	C-reactive Protein
CSR	Clinical study report
CTACE	Common terminology criteria for adverse events
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DMC	Data Monitoring Committee
DMEPA	Division of Medication Error Prevention and Analysis
DOR	Duration of response
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
ECG	Electrocardiogram
eCTD	Electronic Common Technical Document
EGFR	Endothelial growth factor receptor
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FISH	Fluorescence in Situ Hybridization

GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
HbsAg	Hepatitis B surface antigen
HVC	Hepatitis C virus
HIV	Human immunodeficiency virus
HLT	High level term
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
IND	Investigational New Drug
ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ITT	Intention to Treat
IV	Intravenous
IWRS	Interactive web-response system
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
MOA	Mechanism of Action
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
ORR	Overall response rate
OS	Overall survival
OSI	Office of Scientific Investigations
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PFS	Progression free survival
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PPED	Palmar-plantar erythrodysesthesia
PPP	Per-protocol population
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PT	Preferred term
RECIST	Response evaluation criteria in solid tumors
REMS	Risk Evaluation and Mitigation Strategies
RPLS/PRES	Reversible posterior leukoencephalopathy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standard MedDra Query

SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
TMA	Thrombotic microangiopathy
VEGF	Vascular endothelial growth factor

1. Executive Summary

1.1. Product Introduction

PF-06439535 is a proposed biosimilar to US-licensed Avastin (bevacizumab). The nonproprietary name bevacizumab.bvzr was determined after completion of this review, on March 27, 2019. The proposed proprietary name is Zirabev.

Like US-licensed Avastin, PF-06439535 is a recombinant humanized monoclonal IgG1 antibody that binds vascular endothelial growth factor -A (VEGF).

The following are the indications for which Pfizer is seeking licensure:

- 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.
- Recurrent glioblastoma in adults.
- Metastatic renal cell carcinoma, in combination with interferon alfa.
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan.

Pfizer acknowledges that the US-licensed Avastin platinum-resistant and platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer indications are currently protected by orphan drug exclusivity until 2021 and 2023, respectively, and thus licensure for these indications will not be sought until those exclusivities expire.

PF-06439535 is administered intravenously. The proposed dosing regimens for each indication are listed below.

- Metastatic colorectal cancer
 - 5 mg/kg every 2 weeks intravenously in combination with bolus-IFL.
 - 10 mg/kg every 2 weeks intravenously in combination with FOLFOX4.
 - 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a first-line bevacizumab product-containing regimen.
- Non-squamous non-small cell lung cancer
 - 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel
- Glioblastoma

- 10 mg intravenously every 2 weeks
- Metastatic renal carcinoma
 - 10 mg intravenously every 2 weeks in combination with interferon alpha
- Persistent, recurrent, or metastatic cervical cancer
 - 15mg/kg intravenously in combination with paclitaxel and cisplatin, paclitaxel, or topotecan

PF-06439535 is a clear to slightly opalescent, colorless to pale brown solution that will be supplied in cartons containing one single-dose vial in 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) strengths.

1.2. Mechanism of Action, Route of Administration, Dosage Form and Strength

The known mechanism of action for US-licensed Avastin (in all approved indications) is binding to VEGF, which prevents the interaction of VEGF with its receptors on the surface of endothelial cells. Like US-licensed Avastin, PF-06439535 is a recombinant humanized IgG1 kappa monoclonal antibody directed against VEGF. Pfizer provided data (please refer to the comprehensive review by Drs. Jee and Fuchs) that supports the conclusion that PF-06439535 is highly similar to US-licensed Avastin and EU-approved bevacizumab in terms of structure and function. PF-06439535, US-licensed Avastin, and EU-approved bevacizumab exhibited relatively similar in vitro inhibition of VEGF-induced human umbilical vein endothelial cell (HUVEC) proliferation; binding to human VEGF₁₆₅/VEGF₁₂₁/VEGF₁₈₉/VEGF₂₀₆, C1q, FcγR receptors, and FcRn. PF-06439535 also exhibited a lack of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activity, as expected based on a similar lack of activity with the approved products.

US-licensed Avastin and PF-06439535 are injectable biologics administered intravenously. Both US-licensed Avastin and PF-06439535 are supplied in single-dose vials containing 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL).

1.3. Review Summaries from Other Disciplines to Support Assessment of Biosimilarity

Table 1 - Review summaries from other disciplines

Structural and Functional Characterization (copied from Dr. Jee's and Dr. Fuchs' review)
• Pfizer utilized an array of analytical methods to assess the primary and higher order structure, physicochemical properties, and biological functions of PF-06439535 in comparison to US-licensed

Avastin and EU-approved bevacizumab. 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 PF-06439535 is highly similar to US-licensed Avastin. Minor differences in glycosylation profile, charge variant profile, levels of aggregates, and levels of fragments were observed. In each case, the differences did not preclude a demonstration that PF-06439535 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 PF-06439535 to US-licensed Avastin, PF-06439535 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 PF-06439535 to justify the relevance of the comparative clinical data generated using EU-approved bevacizumab.
- There are no residual uncertainties regarding the analytical characteristics as it pertains to the demonstration of biosimilarity between PF-06439535 and US-licensed Avastin.

Animal Studies (copied from Dr Wearne's and Helms' review)

- To support the initial clinical study of PF-06439535, Pfizer compared the nonclinical toxicity and toxicokinetics of PF-06439535 and EU-approved bevacizumab in a GLP-compliant 1-month repeat-dose toxicology study in sexually and skeletally immature male cynomolgus monkeys. Twice weekly intravenous (IV) administration of 10 mg/kg PF-06439535 or EU-approved bevacizumab resulted in minimal to moderate physeal dysplasia in the growth plate of the distal femur, an expected pharmacologic response. The incidence and severity of physeal dysplasia was relatively similar between PF-06439535 and EU-approved bevacizumab. Overall, there were no biologically significant differences in toxicity, toxicokinetics, or immunogenicity between PF-06439535 and EU-approved bevacizumab. Anti-drug antibodies (ADAs) were not detected in monkeys dosed with PF-06439535 or EU-approved bevacizumab.
- Overall, the submitted nonclinical data suggest that PF-06439535 had similar in vitro activity and in vivo toxicity, pharmacokinetics/pharmacodynamics (PK/PD), and immunogenicity as bevacizumab. Thus, the submitted nonclinical data support a demonstration of PK/PD similarity.
- Additional pharmacology studies and a single-dose pharmacokinetic study in rats further support the similarity between PF-06439535 and EU-approved bevacizumab. These studies were not designed to demonstrate statistical significance for similarity.
- There are no residual uncertainties regarding PK/PD and safety as it pertains to a demonstration of biosimilarity between PF-06439535 and US-licensed Avastin.

Clinical Studies (PK and immunogenicity summary copied from Dr Thway's and Olanrewaju's review)

- Study B7391001 was a parallel-group, single-dose, randomized PK study designed to compare the PK profile of PF-06439535 to that of EU-approved bevacizumab and US-licensed Avastin in healthy male volunteers. Subjects were randomized 1:1:1 to receive a single 5 mg/kg dose of one of the three bevacizumab products. The primary endpoint was AUC_{0-inf} and the main secondary endpoint was C_{max} . Ninety percent (90%) confidence intervals (CIs) for the test versus reference ratio for each of the three-pairwise comparisons were constructed on a log scale using the standard 2 One-Sided Tests (TOST) procedure. PK similarity was demonstrated as the 90% CIs for the test-to-reference ratios of C_{max} , AUC_{inf} and AUC_T fell within the 80.00-125.00% bioequivalence window.
- Study B7391003 was a double-blind, active-controlled randomized study in patients with non-small cell lung cancer (NSCLC) receiving first-line chemotherapy with carboplatin and paclitaxel. A total of 719 patients were randomized to receive chemotherapy with PF-06439535 (n: 358) or EU-approved bevacizumab (n: 361) 15 mg/kg every three weeks for up to 6 cycles. The analysis of the study's primary endpoint was the assessment of the risk ratio of overall response rate (ORR) based on investigator assessment. ORR was 45.3% and 44.6% in the PF-06439535 and EU-approved bevacizumab arms, respectively, which corresponded to a risk ratio of ORR of 1.01 (90% CI: 0.88 to 1.16) between the treatment arms, which was within the pre-specified equivalence margin of (0.73, 1.37) and FDA's recommended margin of (0.73; 1.36). The results were similar in various secondary and sensitivity analyses of the primary endpoint, including the ORR based on the randomization stratification factors and the per protocol population. Duration of response, a secondary endpoint, was 8.3 months (95% CI 7.3; 10) and 6.6 months (95% CI 6.2; 8.3) in the PF-06439535 and EU-approved bevacizumab arms, respectively. The rates, severity, and type of toxicities were similar between the treatment groups and consistent with the safety profile described for bevacizumab. There were no new safety signals identified.
- The data demonstrate similar clinical activity and safety between PF-06439535 and bevacizumab in patients with NSCLC. As a bridge between EU-approved bevacizumab, US-licensed Avastin, and PF-06439535 was demonstrated in Study B7391001 and analytical similarity was demonstrated, the totality of the evidence including the results of Study B7391003 demonstrates that PF-06439535 is similar to US-licensed Avastin.

2. Introduction and Regulatory Background

2.1. Important Safety Issues with Consideration to Reference Product

Interference with the VEGF pathway induces a characteristic pattern of toxicity observed in approved and experimental drugs targeting this pathway. Hypertension, gastrointestinal toxicity, proteinuria, thromboembolic events, hemorrhage, reversible posterior

leukoencephalopathy (RPLS) and wound healing are consistently observed across clinical studies and in the post marketing setting following the administration of both biologic and small molecule anti-VEGF or anti-VEGFR agents. The spectrum of adverse reactions in individual patients with different diseases is variable but predictable and reflects several factors: dose of the VEGF inhibitor, specificity of the inhibition of the pathway, disease factors, comorbidities, co-targeting of other pathways, and administration of concomitant chemotherapy.

The box warning in approved labeling for US-licensed Avastin describes the risks of gastrointestinal perforations, surgery and wound healing complications, and hemorrhage. In addition to these adverse reactions, the Warnings and Precautions section describes non-gastrointestinal fistula formation, arterial thromboembolic events, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), and infusion reactions.

VEGF signaling stimulates the production of nitric oxide and prostaglandin I₂ in endothelial cells. Blockage of VEGF leads to vasoconstriction. Vascular rarefaction, alterations in pressure-natriuretic relationships, and other vasoconstrictive have also been postulated as mechanisms for hypertension in patients receiving VEGF inhibitors (Robinson E., 2010).

As described in Dr. Chen's and Dr. Cleck's comprehensive review of adverse events related to inhibition of the VEGF pathway (Chen H., 2009), the effect of anti-VEGF agents on blood pressure is dose-dependent. In a Phase 2 study in patients with RCC treated with bevacizumab 3 mg/kg or 10 mg/kg every 2 weeks, the rate of hypertension was significantly higher in the high-dose group (36%) compared with the low dose group (3%). This dose dependency has also been observed with small-molecule VEGF tyrosine kinase inhibitors. Patients with pre-existing hypertension are generally more likely to develop further elevation in blood pressure when receiving anti-VEGF therapy. The risk of hypertension may be also related to indication or concomitant chemotherapy (although differences in data collection or monitoring between trials may also account for differences in hypertension rates). As described in Dr. Chen's paper, the highest rate of hypertension (36%) occurred in a renal cell cancer trial (10 mg dose) compared to a reported rate (all Grades) of 24% in a trial in patients with breast cancer (AVF2119g). This is an expected finding, as up to 79% of patients with renal cell cancer are diagnosed with hypertension at the time of tumor diagnosis (Stojanovic, 2009).

In a meta-analysis (Rampura, 2010) of 20 randomized controlled trials that included 12,526 patients, bevacizumab was associated with an increased risk of Grade 3-4 hypertension, with an incidence of 7.9% (95% CI: 6.1–10.2) and a relative risk (RR) of 5.28 (95% CI: 4.15–6.71). In most cases, hypertension can be controlled with oral hypertensive agents. However, patients may develop uncontrolled hypertension, hypertensive crisis, or RPLS with life-threatening complications.

RPLS is described in the adverse reactions sections of the labels for the VEGF monoclonal antibodies bevacizumab, ramucirumab and the fusion protein ziv-aflibercept. In both biological drugs and small molecule drugs inhibiting VEGF, the observed incidence was less than 1%.

Scappaticci et al. (Scappaticci, 2007) performed a meta-analysis on the increased risk of thromboembolic events in patients receiving bevacizumab in clinical trials. Data were pooled from five randomized controlled trials that included 1745 patients with metastatic colorectal, breast, or non-small-cell lung carcinoma. Combined treatment with bevacizumab and chemotherapy, compared with chemotherapy alone, was associated with an increased risk of arterial thromboembolic events (HR = 2.0, 95% confidence interval [CI] = 1.05 to 3.75; $p = 0.031$) but not for venous thromboembolic events (HR = 0.89, 95% CI = 0.66 to 1.20; $p = 0.44$). The absolute rate of developing an arterial thromboembolism was 5.5 events per 100 person-years for those receiving combination therapy and 3.1 events per 100 person-years for those receiving chemotherapy alone (ratio = 1.8, 95% CI = 0.94 to 3.33; $p = 0.076$). Development of an arterial thromboembolic event was associated with a prior arterial thromboembolic event ($p < 0.001$) or age of 65 years or older ($p = 0.01$).

Proteinuria has occurred in all bevacizumab clinical trials. Bevacizumab therapy has been associated with the development of proteinuria in up to 36% of patients with colorectal cancer (US-licensed Avastin labeling), where Grade 3–4 proteinuria (>3.5 g protein per 24h urine or nephrotic syndrome) was observed in 6.5% of patients. A meta-analysis of randomized controlled trials with patients receiving bevacizumab indicated a relative risk of 1.4 for proteinuria with bevacizumab at a low dose (2.5 to 7.5 g/kg) and 1.6 at a high dose (10 to 15 mg/kg) suggesting a possible dose dependency to bevacizumab-associated proteinuria (Izzedine H., 2010).

The risk of bleeding and hemorrhage is increased in patients treated with VEGF- and VEGFR-targeting agents. Mild spontaneous mucocutaneous bleeding is the most common type of bleeding; however, serious tumor-related bleeding can also occur. In all trials of bevacizumab, mucocutaneous hemorrhage has been observed in 20–40% of patients, with mild epistaxis being the most common presentation.

Lung carcinomas (especially squamous cell) and gastrointestinal tract tumors are associated with the highest risk and greatest severity of bleeding following VEGF inhibition. Severe or fatal hemorrhage events described in the US-licensed Avastin PI include hemoptysis, gastrointestinal bleeding, hematemesis, central nervous system (CNS) hemorrhage, epistaxis, and vaginal bleeding. Across indications, the incidence of $\geq$ Grade 3 hemorrhagic events among patients receiving bevacizumab ranged from 0.4% to 6.4%. In a randomized study comparing carboplatin/paclitaxel vs. bevacizumab and carboplatin/paclitaxel in previously untreated NSCLC (Johnson D., 2004), six out of 13 patients with squamous cell histology (31%) experienced a major life-threatening bleeding event described as hemoptysis or hematemesis, and four of these events were fatal. All six patients had centrally-located tumors close to major blood vessels. Five patients had cavitation or necrosis of tumors, either at baseline or developing during bevacizumab therapy. Because squamous cell tumors are more frequently centrally located and have a greater tendency to cavitate as compared to adenocarcinoma, it is not clear whether histology alone is the central risk factor for bleeding, or simply a surrogate for other

risk factors.

In the E4599 trial (Sandler, 2006), patients with squamous histology were excluded. Grade 3–5 pulmonary hemorrhage events observed were 2.3% (10 of 427 patients) in the bevacizumab and chemotherapy arm compared with 0.5% (2 of 441) of those treated with chemotherapy only. Five of the hemoptysis events in the bevacizumab-containing arm were fatal.

As described in labeling for US-licensed Avastin, the incidence of gastrointestinal perforation ranged from 0.3 to 3.2% across clinical studies with the highest incidence rate in a clinical trial of patients with cervical cancer.

Wound healing is a complex process involving angiogenesis and closely regulated interactions between endothelial cells, platelets, and the coagulation cascade. VEGF inhibition can impair wound healing at a surgical site through the dehiscence of a previously healed wound, or delay or cause failure of wound healing in patients who underwent surgery following treatment with an anti-VEGF agent. In a clinical trial of patients with metastatic colorectal cancer (mCRC) who underwent surgery during bevacizumab treatment, wound healing complications occurred in 15% of bevacizumab-treated patients versus 4% of patients who did not receive bevacizumab.

In a retrospective analysis of randomized trials in patients with mCRC, for a subset of patients who had surgery 28–60 days before initiating bevacizumab, Scappaticci et al. (Scappaticci, 2005) described a lower incidence of wound complications (1.3%). An adjuvant trial (NSABP-C08) in patients with CRC who received bevacizumab and chemotherapy at least 28 days after colectomy confirmed that although the rate of serious wound complications was low (1.7%), the rate was higher than that in the chemotherapy-alone control arm (0.3%) (Chen H, 2009). Current guidelines are largely empiric and recommend that bevacizumab be withheld for 4 weeks before elective surgery.

Finally, the US-licensed Avastin label contains a Warning about ovarian failure, as the incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving bevacizumab in combination with mFOLFOX chemotherapy as compared to women receiving mFOLFOX chemotherapy alone. In addition, bevacizumab may cause fetal harm based on the drug's mechanism of action and findings from animal studies. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryo-fetal development, and postnatal development.

2.2. Summary of Presubmission Regulatory Activity Related to Submission

The reference product, US-licensed Avastin (bevacizumab), was approved in the U.S. on February 26, 2004.

This summary will only describe interactions and comments regarding the clinical development of PF-06439535. For further details on agreements and advice given regarding product quality and non-clinical data, please refer to the respective reviews.

- May 22, 2013: Biosimilar Initial Advisory meeting held to obtain preliminary feedback on the CMC/quality, nonclinical and clinical development strategy for PF-06439535 as a proposed biosimilar to US-licensed Avastin.

FDA agreed that the standard bioequivalence criteria (including AUC and C_{max}) for comparing the pharmacokinetics of PF-06439535 to US-licensed Avastin was acceptable. FDA recommended that the lowest scientifically relevant doses of PF-06439535, US-licensed Avastin and EU-approved bevacizumab be used in healthy volunteers.

FDA disagreed with Pfizer's proposal to conduct a clinical comparability study (CCS) in the

(b) (4)
[REDACTED] FDA
recommended the CCS be conducted in the NSCLC setting.

- December 6, 2013: Submission of IND 117038 containing Study B7391001, entitled "Phase I, Double Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-06439535 and Bevacizumab Sourced from US and EU Administered to Healthy Male Volunteers" for the development of PF-06439535.
- July 16, 2014: BPD Type 2 meeting held to discuss and obtain regulatory advice on the data generated to date and the proposed CCS, Study B7391003. FDA agreed that the overall design of Study B7391003 could be supportive of a demonstration of no clinically meaningful differences between PF-06439535 and EU-approved bevacizumab. However, FDA disagreed with the proposed similarity margins for the study ((b) (4)). After further review of the study's plan and internal discussion, on September 3, 2014, FDA issued an advice letter recommending implementation of a TOST by comparing a confidence interval for the ratio between the proposed biosimilar product and the reference product to an interval deemed to be clinically acceptable and defined by two preselected margins (a confidence interval being completely within the margins would rule out meaningful differences between the products with respect to the chosen endpoint and subject to a predetermined type one error probability).

FDA stated that one approach to creating the margin is to base the margin on preserving some fraction of the reference product treatment effect estimated by a metaanalysis of placebo-controlled studies. FDA also stated that to account for variability in the estimated drug effect, this margin is often based on the bound representing the lower bound of a confidence interval for the drug effect (on the specific endpoint) from this meta-analysis. FDA clarified that the reference product's effect may not be the most relevant factor on

which to base both the upper and lower margins and therefore, it is possible that non-symmetric margins could be appropriate, but the use of non-symmetric margins should be justified. FDA recommended the Type I error rate of the equivalence test be controlled at 5% and that the selected margin in the CCS should maintain a fraction of at least 50% of the bevacizumab effect on ORR.

- April 15, 2015: BPD Type 3 meeting was held. Pfizer proposed several scenarios for the calculations of the equivalence margin. Pfizer proposed using three randomized controlled studies in a meta-analysis to determine the similarity margin. FDA stated that although the method used by Pfizer is different than what FDA recommends, the similarity margin of (0.73 to 1.37) may be acceptable; however, FDA still recommended determining the similarity margin for bevacizumab using a meta-analysis that includes all of the four published studies that evaluated bevacizumab in combination with chemotherapy (i.e., Sandler et al., NEJM, 2006; Johnson et al., JCO., 2004; Niho et al., Lung Cancer, 2012; and Reck et al., JCO., 2009); or using the meta-analysis in Botrel et al. Lung Cancer, 2011. This advice was reiterated on March 23, 2016.
- July 23, 2015: submission of Study protocol B7391003, “a Phase 3, randomized, double-blind study of PF-06439535 plus paclitaxel-carboplatin and bevacizumab plus paclitaxel-carboplatin for the first line treatment of advanced non-squamous cell lung cancer” to IND 117038.
- February 13, 2017: BPD Type 2 meeting was held to discuss CMC/stability, clinical data, and high-level content and presentation questions for a planned 351(k) BLA submission. Pfizer stated that the initial BLA will contain complete safety data for all patients for all planned cycles of the chemotherapy combination phase, complete efficacy, immunogenicity, and PK concentration data for all patients for the planned cycles of the chemotherapy combination phase, and secondary endpoint data for approximately 75% of patients beyond the chemotherapy combination phase. Supplemental secondary endpoint data for the remaining ~25% of patients beyond the chemotherapy combination phase will be submitted with the 4-month safety update. FDA concurred with the plan.

FDA acknowledged that Pfizer may submit datasets using the Pfizer Data Standard but recommended the submission of datasets using CDISC standards. FDA agreed with a proposed format for Module 5.3.5.3. FDA asked Pfizer to provide all raw data and derived variables in .xpt format, SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis (and if used, all necessary macro programs), SAS programs for derived datasets, and mock-up define file.

- September 12, 2017: BTD Type 4 (pre-BLA) meeting was held to discuss the summary content and format of the 351(k) BLA, the timelines for pre-license inspections and the proposed concept for labeling. FDA agreed that the proposed structure and format of the clinical sections generally appeared to be adequate to support the filing of a BLA and FDA

reiterated the request for submission of SAS programs and define files.

Regarding labeling, FDA clarified that at the time of Pfizer's planned BLA submission, the US-licensed Avastin ovarian cancer indications will remain protected by orphan exclusivity and therefore FDA cannot license PF-06439535 for these indications until after exclusivity expiry. Therefore, information related to this indication should be removed from relevant sections of the proposed PF-06439535 label.

- January 26, 2018: Pfizer submitted a 351(k) BLA for PF-06439535. On February 14, 2018, a planning meeting was held to discuss the the BLA submission contents, which were incomplete and had multiple deficiencies. On February 26, 2018 and March 7, 2018, FDA and Pfizer held meetings to discuss the BLA deficiencies. Pfizer withdrew the BLA submission on March 9, 2018.
- June 6, 2018: FDA and Pfizer held a teleconference to discuss resubmission of the application, including datasets in CDISC format and SAS programs used to compile the data (previously submitted in Pfizer's legacy format), a new define file, etc. In addition, the eCTD submission strategy and manufacturing issues were discussed.

2.3. Studies Submitted by the Applicant

Table 2 - Listing of PF-06439535 clinical studies

Design	Arms	Endpoints	N
Clinical comparative study			
B7391003: A 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			
2-arm, double blind, randomized (1:1) study in NSCLC patients	Carboplatin AUC 6, paclitaxel 200 mg/m ² plus PF-06439535 or EU-approved bevacizumab 15mg/kg every 3 weeks for up to 6 cycles followed by the assigned antibody monotherapy until disease progression or intolerable toxicity.	ORR at Week 19	710
PK similarity assessment			
B7391001: Phase 1, Double Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-06439535 and Bevacizumab Sourced From US and EU Administered to Healthy Male Volunteers			
3-arm, single dose, double-blinded, randomized (1:1:1) study	PF-06439535 vs. US-licensed Avastin vs. EU-approved bevacizumab. All subjects	C _{max} , AUC _T and AUC _{0-∞}	102 subjects (PF-06439535: 33; US-licensed

in male healthy volunteers	received a single 5 mg/kg dose		Avastin: 36; EU-approved bevacizumab: 33)
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3. Ethics and Good Clinical Practice

3.1. Submission Quality and Integrity

The amount of missing data was minimal and did not impact overall conclusions between the effects of proposed biosimilar product and reference product (or comparator product, as appropriate). The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

The size of the safety databased is adequate; however, there were multiple issues with the quality of the safety datasets, including inconsistencies between raw and analysis datasets. As the labeling of PF-06439535 will follow the innovator's product label, FDA review concentrated on evaluation for clinically meaningful differences and will not follow Pfizer's analyses described in the clinical study report (CSR).

In the CSR, Pfizer presented adverse event (AE) summaries that included AEs observed during the treatment period (combination and monotherapy) and the follow-up period, defined as the period up to 28 days after the last dose of study drug or up to subsequent anticancer therapy. The safety dataset contained a column ("EPOCH") flagging the AE to the screening, treatment, and follow-up period. The FDA clinical analysis of safety does not include events occurring during the screening period (with the exception of an infusion-related reaction (IRR) occurring on Day 1 in Patient # (b) (6) that was miscoded as occurring during the screening period). Using the study period flag "AEEXM" and using only events classified as "combination therapy" and "chemotherapy" within 28 days of administration (as flagged in the "ACYSTDY" column and selected for the number of days), this reviewer analyzed 5133 adverse events. Of note, Pfizer's analysis in the study report is based on 4912 adverse events that they considered "treatment emergent"; therefore, FDA's analysis is different from Pfizer's.

A separate analysis for the adverse events occurring in the monotherapy period and 28 after the last bevacizumab product dose is summarized in Section 7.6.3.

Although the safety datasets were not of optimal quality, a comparison between arms to rule out clinically meaningful differences in the safety profile of PF-06439535 and bevacizumab was conducted. The amount of missing data for the primary endpoint was minimal and did not impact overall conclusions between the effects of proposed biosimilar product and US-licensed

Avastin. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

3.2. Statistical Data and Analysis Quality

The primary endpoints were derived and saved in the datasets: “adsl”, “adrsd”, “adtted” and “dm”, which can be found at: <\\CDSESUB1\evsprod\BLA761099\0003\m5\datasets\b7391003>. The statistical reviewer found the data and program quality was acceptable for reproducing the study results.

3.3. Compliance with Good Clinical Practices

Pfizer states that Studies B7391001 and B7391003 were conducted in compliance with good clinical practices (GCP) as described in the ICH Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. Pfizer states that the studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters for the studies received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Patients signed informed consent documents. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

3.4. Financial Disclosures

Pfizer provided financial disclosure information for Studies B7391001, B7391002, and B7391003. Study B7391002 was a small study of a single dose of EU-approved bevacizumab in healthy volunteers to determine the inter-subject PK variability of bevacizumab; data from this study was used to calculate the sample size of Study B7391001 and therefore not described in this review. There were 801 investigators (data submitted in Form 3454) between all three studies; 798 investigators had no financial conflicts. Three investigators were Pfizer employees working at the Pfizer Clinical Research Unit in Belgium conducting Study B7391002. As Study B7391002 assessed the PK of commercial Avastin and it is not part of the biosimilarity exercise, it is unlikely that bias was introduced by a financial conflict.

All 783 investigators in Study B7391003 provided their financial disclosure information. Financial conflicts of interest were reported for 3 of the 783 (0.4%) investigators, who disclosed the following information:

- Dr. (b) (6) site # (b) (6): received honoraria from Pfizer for 25,806.99 USD (investigator's fee).

- Dr. (b) (6), site # (b) (6): held 4,000 Pfizer shares for a value of 131,000 USD as of 2/14/2017. Dr. (b) (6) initially disclosed these shares in 2015 (value of 140,040.00 USD).
- Dr. (b) (6), site # (b) (6): received honoraria from Pfizer for 32,012.96 USD (consultant and other contributions).

(b) (6) enrolled in each of these three sites.

Pfizer states that during the conduct of these trials, including the processing, analyzing and reporting of data, Pfizer applied procedures designed to minimize the potential for bias in the data, including conducting the studies according to all applicable laws and regulations, checking with FDA's Debarment list and the Disqualified/Totally Restricted List for Clinical Investigators as well as the Public Health System Administrative Actions Listing, use of an IWRS for the stratified, blinded assignment to treatment arms, scheduling of procedures and assessments at the same fixed intervals for subjects in all treatment arms, double-blind study design, an external Data Monitoring Committee for safety monitoring, audits to clinical sites, etc.

This reviewer agrees that there was no apparent conflict of interest that could bias the results of the studies. Adequate safeguards to minimize bias were in place to protect the integrity of the study from financial conflicts of interest. CDER's Standard Financial Disclosure Review can be found in the Appendices section (Error! Reference source not found.).

4. Issues Related to Other Review Disciplines

4.1. Chemistry, Manufacturing and Controls

The final reviews of the Office of Biotechnology Products (OBP) team were not complete at the time of completion of this review. The discipline findings below are based on preliminary discussions within the review team. Pfizer utilized an array of analytical methods to assess the primary and higher order structure, physicochemical properties, and biological functions of PF-06439535 in comparison to US-licensed Avastin and EU-approved bevacizumab. 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 PF-06439535 is highly similar to US-licensed Avastin. Minor differences in glycosylation profile, charge variant profile, levels of aggregates, and levels of fragments were observed. In each case, the differences did not preclude a demonstration that PF-06439535 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 pairwise analytical

comparisons of PF-06439535 to US-licensed Avastin, PF-06439535 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 PF-06439535 to justify the relevance of the comparative clinical data generated using EU-approved bevacizumab.

There are no residual uncertainties regarding the assessment of similarity; outstanding issues are related to manufacturing of the drug product/substance.

4.2. Clinical Microbiology

The final reviews of the microbiology team were not complete at the time of completion of this review.

4.3. Office of Scientific Investigations

The Office of Scientific Investigations (OSI) was consulted to conduct routine inspection for clinical sites enrolling patients in Study B7391003. Based on the analysis of the datasets, no centers had outcomes, protocol violations, or safety concerns not aligned with the overall study results. Although 9 US centers were opened to accrual, only 11 patients enrolled across US centers; foreign sites were selected based on number of patients enrolled and feasibility of the inspections. The inspections found the clinical sites to be in compliance with Good Clinical Practices and were without major deficiencies. The final review of the OSI team was not complete at this time of completion of this review. The discipline findings are based on preliminary discussions with the OSI review team.

4.4. Nonclinical Pharmacology and Toxicology

This section summarizes Dr. Wearne's and Dr. Helms' review. PF-06439535, US-licensed Avastin, and EU-approved bevacizumab exhibited relatively similar in vitro inhibition of VEGF-induced human umbilical vein endothelial cell (HUVEC) proliferation; binding to human VEGF165/VEGF121/VEGF189/VEGF206, C1q, FcγR receptors, and FcRn. PF-06439535 also exhibited a lack of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activity, as expected based on a similar lack of activity with the approved products. Based on the results from these in vitro comparative pharmacology studies, Pfizer did not conduct any in vivo pharmacology studies with PF-06439535.

Pfizer compared the nonclinical toxicity and toxicokinetics of PF-06439535 and EU-approved bevacizumab in a GLP-compliant 1-month repeat-dose toxicology study in sexually and skeletally immature male cynomolgus monkeys. Twice weekly intravenous (IV) administration of 10 mg/kg PF-06439535 or EU-approved bevacizumab resulted in minimal to moderate

physeal dysplasia in the growth plate of the distal femur, an expected pharmacologic response. The incidence and severity of physeal dysplasia was relatively similar between PF-06439535 and EU-approved bevacizumab. Overall, there were no biologically significant differences in toxicity, toxicokinetics, or immunogenicity between PF-06439535 and EU-approved bevacizumab. Anti-drug antibodies (ADAs) were not detected in monkeys dosed with PF-06439535 or EU-approved bevacizumab. From a nonclinical perspective, Pfizer provided an acceptable scientific bridge based on comparative analytical similarity data between PF-06439535, US-licensed Avastin, and EU-approved bevacizumab to justify the relevance of the results from the 1-month toxicology study using a non-US-licensed comparator (EU-approved bevacizumab).

The animal studies (including a rat study, not described here because it is not a pharmacologically relevant species for toxicity assessment of bevacizumab) also employed the intended clinical formulation of PF-06439534, which includes compendial excipients not included in bevacizumab, including a high level of succinic acid. The level of succinic acid delivered to rats in the PF-06439535 drug product exceeded the level of succinic acid that patients will receive clinically with PF-06439535 providing reasonable toxicological coverage for this concentration considering that succinic acid is an endogenous substance that is a component of the Krebs cycle, and it occurs widely as a natural constituent of plants and animals consumed orally at high levels as food by humans .

Overall, the submitted nonclinical data suggest that PF-06439535 had similar in vitro activity and in vivo toxicity, pharmacokinetics/pharmacodynamics (PK/PD), and immunogenicity as bevacizumab. Thus, the submitted nonclinical data support a demonstration of PK/PD similarity.

4.5. Clinical Pharmacology

The objectives of the clinical pharmacology program were to evaluate the pharmacokinetic similarity between PF-06439535 and US-licensed Avastin, and to support the scientific bridge between PF-06439535, US-licensed Avastin and EU-approved bevacizumab in order to justify the relevance of data generated using EU-approved bevacizumab in support of the overall demonstration of biosimilarity of PF-06439535 to US-licensed Avastin.

In Study B7391001, 102 healthy volunteers were randomized to receive a single 5 mg/kg dose of PF-06439535, US-licensed Avastin, or EU-approved bevacizumab. The pairwise comparisons of PF-06439535, US-licensed Avastin, and EU-approved bevacizumab met the prespecified acceptance criteria for PK similarity (90% CIs for the ratios of geometric mean of AUC_{inf} , AUC_{last} , and C_{max} , within the interval of 80% to 125%), thus establishing the PK similarity and providing the PK bridging data in addition to the analytical bridging data, to justify the relevance of the comparative data generated using EU-approved bevacizumab. As expected, immunogenicity was very low and comparable between arms. The final review of the clinical pharmacology team was not complete at the time of this review. The clinical pharmacology discipline findings are based on preliminary discussions with the review team.

5 Statistical and Clinical Evaluation

5.1. Statistical and Clinical Executive Summary

The determination of no clinically meaningful differences between PF-06439535 and US-licensed Avastin was based on the totality of evidence from an extensive analytical comparison, comparative PK assessment in humans, and a comparative clinical study in patients with NSCLC.

Study B7391003 was conducted to support the demonstration of no clinically meaningful differences in terms of clinical activity, safety, PK, and immunogenicity of PF-06439535 with EU-approved bevacizumab in combination with paclitaxel and carboplatin as first-line treatment for patients with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC. This was randomized (1:1), double-blind, parallel-group study conducted in 719 patients who were randomized to receive chemotherapy with PF-06439535 or EU-approved bevacizumab 15 mg/kg every three weeks for up to 6 cycles.

Of 719 patients, 358 and 361 were randomized to the PF-06439535 and EU-approved bevacizumab arms, respectively. Most baseline characteristics were balanced between the 2 treatment arms. The analysis of the study's primary endpoint was the assessment of the risk ratio of ORR based on investigator assessment. ORR was 45.3% and 44.6% in the PF-06439535 and EU-approved bevacizumab arms, respectively (analysis based on the intent-to-treat [ITT] population), which corresponded to a risk ratio of ORR of 1.01 (90% CI: 0.88 to 1.16) between the treatment arms, which is within the pre-specified equivalence margin of (0.73, 1.37) and FDA's recommended margin of (0.73; 1.36) (Table 6). The results were similar in various secondary and sensitivity analyses of the primary endpoint, including the ORR based on the randomization stratification factors and per protocol population. Duration of response, a secondary endpoint, was 8.3 months (95% CI 7.3; 10) and 6.6 months (95% CI 6.2; 8.3) in the PF-06439535 and EU-approved bevacizumab arms, respectively (Table 8).

In conclusion, the data demonstrate similar clinical activity between PF-06439535 and EU-approved bevacizumab arms in patients with NSCLC. As a bridge between EU-approved bevacizumab, US-licensed Avastin, and PF-06439535 was demonstrated in Study B7391001 and analytical similarity was demonstrated, the totality of the evidence, including the results of Study B7391003, demonstrates that PF-06439535 is similar to US-licensed Avastin.

5.2. Additional Clinical Study(ies) Scientific Justification and Bridge to U.S.-licensed Reference Product

To justify the use of EU-approved bevacizumab in the clinical comparative study, Pfizer conducted Study B7391001, a randomized (1:1:1), double-blind (sponsor unblinded),

single-dose 3-arm study comparing the PK of PF-06439535, bevacizumab-EU, and bevacizumab-US administered to healthy male subjects. The PK comparative study was conducted in healthy male subjects to avoid interference of potentially confounding subject and treatment-related covariates on the comparison of intrinsic PK properties among the 3 study drugs. The selection of male subjects for this study was based on the documented influence of sex on bevacizumab PK: clearance was approximately 26% faster in males compared with females.

Of the 102 subjects randomized and assigned to study treatment, all received study drug except for 1 subject who did not receive the assigned bevacizumab-EU treatment. Administration of the complete dose of assigned study drug was achieved in 101 subjects. A single dose of PF-06439535, bevacizumab-EU, or bevacizumab-US was administered at a dose of 5 mg/kg as a 90-minute IV infusion using a calibrated infusion pump. Blood samples (5 mL) for PK assessment were collected at pre-dose and at pre-specified time points through Day 71 post-infusion. An additional optional Day 100 visit was added for the collection of serum samples to assess immunogenicity in the absence of interfering drug levels.

5.3. Review Strategy

Study B7391002 provides the primary evidence to support the determination of no clinically meaningful differences between PF-06439535 and US-licensed Avastin. Additional supportive clinical safety and efficacy data and the necessary PK bridge to allow the use of EU-approved bevacizumab in Study B7391002 were derived from the single dose PK study (Study B7391001). A summary of the safety results of Study 7391001 can be found in Section 7.6.3 of this review.

Because the primary objective of a comparative clinical study in a biosimilar development program is not to establish efficacy but to assess for clinically meaningful differences, the primary endpoint selected should be sufficiently sensitive to assess for clinically meaningful differences between the products. As such, it is not scientifically necessary for the primary endpoint in a comparative clinical study to be the same as the endpoint used to demonstrate efficacy of the reference product (Kun H et al., 2016). FDA recommended the use of overall response rate (ORR) as the primary endpoint because response (decrease in size of the primary tumor or metastases or regression of lesions) can only be attributed to treatment and not natural history and would therefore expected to be more sensitive to the effects of treatment than a time to event endpoint that incorporates the effect of both treatment, sequential therapy, and the natural history of the underlying disease.

In agreement with FDA, Pfizer selected ORR as the endpoint for Study B7391003.

The safety analysis concentrates on the results of Study B7391003, particularly in the incidence of toxicities that are related to the anti-VEGF mechanism of action.

The data presented in the review were obtained through FDA analyses; discrepancies between

FDA and Pfizer's data are discussed.

5.4. Review of Individual Clinical Studies

5.4.1. Study B7391003: "A 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"

Note: this summary reflects the latest protocol version (version 3, dated June 10, 2016). There were no significant changes between version 2 (dated July 6, 2015 and the first version to be submitted to the IND) and version 3.

Study Design and Endpoints

Study B7391003 is a randomized, double-blind, active-controlled study in adult subjects with non-small cell lung cancer receiving first-line chemotherapy with carboplatin and paclitaxel. Approximately 710 subjects (355 per treatment group) were to be randomized (1:1) to receive investigational product [PF-06439535 or EU-approved bevacizumab at a dose of 15 mg/kg administered as an IV infusion every three weeks in combination with chemotherapy for at least 4 cycles and up to 6 cycles. Randomization was stratified by geographic region (location of the drug depot supplying the site), sex (sex/female), and smoking history (never/ever).

The primary objective was to compare the ORR by Week 19 per RECIST 1.1 between PF-06439535 and EU-approved bevacizumab. Although the assessments (tumor size) were provided by the study investigators, the determination of response was made by Pfizer.

The secondary objectives were to compare the safety and immunogenicity of PF-06439535 and bevacizumab, evaluate secondary measures of tumor control (duration of response, 1-year PFS, and 1-year OS), and evaluation of population PK.

The study design follows FDA's published guidance for the assessment of bevacizumab biosimilar products and was agreed upon by FDA.

Study Population

Major Inclusion Criteria

- ≥ 18 years old.
- Histologically or cytologically confirmed metastatic or recurrent non-squamous NSCLC. For subjects with recurrent disease, at least 6 months must have elapsed since completing adjuvant chemotherapy
- Measurable disease according to RECIST v1.1.

- ECOG performance status score 0 or 1
- Normal bone marrow function as defined by: ANC $\geq 1.5 \times 10^9/\text{dL}$, platelets $\geq 100 \times 10^9/\text{dL}$, and hemoglobin $\geq 10 \text{ g/dL}$.
- Adequate hepatic and renal function

Major Exclusion Criteria

- Small cell lung cancer or mixed small cell lung cancer and NSCLC, mixed adenosquamous carcinomas with a predominantly squamous component
- Known sensitizing EGFR mutations or ALK translocations.
- Tumor invading or compressing major blood vessels or tumor cavitation
- History or known presence of CNS metastases
- Malignancy other than NSCLC within 5 years (except adequately treated in-situ cervical cancer, or squamous or basal cell carcinoma of the skin)
- Palliative radiotherapy for bone lesions inside the thorax within 2 weeks before randomization
- Prior systemic therapy for NSCLC; prior neoadjuvant therapy is allowed if surgical resection for primary disease was performed.
- Any unhealed wound or bone fracture.
- Major surgery within 4 weeks before randomization or not yet recovered from prior surgery
- Any of the following prior to randomization:
 - within 12 months: clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure NYHA $\geq$ Class III, serious uncontrolled cardiac arrhythmia); peripheral vascular disease, cerebrovascular accident or transient ischemic attack
 - within 3 months: history of hemoptysis greater than 2.5 mL or severe bleeding
 - at any time: history of thrombotic or hemorrhagic disorders
- Therapeutic anticoagulation and/or coagulation abnormalities (INR > 1.5 and aPTT greater than ULN unless on prophylactic anticoagulation.
- Proteinuria (with a urine dipstick value of 2+ or above or $>100 \text{ mg/dL}$)
- Uncontrolled hypertension or systolic blood pressure $> 150 \text{ mmHg}$ or diastolic blood pressure $> 100 \text{ mmHg}$
- Significant unplanned weight loss (more than 10% body weight) attributed to cancer during previous 6 months
- Positive for HBsAg, HCV, or HIV

Treatment

The selected treatment is standard of care in the US. Patients were randomly allocated (Interactive Web-Based Response System) to receive

- PF-06439535 15 mg/kg IV every 3 weeks, or
- EU-approved bevacizumab 15 mg/kg every 3 weeks.

All subjects were to receive at least 4 and a maximum 6 cycles of

- Carboplatin IV AUC 6 every 3 weeks
- Paclitaxel 200 mg/m² every 3 weeks

No dose reductions from were allowed for PF-06439535 or EU-approved bevacizumab; however, if deemed necessary, the investigator could decrease the dose of blinded bevacizumab to 7.5 mg/kg with the concurrence of Pfizer. In the event of toxicity attributed to EU-approved bevacizumab or PF-06439535, treatment was to be either temporarily held.

Treatment should be discontinued in the event of:

- o Life threatening allergic reaction
- o Uncontrolled hypertension (Grade 3 not responsive to therapy or Grade 4)
- o Grade 4 fistula
- o Necrotizing fasciitis
- o Need for full-dose anticoagulation
- o Nephrotic syndrome
- o Arterial thromboembolism, Grade 4 pulmonary thrombosis
- o Severe (Grade 3) uncontrollable or recurrent hemorrhage
- o Grade 3-4 hemorrhage, or intracranial bleeding
- o Any Grade gastrointestinal perforation,
- o Any Grade wound dehiscence requiring medical or surgical therapy,
- o RPLS/PRES.

Instructions for paclitaxel and carboplatin toxicity management followed standard of care and approved product labeling for these drugs.

Efficacy and Safety Assessments

The primary clinical analysis is the risk ratio of ORR as defined by RECIST v 1.1. Patients were scanned at baseline, Week 7 (end of Cycle 2), Week 13 (end of Cycle 4), and Week 19 (end of treatment).

Clinical and laboratory assessments (serum chemistry, hematology, urine, etc.) were performed every three weeks, prior to each chemotherapy cycle. Toxicities were assessed for severity according to the CTCAE version 4.03. For a complete schedule of study assessments and procedures, please refer to Table 34 in the Appendices section.

Statistical Analysis Plan

The planned sample size was 710 subjects (355 patients per treatment arm), in order to achieve at least 85% power to demonstrate equivalence between PF-06439535 and bevacizumab on the primary ORR endpoint with a margin of (0.73, 1.37) with an overall type I error of 0.05,

assuming that the ORR is approximately 38% (Botrel et al, 2011) in both the PF-06439535 and bevacizumab arms. With an ORR of 41%, the power for this study is 95%.

The margin was selected based on the results of a meta-analysis combining studies E4599, AVAIL, and JO19907 (Sandler 2006, Johnson 2004, and Niho 2012 respectively). The ORR for the bevacizumab in combination with carboplatin and paclitaxel arms was estimated to be approximately 41% based on a fixed effect model, and the response rate to chemotherapy alone was estimated to be 21% based on the fixed model. The relative risk (RR) was estimated to be 2.17 (95% CI 1.74, 2.70). The margin (0.73, 1.37) maintained 43% of the effect size of the lower bound 95% CI of the effect size based on the historical ORR data based on the meta-analysis treatment estimate of bevacizumab + chemotherapy over chemotherapy alone based on a log scale (or about 50% on the linear scale).

Patients were randomized in a 1:1 ratio to receive PF-06439535 or bevacizumab plus carboplatin and paclitaxel. Randomization was stratified by geographic region (location of the drug depot supplying the site), sex (male vs. female), and smoking history (never or ever, ever includes ex-smokers and smokers).

The primary endpoint of the study is response at Week 19. The primary efficacy analysis was performed when all patients had completed the Week 19 tumor assessment and had a confirmed response at Week 25. The primary analysis of ORR is based on the ITT population. For the US, equivalence was considered established if the 90% confidence interval of the observed risk ratio was within the pre-specified margins (0.73, 1.37).

In addition, the following factors at screening were used in the subgroup analyses for the primary endpoint:

- Smoking history (never or ever (includes ex-smoker and smoker))
- Gender (male/female)
- Region (according to the location of the drug depot supplying the site). Regions might be combined into aggregated levels to facilitate related analyses.
- Age (≥ 65 , < 65)
- Race (White, Black, Asian, Other)
- Disease Stage (IIIB, IV, recurrent)
- Prior radiation therapy (Yes, No)
- Any prior systemic therapy, including adjuvant/neoadjuvant (Yes, No)
- ECOG PS (0, 1)

Secondary endpoints included duration of response (DOR), progression-free survival (PFS) rate at 1 year, and overall survival (OS) rate at 1 year. Please refer to Appendix 11.4 for definitions and censoring rules for these time-to-event endpoints.

- Safety

- Safety was characterized by type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events, including cardiotoxicity and infusion-related reactions, and laboratory abnormalities at 1 year from randomization.
- Peak and trough PF-06439535 and bevacizumab concentrations were assessed at selected cycles up to 1 year from randomization
- The incidence of ADA, including neutralizing antibodies, was assessed up to 1 year from randomization.

Subject Disposition

All 719 randomized patients were included in the ITT population, with 358 and 361 patients in the PF-06439535 and EU-approved bevacizumab arms respectively. Five patients were randomized but did not receive treatment, including 2 patients in the PF-06439535 arm and 3 patients in the EU-approved bevacizumab arm. The safety population then includes 714 patients, 356 and 358 patients in the PF-06439535 and EU-approved bevacizumab arms respectively. All patients have discontinued treatment at the time of analysis. Table 3 summarizes the patient disposition.

Table 3 - Study B7391003: Patient disposition

	PF-06439535 N; (%)	EU-approved bevacizumab N; (%)
Randomized (ITT)	358 (100)	361 (100)
Treated (SAF)	356 (99)	358 (99)
Completed study	193 (54)	187 (52)
Discontinued before completion	165 (46)	174 (48)
Reasons for discontinuation		
- Death	136 (38)	138 (38)
- Lost to follow-up	10 (3)	15 (4)
- Other	1 (<1)	4 (1)
- Protocol violations	4 (1)	3 (1)
- Refused further follow-up	14 (4)	14 (4)
Per-protocol population (PPP)	351 (98)	355 (98)
Reasons for exclusion		
- Incorrect histology*	1 (<1)	0 (0)
- Randomized but not received IP	3 (1)	3 (1)
- Prior therapy for Stage IIIB-IV	3 (1)	2 (1)
- Inadvertent blinding	1 (<1)	1 (<1)
- Screening scan $\geq$ 42 days	1 (<1)	1 (1)

Source: Generated by FDA reviewer using sponsor provided dataset ADSL

Protocol Violations/Deviations

Protocol violations were reported in 607 patients, 300 (86%) patients in the PF-06439535 arm and 307 (85%) in the EU-approved bevacizumab arm. Table 35 summarizes the protocol violations per treatment arm. Of these protocol violations, most could have compromised patient safety but not study results. The following are protocol violations with potential impact on the study primary endpoint assessment:

- Prior chemotherapy for metastatic disease
- Baseline scans obtained ≥ 28 days prior to randomization
- Sensitizing EGFR mutations
- Blind broken
- No chemotherapy treatment
- No IP
- Different chemotherapy than the one prescribed in the protocol
- Randomization errors
- Randomized but not dosed.

Protocol violations were balanced between arms, with the exception of 6 patients in the EU-approved bevacizumab arm and one patient in the PF-06439535 arm who received incorrect medication, had incorrectly entered randomization stratification factors in the IWRS system, or were randomized but not dosed. Although these may be considered major violations, the number of affected patients is small and therefore these protocol violations are unlikely to have had a statistical impact on study results. In addition, in many cases, the same protocol violation was featured in more than one category (e.g., patient ID# (b) (6) is listed under “inadvertent unblinding before receipt of IP” and “unblinded because blinded personnel administered treatment” categories). When looking by center, three of the four unblinded patients were enrolled in a single study site (1025, Poltava Reg. Clinical Oncology Dispensary, Ukraine), which only enrolled these three patients.

In addition, in the safety dataset, Pfizer flagged (AECAT = medication error) medication errors, summarized in Table 36 in the Appendices section. Although the number of medication errors is higher in the PF-06439535 arm (52 vs. 36), it is unlikely that these medication errors impacted impact in the study results.

Demographics and Baseline Characteristics

A total of 719 patients were enrolled and randomized, 358 to PF-06439535 and 314 to EU-approved bevacizumab. The first patient was enrolled in November 2013 and the last patient completed treatment in July 2015. Patients were enrolled in 159 centers and 87% of the centers enrolled fewer than 10 patients. Twenty four percent (176) of patients were enrolled in Russia and 21% (152) were enrolled in Ukraine.

Demographic characteristics were well balanced between arms. The study population is similar to the studies used for the calculation of the bevacizumab historical effect, with the exception of enrollment of a higher proportion of Asian patients. Table 4 summarizes the demographic characteristics of the ITT population.

Table 4 - Demographic characteristics of Study B7391003

Characteristics	PF-06439535 (n:358) N (%)	EU-approved bevacizumab (n:361); N (%)
Male	237 (66)	230 (64)
Female	121 (34)	131 (36)
Mean age (SD)	61.7 (9.5)	60.9 (8.9)
Median age (range)	62 (25-87)	61 (31-83)
Patients ≥65 y.o.	141 (39)	122 (34)
White	319 (89)	319 (88)
Asian*	36 (10)	40 (11)
Other	3 (1)	2 (1)
America and Western Europe	140 (39)	135 (37)
Eastern Europe	164 (46)	164 (45)
Other	54 (15)	62 (17)

Source: Generated by FDA reviewer using sponsor provided dataset ADSL

Table 5 summarizes the baseline disease characteristics for Study B7391003. Almost all patients (97% in each arm) had a disease histology of adenocarcinoma.

Genetic testing for ALK rearrangements was not conducted in most patients (73%); among tested patients, none tested positive for the mutation. Genetic testing for EGFR mutations was not conducted in most patients (65%); among tested patients, three patients tested positive for the mutation. ROS mutation testing was performed in less than 5% of patients, and no patients tested positive for the mutation.

Table 5 - Study B7391003: Disease baseline characteristics

	PF-06439535 N: 358; n (%)	EU-approved bevacizumab N:361; n (%)
Newly diagnosed	313 (87)	311 (87)
– Stage IIIB	48 (13)	29 (8)
– Stage IV	265 (74)	282 (78)
– Recurrent	45 (13)	50 (14)
Prior surgery for primary	61 (17)	68 (19)
Prior chemotherapy	15 (4)	20 (6)
Prior radiation	24 (7)	23 (6)
ECOG PS		
- 0	105 (29)	122 (34)

	PF-06439535 N: 358; n (%)	EU-approved bevacizumab N:361; n (%)
- 1	272 (70)	239 (66)
- Missing	1 (<1)	0
Smoking history		
- Never	103 (29)	309 (30)
- Smoker	127 (36)	117 (32)
- Ex-smoker	128 (36)	135 (37)

Source: Generated by FDA reviewer using sponsor provided datasets (ADSL, ADPR)

The median time since diagnosis was 1.2 months (range: 0.2 to 210.9 months) and 1.3 months (range: 0.1 to 137.9 months) for the PF-06439535 and EU-approved bevacizumab arms, respectively. Of the comorbidities at diagnosis, hypertension was reported in 137 (38%) and 124 (34%) patients in the PF-06439535 and EU-approved bevacizumab arms, respectively.

Analysis of Primary Clinical Endpoint(s)

Two analysis populations were used for efficacy analyses: the Intent-to-Treat (ITT) population and the Per-Protocol (PP) population. The ITT population, defined as all randomized patients, was used for all efficacy analyses. The PP population, defined as all patients who were randomized and received study treatment (PF-06439535 or EU-approved bevacizumab) as planned and had no major protocol deviations, was used for sensitivity analyses of the primary and secondary endpoints.

The primary efficacy endpoint of the study was ORR, defined as the percent of patients within each treatment group who achieved a best overall response (BOR) of complete response (CR) or partial response (PR) by Week 19, in accordance with RECIST version 1.1, and which was subsequently confirmed on a follow-up tumor assessment by Week 25. The primary endpoint of ORR was based on Pfizer's derived BOR using tumor measurements reported by the investigator in the CRF. Table 6 summarizes the results. The ORR for the PF-06439535 arm was 45.3% (95% CI: 40.0, 50.6) and 44.6% (95% CI: 39.7, 49.9) for the EU-approved bevacizumab arm.

The unstratified risk ratio of 1.01 (PF-06439535 versus bevacizumab-EU), with a 90% CI of (0.89, 1.16), fell within the pre-specified equivalence margin of (0.73, 1.37) for US-approved Avastin. The 90% CI of the risk ratio stratified by smoking status, gender, and region was (0.90, 1.18), which also fell within the equivalence margin.

Table 6 - Study B7391003: Summary of response at Week-19 confirmed per Pfizer's derivation (ITT analysis set)

	PF-06439535 N=358	EU-approved bevacizumab N=361
Response at week-19 confirmed, n (%)		
Complete remission (CR)	9 (3)	4 (1)
Partial remission (PR)	153 (43)	157 (44)
Stable disease (SD)	154 (43)	167 (46)
Progressive disease (PD)	15 (4)	14 (4)
Not evaluable (NE)	27 (7)	19 (5)
ORR (CR+PR), % (95% CI)	45.3 (40.0, 50.6)	44.6 (39.7, 49.9)
Treatment comparison (PF-06439535 vs - EU-approved bevacizumab)		
Un-stratified risk difference, %(95% CI)	0.7 (-6.6, 7.9)	
Stratified risk difference, %(95% CI)	1.2 (-6.0, 8.4)	
Un-stratified ORR risk ratio	1.01	
(95% CI)	(0.86, 1.19)	
(90% CI)	(0.89, 1.16)	
Stratified ORR risk ratio	1.03	
(95% CI)	(0.87, 1.21)	
(90% CI)	(0.90, 1.18)	

Source: Generated by statistical reviewer using sponsor provided datasets (ADSL, ADRSD, ADTTED)

Reviewer comments: Although similarity between PF-06439535 and EU-approved bevacizumab was statistically demonstrated for the protocol-specified primary efficacy endpoint of ORR based upon Pfizer's assessment of response, FDA considers ORR according to the investigator to assessment of response to be the primary endpoint of the study. Therefore, FDA analyses using investigator-assessed ORR as the primary endpoint are summarized in Table 7. Table 7

The unstratified risk ratio using investigator assessment of ORR is 0.99 (PF-06439535 versus EU-approved bevacizumab), with a 90% CI of (0.88, 1.10) in ORR, which falls within the prespecified equivalence margin of (0.73, 1.37). The 90% CI of risk ratios stratified by smoking status, gender, and region was (0.90, 1.17), which also falls within the prespecified equivalence margin.

Table 7 - Study B7391003: Summary of response at Week-19 confirmed per investigator-assessed (ITT analysis set)

	PF-06439535 N=358	EU-approved bevacizumab; N=361
Response at week-19 confirmed, n (%)		
Complete remission (CR)	9 (3)	4 (1)
Partial remission (PR)	154 (43)	158 (44)

Stable disease (SD)	155 (43)	167 (46)
Progressive disease (PD)	15 (4)	14 (4)
Not evaluable (NE)	25 (7)	18 (5)
ORR (CR+PR), %(95% CI)	45.5 (40.3, 50.9)	44.9 (39.7, 50.2)
Treatment comparison (PF-06439535 vs EU-approved bevacizumab)		
Un-stratified risk difference, %(95% CI)	0.7 (-6.6, 7.9)	
Stratified risk difference, %(95% CI)	1.2 (-6.0, 8.4)	
Un-stratified ORR risk ratio	0.99	
(95% CI)	(0.86, 1.13)	
(90% CI)	(0.88, 1.10)	
Stratified ORR risk ratio	1.03	
(95% CI)	(0.87, 1.21)	
(90% CI)	(0.90, 1.17)	

Source: Generated by statistical reviewer using sponsor provided datasets (ADSL, ADRS, ADTTE)

In addition, the analyses of ORR for patients in the PP population were consistent with that of the ITT population (Table 37 & Table 38 in 12.3 Appendices – Additional Tables).

Study B7391003 demonstrated that there was no statistical difference in ORR between PF-06439535 and EU-approved bevacizumab in combination with carbo/paclitaxel for the treatment of NSCLC.

Analysis of Secondary Clinical Endpoint(s)

Table 8 summarized the analyses of the secondary endpoints.). The results were consistent with analyses of the primary endpoint.

Table 8 - Study B7391003: Summary of Secondary Endpoints per applicant's derivation (ITT analysis set)

	PF-06439535 N=162	EU-approved bevacizumab; N=161
Patients with PFS Event, n (%)	107 (66)	119 (74)
Type of Event, n (%)		
Progressive Disease	101 (62)	110 (68)
Death	6 (4)	9 (6)
Number Censored, n (%)	55 (34)	42 (26)
Reason for Censoring, n (%)		
In follow-up	40 (25)	23 (14)

Given new anti-cancer treatment prior to PD	4 (3)	7 (4)
Other	11 (7)	12 (8)
Duration of Response (months) (95% CI)		
Median	8.3 (7.3, 10.0)	6.6 (6.2, 8.3)
DOR landmark analyses, %		
Patients with DOR <6 months	36	46
Patients with DOR 6 – 12 months	40	32
Patients with DOR >12 months	24	22
Median PFS months (95% CI)	9.5 (7.6, 9.7)	7.7 (7.6, 8.5)
Hazard Ratio (95% CI)	0.93 (0.78, 1.12)	
Median OS months (95% CI)	19.4 (16.5, NE)	17.8 (15.9, 23.5)
Hazard Ratio (95% CI)	0.92 (0.73, 1.16)	

Source: Generated by statistical reviewer using sponsor provided datasets (ADSL, ADRSD, ADTTED)

Additional Analyses

Analysis of Subgroups

Table 9 presents a summary of subgroup analyses of ORR (Week 19) by smoking history, gender, region, age, race, disease stage, prior radiation therapy, prior systemic therapy, and ECOG performance status for patients in the ITT population.

Table 9 - Study B7391003: PF-06439535 vs Bevacizumab-EU Risk Ratio in Best Overall Response with 90% Confidence Interval (Week 19)(ITT analysis set)

Subgroup Factor	Risk Ratio (90% CI) ^[1]
Smoking History	
Ever	1.08 (0.92, 1.28)
Never	0.88 (0.70, 1.12) ^[2]
Gender	
Male	1.08 (0.92, 1.29)
Female	0.89 (0.71, 1.12) ^[2]
Region	
America and West Europe	0.94 (0.71, 1.25) ^[2]
East Europe	1.01 (0.85, 1.21)
Other Region	1.19 (0.89, 1.57)
Age Group	
Age <65	1.02 (0.86, 1.20)
Age ≥65	1.02 (0.80, 1.29)
Race	
White	0.99 (0.86, 1.15)
Asian	1.22 (0.87, 1.74)
Black and Other	NA
Disease Stage	

Subgroup Factor	Risk Ratio (90% CI ^[1])
Newly Diagnosed Stage IIIB	1.21 (0.89, 1.72)
Newly Diagnosed Stage IV	0.92 (0.77, 1.08)
Recurrent	1.21 (0.86, 1.70)
Prior Radiation Therapy	
Yes	1.53 (0.70, 3.45) ^[2]
No	0.99 (0.87, 1.15)
Prior Systemic Therapy	
Yes	1.87 (0.86, 4.13) ^[2]
No	0.99 (0.86, 1.13)
ECOG PS	
0	0.99 (0.78, 1.26)
1	1.03 (0.87, 1.21)

^[1] Calculated based on 2-sided Miettinen and Nurminen Method without strata for risk ratio.

^[2] Either lower boundary or upper boundary of the 90% CI were outside of the pre-specified equivalence margins of (0.73, 1.37).

Source: Generated by statistical reviewer using sponsor provided datasets (ADSL, ADRSD).

Reviewer comments: The 90% CI of risk ratios for majority of the subgroups fell within the prespecified equivalence margin. Either the lower boundary or upper boundary of the 90% CI of risk ratio for a few subgroups were outside of the pre-specified equivalence margins of (0.73, 1.37); considering the relatively small sample sizes of the subgroups, this may be due to chance. These subgroup analyses should be interpreted with caution.

5.5. Review of Safety

5.5.1. Methods

This analysis centers on Study B9371003 and primarily focuses on FDA's review of the combination treatment phase of the trial. Additional supportive analyses of safety data collected during the monotherapy period of Study B9371003 and in PK Study B7391001 in healthy volunteers were also performed.

Population Demographics

Of the 719 patients in the ITT population, all but 5 received the assigned treatment and therefore the demographic characteristics of the safety population are comparable to the ITT population.

Categorization of Adverse Events

Pfizer used the NCI CTACE v4.03 dictionary to grade the severity of AEs and MedDRA dictionary v20.1 to code AEs. The safety dataset was audited for accuracy in coding (of verbatim terms when compared to preferred terms) and the coding was determined to be acceptable. Of the 5133 AEs, the verbatim term (AETERM) used by investigators did not match the coded (MedDRA) term for 2543 events. All mismatches were related to spelling (e.g., anemia vs. anaemia) or dictionary style differences (e.g., verbatim term “epigastric pain” is coded as “abdominal pain upper”). All AEs reported for the treatment period were analyzed, irrespective of Pfizer’s attribution of treatment emergent or relatedness. As summarized in Section 3.1, the safety review is based on 5133 adverse events. Of note, Pfizer’s analysis in the study report is based on 4912 adverse events that they considered “treatment emergent”; therefore, FDA’s analysis is different from Pfizer’s.

A separate analysis for the adverse events occurring in the monotherapy period and 28 after the last bevacizumab product dose is summarized in Section 7.6.3.

5.5.2. Major Safety Results

Table 10 summarizes the major safety results. There are minimal differences between arms.

Table 10 - Study B7391003: Major safety results.

	PF-06439535; n:356 N (%)	EU-approved bevacizumab; n: 358 N (%)
N AEs	2537	2596
N patients with AEs	335 (94)	339 (95)
N pts with SAEs	60 (17)	66 (18)
N patients with Grade 3-4 AEs	123 (35)	126 (35)
N patients with Grade 5 AEs	15 (4)	17 (5)

Table 11 summarizes the per-patient incidence (by subject) of AEs by system organ class (SOC).

Table 11 - Study B7391003: AEs by SOC

SOC	PF-06439535 n:356 N (%)		EU-approved bevacizumab n: 358 N (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Skin and subcutaneous tissue	177 (50)	2 (1)	181 (51)	0

SOC	PF-06439535 n:356 N (%)		EU-approved bevacizumab n: 358 N (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Nervous system	167 (47)	8 (2)	177 (49)	11 (3)
Blood and lymphatic system	138 (39)	47 (13)	158 (44)	58 (16)
Gastrointestinal disorders	135 (38)	6 (2)	134 (37)	12 (3)
General disorders and administration site	126 (35)	17 (5)	119 (33)	16 (4)
Musculoskeletal and connective tissue	110 (31)	7 (2)	121 (34)	4 (1)
Respiratory	105 (29)	13 (4)	106 (30)	16 (4)
Investigations	100 (28)	18 (5)	87 (24)	18 (5)
Metabolism and nutrition	59 (17)	17 (5)	66 (18)	9 (3)
Infections and infestations	55 (15)	13 (4)	62 (17)	20 (6)
Vascular	52 (15)	27 (8)	55 (15)	20 (6)
Renal and urinary	24 (7)	3 (1)	26 (7)	2 (1)
Injury, poisoning and procedural complications	19 (5)	1 (<1)	27 (8)	2 (1)
Cardiac	16 (4)	3 (1)	17 (5)	4 (1)
Psychiatric	11 (3)	1 (<1)	23 (6)	0
Eye	7 (2)	0	6 (2)	1
Ear and labyrinth	5 (1)	0	3 (1)	0
Neoplasms	4 (1)	1 (<1)	3 (1)	2 (1)
Reproductive system	3 (1)	0	1 (<1)	0
Hepatobiliary	1 (<1)	1	4 (1)	0
Immune system	1 (<1)	0	5 (1)	1 (<1)

For most SOC, there are minimal differences between the study arms. Differences of $\geq 3\%$ were observed in the blood and lymphatic SOC, musculoskeletal and connective tissue SOC, investigations SOC, procedural complications SOC, and psychiatric SOC. In the blood and lymphatic SOC, the incidence of anemia (24% vs. 27% in the PF-06439535 and EU-approved bevacizumab arms respectively), neutropenia (15% vs. 16% in the PF-06439535 and EU-approved bevacizumab arms respectively), and thrombocytopenia (15% vs. 16% in the PF-06439535 and EU-approved bevacizumab arms respectively) were higher in the EU-approved bevacizumab arm. The incidence of events in the musculoskeletal SOC was increased in the EU-approved bevacizumab arm mainly due to an increased incidence of pain in extremity (3% and 5% in the PF-06439535 and EU-approved bevacizumab arms respectively); most events in this SOC were Grade 1-2. The incidence of psychiatric disorders was increased in the EU-approved bevacizumab arm because of insomnia (2.5% vs. 4.5% in the PF-06439535 and the EU-approved bevacizumab arm respectively). The incidence in the of injury, poisoning and procedural complications was increased in the EU-approved bevacizumab arm because there were more

infusion-related reactions (4% vs. 6% in the PF-06439535 and EU-approved bevacizumab arms respectively); IRRs are further described in this section, under the subheading “Product Specific Concerns”. Investigations are summarized in Sections 7.5.1 (proteinuria and renal function) and 7.6.3.

Table 12 summarizes the incidence of AEs analyzed by high-level term.

Table 12 - Study B7391003: AEs by HLT (incidence $\geq$ 5%)

HLT	PF-06439535 n:356 N (%)		EU-approved bevacizumab n: 358 N (%)	
	All grades	Grade 3-4	All Grades	Grades 3-4
Alopecias	165 (46)	2 (1)	163 (46)	0
Peripheral neuropathies	102 (29)	6 (2)	117 (33)	7 (2)
Asthenic conditions	93 (26)	12 (3)	82 (23)	14 (4)
Anemias	85 (24)	14 (4)	97 (27)	18 (5)
Nausea and vomiting symptoms	75 (21)	1 (<1)	78 (22)	2 (1)
Neutropenias	59 (17)	31 (9)	67 (19)	38 (11)
Thrombocytopenias	53 (15)	8 (2)	59 (16)	13 (4)
Muscle pains	52 (15)	2 (1)	47 (13)	0
Paresthesias and dysesthesias	43 (12)	0	35 (10)	0
Vascular hypertensive disorders	40 (11)	22 (6)	47 (13)	20 (6)
Diarrhea (excl infective)	37 (10)	0	45 (13)	4 (1)
Coughing and associated symptoms	37 (10)	1 (<1)	43 (12)	3 (1)
Appetite disorders	36 (10)	1 (<1)	38 (11)	3 (1)
Joint related signs and symptoms	36 (10)	1 (<1)	41 (11)	1 (<1)
Gastrointestinal atonic and hypomotility disorders	35 (10)	0	27 (8)	1 (<1)
Nasal disorders	36 (10)	0	28 (8)	0
Liver function analyses	34 (10)	5 (1)	26 (7)	3 (1)
Bone related signs and symptoms	26 (7)	2 (1)	23 (6)	1 (<1)
Physical examination procedures	24 (7)	0	23 (6)	0
Leukopenias	21 (6)	2 (1)	28 (8)	4 (1)
Breathing abnormalities	23 (6)	5 (1)	25 (7)	10
Urinary abnormalities	20 (6)	2 (1)	19 (5)	2

HLT	PF-06439535 n:356 N (%)		EU-approved bevacizumab n: 358 N (%)	
	All grades	Grade 3-4	All Grades	Grades 3-4
Platelet analyses	23 (6)	4 (1)	16 (4)	4
Musculoskeletal and connective tissue pain and discomfort	18 (5)	2 (1)	27 (8)	1
Headaches	18 (5)	2 (1)	24 (7)	2 (1)
Non-site specific procedural complications	17 (5)	0	23 (6)	2 (1)
Febrile disorders	17 (5)	0	18 (5)	0
Upper respiratory tract infections	18 (5)	1 (<1)	17 (5)	2 (1)
Upper respiratory tract signs and symptoms	17 (5)	0	18 (5)	0
Pain and discomfort	19 (5)	3 (1)	15 (4)	2 (1)
Lower respiratory tract and lung infections	14 (4)	7 (2)	24 (7)	12 (3)
Rashes, eruptions and exanthems	13 (4)	0	25 (7)	0
White blood cell analyses	15 (4)	6 (2)	21 (6)	11 (3)

Increased (2-3%) incidence of asthenic conditions, gastrointestinal hypomotility, liver function analyses, muscle pains, nasal disorders, paresthesias, and platelet analysis were observed in the PF-06439535 arm. Increased (2-3%) incidence of anemias, coughing, diarrhea, headaches, leukopenias, lower respiratory tract infections, neutropenias, peripheral neuropathies, rashes, hypertension, and white blood cell analyses were observed in the EU-approved bevacizumab arm. These small differences don't follow any pattern of toxicity and typical in large clinical trials. The incidence of Grade 3-4 AEs was very similar between arms.

Table 7 summarizes the incidence of the most commonly reported AEs by preferred term.

Table 13 - Study B7391003: AEs by PT (incidence ≥ 10%)

PT	PF-06439535 n:356 N (%)		EU-approved bevacizumab n: 358 N (%)	
	All grades	Grade 3-4	All grades	Grade 3-4
Alopecia	165 (46)	2 (1)	163 (46)	0
Anemia	85 (24)	14 (4)	97 (27)	18 (5)
Nausea	64 (18)	0	66 (18)	2 (1)

PT	PF-06439535 n:356 N (%)		EU-approved bevacizumab n: 358 N (%)	
	All grades	Grade 3-4	All grades	Grade 3-4
Fatigue	56 (16)	6 (2)	48 (13)	6 (2)
Neutropenia	54 (15)	26 (7)	58 (16)	29 (8)
Thrombocytopenia	53 (15)	8 (2)	59 (16)	13 (4)
Myalgia	52 (15)	2 (1)	47 (13)	0
Neuropathy peripheral	49 (14)	5 (1)	58 (16)	4 (1)
Hypertension	40 (11)	22 (6)	45 (13)	20 (6)
Paresthesia	38 (11)	0	30 (8)	0
Diarrhea	37 (10)	0	45 (13)	4 (1)
Arthralgia	36 (10)	1 (<1)	41 (11)	1 (<1)
Decreased appetite	36 (10)	1 (<1)	38 (11)	3 (1)
Asthenia	36 (10)	7 (2)	33 (9)	8 (2)
Constipation	35 (10)	0	26 (7)	1 (<1)
Epistaxis	36 (10)	0	26 (7)	0
Peripheral sensory neuropathy	33 (9)	0	43 (12)	2 (1)

The PT analysis is consistent with the HLT analysis. There are no clinically meaningful differences between arms.

Deaths

In FDA's analysis of the fatal AEs in the combination period, 15 (4%) and 17 (5%) patients died in the PF-06439535 and EU-approved bevacizumab arms, respectively. *Reviewer note: disease progression should have not been reported as an AE, as it is an expected disease outcome.* All the listed causes of death are expected fatal events in the setting of advanced NSCLC and treatment with chemotherapy and bevacizumab products. There were no clinically significant differences between arms.

Table 14 - Study B7391003: Fatal adverse events

PT	PF-06439535	EU-approved bevacizumab
Disease progression	2	5
Pulmonary hemorrhage	2	3
Death	1	3
Acute myocardial infarction	1	1
Acute coronary syndrome	1	0
Cardiovascular insufficiency	1	0

PT	PF-06439535	EU-approved bevacizumab
Embolism arterial	1	0
Febrile neutropenia	1	0
Hemorrhage	1	0
Hemorrhagic stroke	1	0
Myocardial infarction	1	0
Pneumonia	1	0
Respiratory failure	1	0
Acute respiratory failure	0	1
Cardio-respiratory arrest	0	1
Pulmonary edema	0	1
Right ventricular failure	0	1
Shock hemorrhagic	0	1
Subarachnoid hemorrhage	0	1

Pfizer provided narratives for all deaths that occurred within 28 days after the last dose of study therapy or the start of subsequent anti-cancer therapy. In Pfizer's analysis, 21 (6%) patients in the PF-06439535 arm and 24 (7%) patients experienced Grade 5 events.

For cases in which a specific cause of death was not reported, narratives showed

- PF-06439535 arm: one patient (ID (b) (6)) with COPD and respiratory insufficiency died at home 17 days after the last cycle of treatment;
- EU-approved arm:
 - one patient died 7 days after the second cycle treatment administration (ID (b) (6)),
 - two patients (ID (b) (6) and (b) (6)) with a death of unknown cause 4 days after receipt of the first and 4th dose, respectively, of treatment and no confounding factors.

The narrative for the patient who died due to hemorrhage (ID (b) (6)) did not provide information regarding the location of the hemorrhage; as per the narrative, the patient who died of arterial embolism (ID (b) (6)) is believed to have had a pulmonary thromboembolism based on telephone interrogation of the patient's wife.

In the EU-approved bevacizumab arm, the narrative for patient ID (b) (6) indicated that the patient had hemoptysis and mild thrombocytopenia immediately before the onset of fatal hemorrhagic shock (day 13 after the last treatment).

Treatment Emergent Adverse Events

Table 15 displays the SAEs that occurred in at least 2 patients ($\geq 1\%$). In FDA's analysis, 16% and 17% patients in the PF-06439535 and EU-approved bevacizumab arms, respectively,

experienced an SAE while on the combination treatment phase. Overall, there do not appear to be clinically meaningful differences in the incidence and patterns of SAEs between the treatment arms. More patients in the PF-06439535 arm experienced (HLT) pulmonary embolisms (6 vs. 1 in the PF-06439535 and EU-approved bevacizumab arms).

Table 15 - Study B07391003: SAEs (incidence of $\geq 1\%$)

HLT	PT	PF-06439535; n:356 N; (%)		EU-approved bevacizumab; n: 358; N (%)	
		All Grades	Grades 3-5	All Grades	Grades 3-5
Anemias	Anemia	2 (1)	1 (<1)	4 (1)	4 (1)
Asthenic conditions	Asthenia	4 (1)	2 (1)	1 (<1)	1 (<1)
Lower respiratory tract and lung infections	Pneumonia	5 (1)	5 (1)	5 (1)	4 (1)
Neutropenias	Febrile neutropenia	5 (1)	5 (1)	7 (2)	7 (2)
	Neutropenia	4 (1)	3 (1)	6 (2)	6 (2)
Pulmonary thrombotic and embolic conditions	Pulmonary embolism	6 (2)	5 (1)	1 (<1)	1 (<1)
Sodium imbalance	Hyponatremia	4 (1)	3 (1)	0	0

In Pfizer's analysis (using a different timeline), 23% and 22% patients in the PF-06439535 and EU-approved bevacizumab arm respectively had an SAE. The most frequently reported SAEs were pneumonia (2% patients in each arm), febrile neutropenia (1% and 2% patients in the PF-06439535 and EU-approved bevacizumab arms respectively), and neutropenia (1% and 2% patients in the PF-06439535 and EU-approved bevacizumab arms respectively).

Dropouts and/or Discontinuations

Table 16 reflects FDA's analysis of the treatment discontinuations in the combination period as per the safety database. A total of 27 (8%) patients and 28 (8%) patients the PF-06439535 arms respectively discontinued all treatment because of AEs; in 5 patients in the PF-06439535 arm and 8 patients in the EU-approved bevacizumab arm these events were fatal.

Bevacizumab products were discontinued in 39 (11%) patients in the PF-06439535 arm and 33 (9%) patients in the EU-approved bevacizumab arm. The adverse event PTs resulting in treatment discontinuation in at least 1% of patients were pulmonary embolism (2%), asthenia, dyspnea, embolism, epistaxis, and proteinuria (1%) in the PF-06439535 arm, and asthenia (2%), dyspnea, anemia, death, disease progression, fatigue, peripheral motor neuropathy,

pneumonia (1% each), and sepsis in the EU-approved bevacizumab arm. To further explore signals, Table 16 summarizes the reasons for bevacizumab products discontinuation by HLT (incidence of at least 1%).

Table 16 - Study B07391003: Bevacizumab products treatment discontinuations

HLT	PF-06439535 n:356 N (%)	EU-approved bevacizumab n: 358 N (%)
Pulmonary thrombotic and embolic conditions	7 (2)	1 (<1)
Asthenic conditions	3 (1)	6 (2)
Breathing abnormalities	2 (1)	2 (1)
Nasal disorders	2 (1)	0
Non-site specific embolism and thrombosis	3 (1)	0
Urinary abnormalities	2 (1)	0
Anemias	0	3 (1)
Coughing and associated symptoms	1 (<1)	2 (1)
Death and sudden death	1 (<1)	3 (1)
General signs and symptoms	1 (<1)	4 (1)
Lower respiratory tract and lung infections	1 (<1)	3 (1)
Peripheral neuropathies	0	2 (1)
Sepsis, bacteremia, viremia and fungaemia	0	2 (1)

The imbalance in emboli between arms (10 patients in the investigational arm vs. 1 patient in the EU-approved bevacizumab arm) is further explored below, in the subsection on product specific safety concerns.

A total of 43 (12%) patients in the PF-06439535 arm and 48 (13%) patients in the EU-approved bevacizumab discontinued both carboplatin and paclitaxel because of AEs. Additionally, 6 patients in the PF-06439535 arm and 7 patients in the EU-approved bevacizumab arm discontinued carboplatin or paclitaxel due to AEs. Table 17 Error! Reference source not found.summarizes the reasons for treatment discontinuations of one or both chemotherapy agents (incidence of at least 1%). There were no clinically significant differences between arms.

Table 17 - Study B07391003: Carboplatin and/or paclitaxel treatment discontinuations

HLT	PF-06439535 n:356 N (%)	EU-approved bevacizumab n: 358 N (%)
Peripheral neuropathies	13 (4)	9 (3)
Asthenic conditions	3 (1)	6 (2)
Neutropenias	3 (1)	5 (1)
Non-site specific embolism and thrombosis	2 (1)	0
Pulmonary thrombotic and embolic conditions	5 (1)	1 (<1)

HLT	PF-06439535 n:356 N (%)	EU-approved bevacizumab n: 358 N (%)
Thrombocytopenias	5 (1)	1 (<1)
Urinary abnormalities	2 (1)	0
Allergic conditions	0	2 (1)
Anemias	0	3 (1)
Breathing abnormalities	1 (<1)	2 (1)
Death and sudden death	1 (<1)	3 (1)
General signs and symptoms	1 (<1)	4 (1)
Ischemic coronary artery disorders	1 (<1)	2 (1)
Lower respiratory tract and lung infections	1 (<1)	3 (1)
Nervous system disorders	0	2 (1)
Non-site specific procedural complications	0	4 (1)
Paranesthesia's and dysesthesias	0	2 (1)
Physical examination procedures and organ system status	0	2 (1)
Sepsis, bacteremia, viremia and fungaemia	0	2 (1)
Vascular hypertensive disorders	1 (<1)	2 (1)
White blood cell analyses	1 (<1)	2 (1)

Product Specific Safety Concerns

Based on the known safety profile of bevacizumab (including VEGF inhibition-related AEs and AEs that although not related to VEGF inhibition are commonly increased in bevacizumab-containing arms in clinical studies), the following class-related toxicities were considered events of interest and analyzed using Standardized MedDRA Queries (SMQs) (when available) or customized searches; the comparative assessment of these toxicities could be considered more meaningful than the general comparisons of adverse events.

- arterial thromboembolic events (ATE)
- venous thromboembolic events (VTE)
- bleeding/hemorrhages
- pulmonary hemorrhage
- cardiac disorders and congestive heart failures (CHF)
- hypertension
- reversible posterior leukoencephalopathy syndrome-related (RPLS)
- thrombotic microangiopathy (TMA)
- proteinuria and renal function
- gastrointestinal perforations and fistula
- non-gastrointestinal fistula formation
- surgery and wound healing complications

- infusion reactions (IRR)
- hypersensitivity reactions
- neutropenia and infections
- peripheral sensory neuropathy
- osteonecrosis of the jaw

ATE/VTE

To investigate the events of ATE/VTE, a narrow SMQ was conducted. Twenty patients (5.6%) in the PF-06439535 arm and 8 (2.2%) patients in the EU-approved bevacizumab had an event included in the “embolic and thrombotic events”, “embolic and thrombotic events, arterial”, “embolic and thrombotic events, venous”, and “Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous” narrow SMQs. The result of these queries is summarized in Table 18. Error! Reference source not found.. Please note that events may be repeated if they belong to more than one SMQ.

Table 18 - Study B07391003: ATE/VTE narrow SMQs events

SMQ	PT	PF-06439535 N: 356 n (%)	EU-approved bev N: 358 n (%)
Embolic and thrombotic events	Acute myocardial infarction	1 (0.28)	1 (0.27)
	Brachiocephalic vein occlusion	1 (0.28)	0
	Cerebrovascular insufficiency	1 (0.28)	0
	Deep vein thrombosis	1 (0.28)	1 (0.27)
	Embolism	2 (0.56)	0
	Embolism arterial	2 (0.56)	0
	Hemorrhagic stroke	1 (0.28)	0
	Myocardial infarction	1 (0.28)	1 (0.27)
	Peripheral artery thrombosis	1 (0.28)	0
	Pulmonary embolism	8 (2.24)	2 (0.55)
	Pulmonary infarction	0	1 (0.27)
	Subclavian vein thrombosis	0	1 (0.27)
	Thrombophlebitis superficial	0	1 (0.27)
	Thrombosis	1 (0.28)	0
	Venous thrombosis	0	1 (0.27)
Embolic and thrombotic events, arterial	Acute myocardial infarction	1 (0.28)	1 (0.27)
	Cerebrovascular insufficiency	1 (0.28)	0
	Embolism arterial	2 (0.56)	0
	Myocardial infarction	1 (0.28)	1 (0.27)
	Peripheral artery thrombosis	1 (0.28)	0
Embolic and thrombotic	Brachiocephalic vein occlusion	1 (0.28)	0
	Deep vein thrombosis	1 (0.28)	1 (0.27)

SMQ	PT	PF-06439535 N: 356 n (%)	EU-approved bev N: 358 n (%)
events, venous	Pulmonary embolism	8 (2.24)	2 (0.55)
	Pulmonary infarction	0	1 (0.27)
	Subclavian vein thrombosis	0	1 (0.27)
	Thrombophlebitis superficial	0	1 (0.27)
	Venous thrombosis	0	1 (0.27)
Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous	Embolism	2 (0.56)	0
	Hemorrhagic stroke	1 (0.28)	0
	Thrombosis	1 (0.28)	0

There were 6 (1.7%) patients in the PF-06439535 and 2 (0.55%) patients in the EU-approved bevacizumab arm with ATEs; 4 fatal ATEs in the PF-649535 arm (arterial embolism, hemorrhagic stroke, and 2 myocardial infarctions) and one in the EU-approved bevacizumab arm (myocardial infarction). Grade 3-4 ATEs were observed in 4 patients in the PF-06439535 arm (peripheral artery thrombosis, arterial embolism, and two patients with embolism) and one patient in the EU-approved bevacizumab arm (myocardial infarction).

There were 10 (2.8%) patients in the PF-06439535 and 6 (1.7%) patients in the EU-approved bevacizumab arm with VTEs, none fatal. Seven patients had Grade 3-4 VTEs in the PF-649535 arm, all pulmonary embolisms (an additional patient was coded as having a Grade 2 pulmonary embolism; as per CTCAE, all pulmonary embolisms are Grade 3 and above). Grade 3-4 VTEs (all pulmonary embolisms) were observed in two patients in the EU-approved bevacizumab arm.

FDA's analysis differs from Pfizer's. Pfizer states that 8 (2.2%) patients in the PF-06439535 arm and 7 (2.0%) patients in the EU-approved bevacizumab arm group had an ATE. These differences may be attributed to the definition of ATE (e.g., Pfizer included ischemic stroke but not hemorrhagic stroke) and the patients included in the analysis.

Although numerically there were more arterial and venous thromboembolic events in the PF-06439535 arm, there are no clinically or meaningful differences between arms. The incidence of these events is within the expected incidence as described in the Avastin U.S. Package Insert (USPI).

Bleeding/hemorrhage and epistaxis

To investigate hemorrhagic events, a modified narrow SMQ was conducted, including SMQs “Central nervous system hemorrhages and cerebrovascular conditions”, “Gastrointestinal hemorrhage”, “Gastrointestinal perforation, ulcer, hemorrhage, obstruction non-specific findings/procedures”, “Gastrointestinal perforation, ulceration, hemorrhage or obstruction”, “Hemorrhage terms (excl. laboratory terms)”, “Hemorrhages”, and “Hemorrhagic central nervous system vascular conditions” and deleting PTs abdominal discomfort, cerebrovascular insufficiency, duodenal ulcer, gastric ulcer, peptic ulcer, petechiae, small intestinal perforation, subileus, and vascular encephalopathy; all selected PTs contain the word hemorrhage or the medical term for a specific bleeding, like hemoptysis or epistaxis. A total of 70 (20%) patients in the PF-06439535 arm and 57 (16%) patients in the EU-approved bevacizumab experienced one or more bleeding events as summarized in Table 19.

Table 19 - Study B07391003: Hemorrhages/bleeding events.

PT	PF-06439535 N: 356; n (%)	EU-approved bevacizumab N: 358; n (%)
Epistaxis	36 (10)	26 (7)
Gingival bleeding	13 (4)	12 (3)
Hemoptysis	9 (3)	10 (3)
Hematuria	7 (2)	5 (1)
Hematochezia	3 (1)	1 (<1)
Pulmonary hemorrhage	2 (1)	3 (1)
Hemorrhoidal hemorrhage	2 (1)	0
Rectal hemorrhage	1 (<1)	1 (<1)
Anal hemorrhage	1 (<1)	0
Cerebral hemorrhage	1 (<1)	0
Hemorrhage	1 (<1)	0
Hemorrhagic stroke	1 (<1)	0
Laryngeal hemorrhage	1 (<1)	0
Lip hemorrhage	1 (<1)	0
Lower gastrointestinal hemorrhage	1 (<1)	0
Melena	1 (<1)	0
Procedural hemorrhage	1 (<1)	0
Subgaleal hematoma	1 (<1)	0
Hematemesis	0	1 (<1)
Shock hemorrhagic	0	1 (<1)
Subarachnoid hemorrhage	0	1 (<1)

There were 4 fatal hemorrhagic events in the PF-06439535 arm: hemorrhagic stroke, hemorrhage, and pulmonary hemorrhage (2). There were 5 fatal hemorrhagic events in the EU-approved bevacizumab arm: hemorrhagic shock, subarachnoid hemorrhage, and pulmonary

hemorrhage (3). There were no Grade 4 hemorrhagic events. Grade 3 events were subgaleal hematoma and hemorrhoidal hemorrhage in the PF-06439535 arm and hematuria, hemoptysis (2) and rectal hemorrhage in the EU-approved bevacizumab arm.

In all patients, epistaxis was Grade 1-2.

Although the incidence of hemorrhagic events is slightly higher in the PF-06439535 arm than in the control arm, Grade 3-5 events were similar. None of these differences are likely to be clinically meaningful.

Cardiac disorders and CHF

Cardiac disorders in the combination portion of the study were observed in 16 (4.5%) and 17 (4.7%) patients in the PF-06439535 and EU-approved arms, respectively. The most common disorders (HLT) are rate and rhythm disorders (4 patients in each arm), which included bradycardia, tachycardia, arrhythmia, and extrasystoles; supraventricular arrhythmias (2 and 5 patients in the PF-06439535 and EU-approved arms, respectively), including atrial fibrillation, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, and supraventricular tachycardia; ischemic coronary artery disorders (4 and 3 patients in the PF-06439535 and EU-approved arms, respectively), including acute coronary syndrome, acute myocardial infarction, angina unstable, myocardial infarction, and myocardial ischemia; and ventricular arrhythmias and cardiac arrest (3 and 2 patients in the PF-06439535 and EU-approved arms, respectively). There was one ventricular dysfunction the PF-06439535 arm and one event of left ventricular hypertrophy and an event of cardiomyopathy in the EU-approved bevacizumab arm.

Fatal cardiac events in the PF-06439535 arm were cardiovascular insufficiency, acute coronary syndrome, and myocardial infarction (2). Fatal events in the EU-approved bevacizumab arm were right ventricular failure, cardiorespiratory arrest and myocardial infarction.

Overall, cardiac disorders were comparable and no clinically meaningful differences were noted between the treatment arms.

Hypertension, RPLS, and TMA

The database was queried for the SMQ "hypertension", including the following PTs: blood pressure increased, blood pressure systolic increased, diastolic hypertension, essential hypertension, hypertension, and systolic hypertension. In the combination period, 42 (12%) and 48 (13%) patients experienced a hypertensive event. There were no Grade 4 or 5 events. Grade 3 hypertension was observed in 6% patients in each arm. There were no meaningful differences in the incidence of hypertension between arms.

As shown in Figure 1 and Figure 2Error! Reference source not found., in both arms most events of hypertension were first reported in the first 2 cycles of treatment (median time to first event was 24.5 days in the PF-06439535 arm and 27 days in the EU-approved bevacizumab arm) and 75% of hypertension events were reported within the first 66 days of treatment.

Figure 1 - Study B7391003: Distribution of first reported event of hypertension (days), PF-06439535 arm

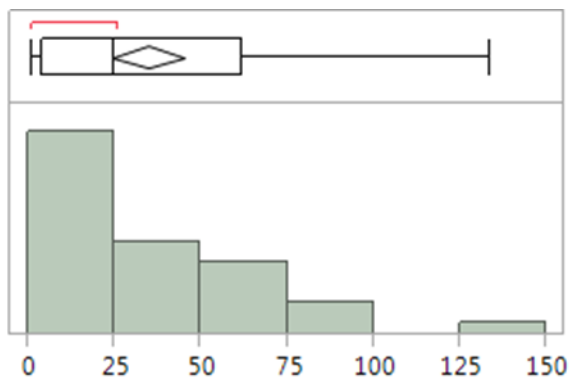
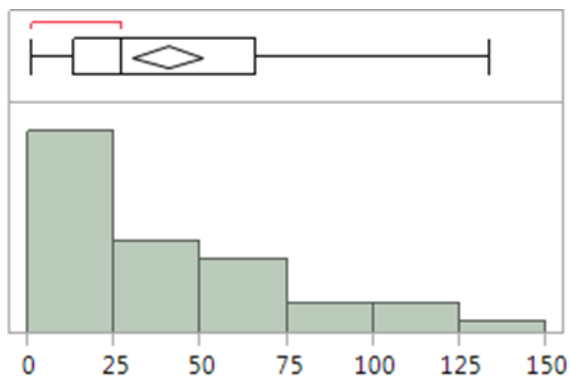


Figure 2 - Study B7391003: Distribution of first reported event of hypertension (days), EU-bevacizumab arm



Any differences in anti-VEGF activity between products would most likely be noticed in the assessment of blood pressure. As per study protocol, monitoring of blood pressure was systematic (-30' before bevacizumab product infusion and 30' at the end of the last infusion on the day of infusions and then assessed when clinically deemed necessary. Figure 3 and Figure 4 display (using data from the vital signs dataset) the distribution of systolic blood pressure by visit in the PF-06439535 and EU-approved bevacizumab arms, respectively.

Figure 3 - Study B7391003: Systolic blood pressure by visit, PF-06439535 arm

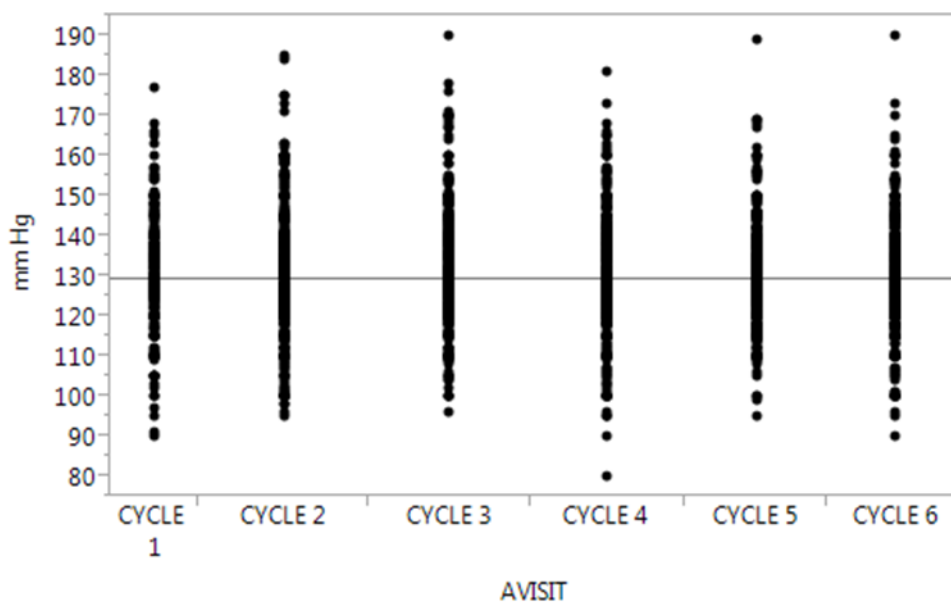
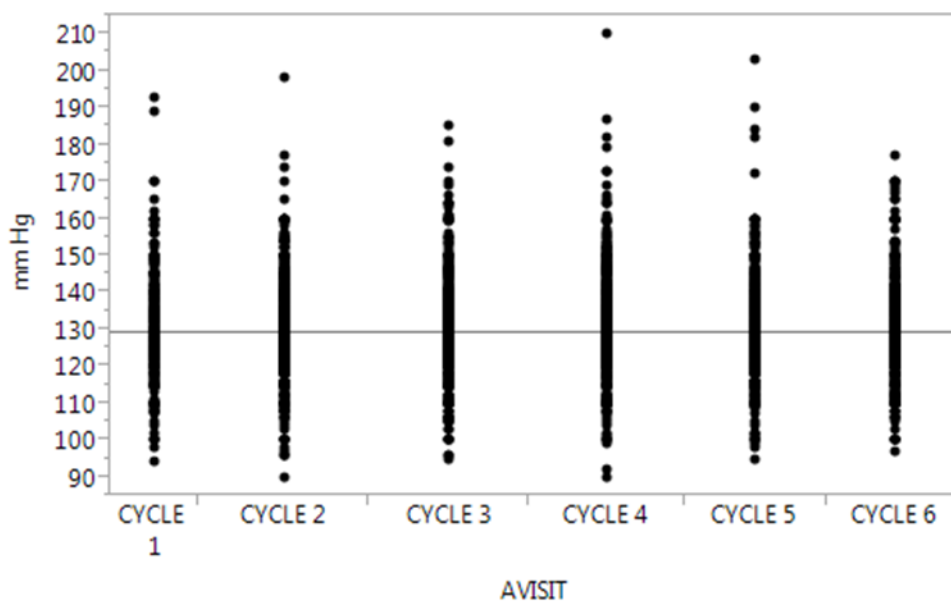


Figure 4 - Study B7391003: Systolic blood pressure by visit, EU-approved bevacizumab arm



As summarized in Table 20, variations in mean systolic blood pressure were minimal between cycles (Δ between Cycle 1 and the highest mean observed – Cycle 3- in the PF-06439535 arm was 0.44 mm Hg and the Δ between Cycle 1 and the highest mean observed – Cycle 4- in the EU-approved bevacizumab arm was 0.28 mm Hg) and between arms. For each cycle, the

difference of mean systolic blood pressure between arms was less than 2.3 mm Hg, a finding of no clinical significance.

Table 20 - Study B7391003: Mean systolic blood pressure (mm Hg) by visit

Cycle	PF-06439535 (n: 356)			EU-approved bevacizumab (n:358)			Δ means
	N	Mean SBP	Std Dev	N	Mean SBP	Std Dev	
1	348	129.91	12.38	356	129.92	12.93	-0.01
2	336	129.26	12.71	345	129.97	11.81	-0.71
3	318	130.35	12.07	326	129.65	11.96	0.7
4	306	129.23	12.12	314	130.20	12.49	-0.97
5	285	128.89	10.85	290	127.17	12.23	1.72
6	269	128.94	11.78	278	126.64	11.69	2.3

Figure 5 and Figure 6 display (using data from the vital signs dataset) the distribution of systolic blood pressure by visit in the PF-06439535 and EU-approved bevacizumab arms, respectively.

Figure 5 - Study B7391003: Diastolic blood pressure by visit, PF-06439535 arm

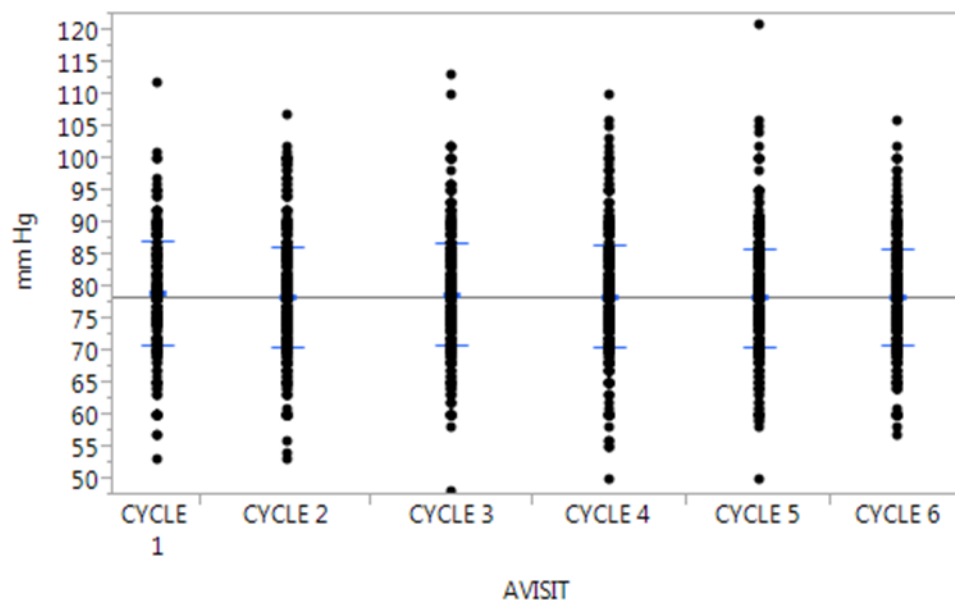
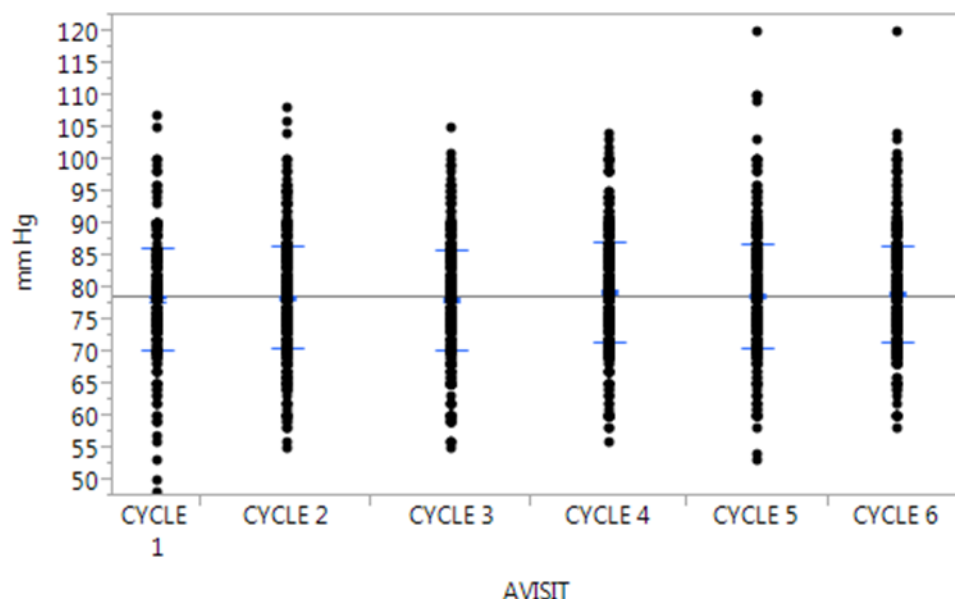


Figure 6 - Study B7391003: Diastolic blood pressure by visit, EU-approved bevacizumab arm



As summarized in Table 21^{Error! Reference source not found.}, variations in mean diastolic blood pressure were minimal between cycles (in the PF-06439535 arm, the highest mean diastolic blood pressure was observed in Cycle 1; in the EU-approved bevacizumab arm, the Δ between Cycle 1 and the highest mean diastolic blood pressure observed – Cycle 4- was 0.99 mm Hg) and between arms. For each cycle, the difference of mean systolic blood pressure between arms was less than 0.9 mm Hg, a finding with no clinical significance.

Table 21 - Study B7391003: Mean diastolic blood pressure (mm Hg) by visit

Cycle	PF-06439535 (n: 356)			EU-approved bevacizumab (n:358)			Δ means
	N	Mean DBP	Std Dev	N	Mean DBP	Std Dev	
1	348	79.06	7.97	356	78.36	7.98	0.7
2	336	78.49	7.89	345	78.55	7.89	-0.06
3	318	78.85	7.97	326	78.22	7.27	0.63
4	306	78.48	7.99	314	79.35	7.87	-0.87
5	285	78.29	7.75	290	78.86	8.09	-0.57
6	269	78.44	7.49	278	79.15	7.44	-0.71

The database was searched for events of TMA and PRLS; no events were found. There was one patient with a Grade 2 metabolic encephalopathy in the PF-06439535 arm and one patient with Grade 1 encephalopathy in the EU-approved bevacizumab arm.

Proteinuria and renal function

Proteinuria (data from the safety database) was observed in 13 (4%) and 17 (5%) patients in the PF-06439535 and EU-approved bevacizumab arms, respectively, during the combination treatment period. There were no Grade 4 events and Grade 3 proteinuria was observed in 1 and 2 patients in the PF-06439535 and EU-approved bevacizumab arms, respectively. The only event of nephrotic syndrome was reported in a patient in the PF-06439535 arm after Cycle 19.

Table 22 summarizes proteinuria based on the laboratory dataset (for pre-specified visits, dipstick analysis).

Table 22 - Study B7391003: Urinary protein analysis

	PF-06439535 N: 356; n (%)	EU-approved bevacizumab N: 358; n (%)
N patients analyzed	336 (94)	339 (95)
Negative	264 (74)	245 (68)
Grade 1	73 (21)	85 (24)
Grade 2	2 (1)	5 (2)

There were minor discordances between the AE dataset and the lab dataset; a thorough search of the laboratory dataset for collection of urinary protein data for all cycles, including monotherapy bevacizumab product treatment and unscheduled visits, revealed a Grade 3 laboratory abnormality of proteinuria in a patient in the PF-06439535 arm at the end of treatment; this patient had a Grade 2 AE of proteinuria while receiving combination therapy but no documentation of Grade 3 proteinuria as an AE in the AE dataset. Additionally, Grade 3 proteinuria was recorded in the PF-06439535 arm but was not supported by data in the laboratory dataset for this patient.

Renal injury was infrequent and of low grade (one patient in each arm). Acute kidney injury (Grade 1 and 2) was reported in two patients. In the lab dataset, there were no Grade 4 creatinine elevations during the combination therapy. Grade 3 creatinine increases were observed in one patient between Cycle 2 and Cycle 3 and in another patient in the monotherapy period (both patients in the PF-06439535 arm).

Gastrointestinal ulcers, perforations, and fistula

Three SMQs had reported events related to ulcers, perforations, or fistula: gastrointestinal perforation, gastrointestinal perforation, ulcer, hemorrhage, obstruction non-specific findings/procedures, and gastrointestinal perforation, ulceration, hemorrhage or obstruction. These SMQs contain events of abdominal discomfort, hemorrhages, ulcers, peritonitis, perforations, and subileus. Ten patients (3%) in the PF-06439535 arm and 6 (2%) patients in the EU-approved bevacizumab arm experienced one of these events. However, the SMQs are not specific for perforation or fistula, which have smaller incidences in the setting of non-peritoneal malignancies (the incidence of perforations varies from 0.3% to 3% and the incidence of fistulas

varies from <1% to 1.8% across Avastin studies). The database was queried for any event of perforation, ulcer (excluding oral ulcers), or fistula. There was only one patient (in the EU-approved bevacizumab arm) with a perforation (Grade 4 small intestinal perforation). Duodenal and gastric ulcers were reported in 3 patients (Grade 4 and 2 in two patients in the PF-06439535 arm and Grade 2 in one patient in the EU-approved bevacizumab arm). There was one non-gastrointestinal fistula diagnosed in the PF-06439535 arm (soft tissue, Grade 1).

In summary, the events of perforation or fistula were rare. No clinically significant differences were observed between arms.

Wound healing complications

No wound healing complications were reported during the combination portion of the study. There was a Grade 1 wound abscess reported in one patient in the PF-06439535 arm after Cycle 7 (monotherapy).

Infusion-related reactions/hypersensitivity

The analysis of the database using the “hypersensitivity” SMQ shows 58 (16%) and 76 (21%) patients in the PF-06439535 and EU-approved bevacizumab arms, respectively, as having one event, independent of the attribution to relatedness to any of the study drug components; however, the SMQ included terms that may be a manifestation of an IRR only within a particular timeframe (i.e., a stomatitis at day 7 after infusion is likely related to the impairment in mucosal growth secondary to the use of chemotherapy and not an IRR; hypertension could be related to an infusion, but unless occurring within the first 24-hours it is likely related to the administration of a bevacizumab product). Table 23 summarizes the reported AEs that investigators attributed to an infusion-related reaction, allergies, hypersensitivity or anaphylaxis.

Table 23 - Study B7391003: Infusion-related and hypersensitivity reactions

PT	PF-06439535 N: 356; n (%)	EU-approved bevacizumab N: 358; n (%)
Infusion related reaction	15 (4)	22 (6)
Hypersensitivity	1 (<1)	4 (1)
Infusion site pain	1 (<1)	0
Allergic respiratory symptom	0	2 (1)
Anaphylactic reaction	0	1 (<1)
Infusion site irritation	0	1 (<1)
Infusion site edema	0	1 (<1)

In 8 and 9 patients in the PF-06439535 and EU-approved bevacizumab arm, respectively, the events were considered related to the bevacizumab product. Three events (IRR and anaphylactic reaction) were Grade 3 events, all in the EU-approved arm. The anaphylactic reaction was attributed to paclitaxel.

A broader search looking for all AEs that occurred while treatment was being administered or within the following 24 hours was conducted. One hundred and one (28%) and 103 (29%) patients in the PF-06439535 and EU-approved bevacizumab arm, respectively, experienced an AE in this timeframe during the combination period. Table 24 summarizes the Grade 3-5 events occurring in while the treatment was being infused or within the first 24 hours after infusion.

Table 24 - Study B7391003: Grade 3-5 events occurring in the 24 hours after infusion

PT	PF-06439535 N: 356; n (%)	EU-approved bevacizumab N: 358; n (%)
Hypertension	7 (2)	5 (1)
Asthenia	3 (1)	1 (<1)
Dyspnea	1 (<1)	1 (<1)
Acute myocardial infarction	1 (<1)	0
ALT increased	1 (<1)	0
AST increased	1 (<1)	0
Peripheral artery thrombosis	1 (<1)	0
Anaphylactic reaction*	0	1 (<1)
Fatigue	0	1 (<1)
Flushing	0	1 (<1)
Hypoxia	0	1 (<1)
Lacrimation increased	0	1 (<1)
Nausea	0	1 (<1)
Pulmonary embolism	0	1 (<1)
Respiratory disorder	0	1 (<1)
Tachycardia	0	1 (<1)
Upper respiratory tract infection	0	1 (<1)

* Paclitaxel -related

In the PF-06439535 arm, there was a fatal event of myocardial infarction that started 5 hours after end of infusion and the patient died on Study Day 2. She had a history of coronary disease and chronic heart failure. An autopsy confirmed the cause of death as related to acute myocardial infarction and not disease progression. There were no other fatal events. All other events in the PF-06439535 arm were Grade 3. The only Grade 4 events event (EU-approved bevacizumab arm) was pulmonary embolism.

In the dataset, Pfizer considered infusion-related reactions as a separate category than adverse events (AECAT column); however, when selecting the PT “infusion related reaction” (AEDECOD column), only 3 of 48 events were categorized as such in the AECAT column. In addition, the outcome column “AEOUT”, classified some all fatal events in the combination portion as

“recovered/resolved”. Therefore, Pfizer’s categorization of the event and outcomes were not used for this analysis.

In summary, during the combination treatment period, there were no clinically significant differences in IRR/anaphylactic/hypersensitivity adverse events between arms.

Neutropenia and febrile neutropenia

As per the safety database, during the combination period, 59 (17%) and 68 (19%) patients experienced neutropenia, febrile neutropenia, or any infection with neutropenia. Table 25 summarizes these events.

Table 25 - Study B7391003: Neutropenic AEs (safety dataset)

PT	PF-06439535 N: 356; n (%)		EU-approved bevacizumab N: 358; n (%)	
	All grades	Grade 3-5	All grades	Grade 3-5
Neutropenia	54 (15)	26 (7)	58 (16)	29 (8)
Febrile neutropenia	9 (3)	9 (3)	9 (3)	9 (3)
Neutropenic colitis	0	0	1 (<1)	1 (<1)

The only fatal event was occurred in a 70 y.o. patient in the PF-06439535 arm who experienced Grade 4 febrile neutropenia in Cycle 3; he recovered and received Cycle 4 with no dose modifications. On Study Day 69, he experienced what was initially a Grade 4 febrile neutropenia (ANC 80 cells/mL) and was treated with G-CSF, but died 3 days later in a coma (please note that the database contains three events for this patient, when it should contain only two with the worst grading of 5 for the second event).

As per CTCAE (and these criteria are used in clinical practice to determine treatment, dose reductions, etc.), ANC below the lower limit of normal (LLN) and up to 1500/mm³ is Grade 1; <1500/mm³-1000/mm³ is Grade 2; <1000/mm³ to 500/mm³ is Grade 3 and <500/mm³ is Grade 4. However, Pfizer (Table 14.3.4.1.1 of the CSR) chose to analyze neutropenia using different different cutoffs for neutropenia. In Pfizer’s analysis, of 340 patients in each arm, 72 (21%) and 81 (23%) patients in the PF-06439535 arm and EU-approved bevacizumab arm respectively had counts <0.8 x LLN. As shown in as per the lab dataset, 43 (12%) and 29 (8%) patients in the PF-06439535 and EU-approved bevacizumab arms respectively experienced a Grade 3-4 neutropenia. Although FDA’s analysis is consistent with Pfizer’s analysis as described in Section 12.4.2.1 of the CSR, FDA’s analyses of neutropenia using CTCAE-defined thresholds better describe the incidence and clinical implications of treatment-emergent neutropenia.

5.5.3. Additional Safety Evaluations

Monotherapy period

In both arms, the median number of bevacizumab cycles was 11 (ranging from 1-41 in the PF-06439535 arm and 1-38 in the EU-approved bevacizumab arm). To identify the monotherapy period, AEs were selected if the AEEXM column flagged these events as “monotherapy” (2075 events). However, the dataset AEEXM contains coding errors; for example, there are at least 14 events occurring before Study Day 30 in patients who received more than 1 cycle of combination therapy (these should have been flagged as “combination therapy” and analyzed as such).

Table 26 summarizes the major safety results in the monotherapy period. There were no meaningful differences between arms.

Table 26 - Study B7391003: Summary of safety in the monotherapy period

	PF-06439535 N: 356; n (%)	EU-approved bevacizumab N: 358; n (%)
All grades	203 (57)	202 (56)
Grades 3-4	59 (17)	55 (15)
Deaths	6 (2)	7 (2)
SAEs	21 (6)	26 (7)

Table 27 summarizes the most frequent AEs observed in the monotherapy period. There were no meaningful differences between arms.

Table 27 - Study B7391003: Most frequent AEs (incidence $\geq$ 5%) in the monotherapy period

PT	PF-06439535 N: 356; n (%)	EU-approved bevacizumab N: 358; n (%)
Anemia	40 (11)	24 (7)
AST increased	30 (8)	24 (7)
ALT increased	27 (8)	23 (6)
Fatigue	26 (7)	29 (8)
Hypertension	26 (7)	26 (7)
ALK increased	20 (6)	21 (6)
Proteinuria	23 (6)	23 (6)
Cough	19 (5)	20 (6)
Thrombocytopenia	19 (5)	21 (6)
Neutropenia	17 (5)	16 (4)
Weight decreased	18 (5)	14 (4)
Headache	14 *4)	17 (5)

Laboratory findings

As proteinuria could be a VEGF-related AE, proteinuria and renal function analysis were summarized in Section 7.5.1 and Table 22.

Table 28 Error! Reference source not found.summarizes the worst Grade RBC abnormality throughout treatment; the majority of patients experience some degree of anemia, but only 5% and 6% in the PF-06439535 and EU-approved bevacizumab arms, respectively, experienced a Grade 3 decrease in hemoglobin. These data are supported by the safety AE dataset analysis: anemia (PTs anemia, hemoglobin decreased, or RBC decreased) was reported in 87 (24%) and 97 (27%) patients in the PF-06439535 and EU-approved bevacizumab arms respectively; Grade 3 anemia was reported in 4% and 5% patients in the PF-06439535 and EU-approved bevacizumab arms respectively.

Table 28 - Study B7391003: Worst grade hemoglobin (lab dataset)

	PF-06439535 N: 356; n (%)	EU-approved bevacizumab N: 358; n (%)
Grade 0	49 (14)	34 (9)
Grade 1	200 (56)	220 (61)
Grade 2	88 (25)	84 (23)
Grade 3	19 (5)	20 (6)

Table 29 summarizes the worst Grade platelet count throughout treatment; Grade 3-4 thrombocytopenia was observed in 4% and 5% patients in the PF-06439535 and EU-approved bevacizumab arms, respectively. These data are supported by the analysis of thrombocytopenia reported as an adverse event: 2% and 4% patients in the PF-06439535 and EU-approved bevacizumab arms experienced a Grade 3-4 AE of thrombocytopenia.

Table 29 - Study B7391003: Worst grade platelet count (lab dataset)

	PF-06439535 N: 356; n (%)	EU-approved bevacizumab N: 358; n (%)
Grade 0	169 (47)	168 (47)
Grade 1	150 (42)	160 (44)
Grade 2	23 (6)	11 (3)
Grade 3	11 (3)	11 (3)
Grade 4	3 (1)	8 (2)

The analysis of ANC can be found in Section 7.5.1 and Table 25.
There were no clinically significant differences in blood cell counts between arms.

Liver function was analyzed using the JMP Clinical software and including data throughout treatment (Table 30).

Table 30 - Study B7391003: Liver function (lab dataset)

Liver Lab Test	PF-06439535 N: 356; n (%)	EU-approved bevacizumab N: 358; n (%)
ALT ≥ ULN		
2x ULN	48 (13)	47 (13)
3x ULN	18 (5)	17 (5)
5x ULN	10 (3)	3 (1)
10x ULN	3 (1)	1 (<1)
20x ULN	0	0
AST ≥ ULN		
2x ULN	38 (11)	45 (13)
3x ULN	16 (4)	17 (5)
5x ULN	7 (2)	6 (2)
10x ULN	3 (1)	1 (<1)
20x ULN	1 (<1)	0
ALP ≥ ULN		
2x ULN	29 (8)	33 (9)
3x ULN	12 (3)	14 (4)
5x ULN	1 (<1)	3 (1)
10x ULN	0	2 (1)
20x ULN	0	0
Total bilirubin ≥ ULN		
1.5x ULN	16 (4)	15 (4)
2x ULN	11 (3)	7 (2)
3x ULN	7 (2)	3 (1)

There were no meaningful differences between arms. In 3 and 2 patients in the PF-06439535 and EU-approved bevacizumab arms respectively there was a concomitant elevation of transaminases and bilirubin, but no cases consistent with Hy's Law; ALT/AST were > 5 x ULN in only one patient per arm. These data are consistent with the AE safety database. In the combination period, 33 (9%) and 26 (7%) patients in the PF-06439535 and EU-approved bevacizumab arms, respectively, were reported as having an AE of increased AST/ALT or bilirubin (under the investigation SOC); 5 and 2 patients in the PF-06439535 and EU-approved bevacizumab arms, respectively, experienced a Grade 3 event.

Age

As shown in Table 4Error! Reference source not found., 141 (39%) and 122 (34%) patients in the PF-06439535 and EU-approved bevacizumab arm, respectively, were 65 years of age or

older at the time of study enrollment. All but two in the PF-06439535 arm received treatment. Table 31 summarizes the AEs in patients 65 years of age or older (incidence of at least 5% of all grades AEs and/or at least 2% for Grade 3-4 AEs).

Table 31 - Study B7391003: AEs by PT in patients ≥ 65 y.o.

PT	PF-06439535 N: 139; n (%)		EU-approved bevacizumab N: 122; n (%)	
	All grades	Grade 3-5	All grades	Grade 3-5
Anemia	37 (27)	5 (4)	38 (31)	8 (7)
Nausea	26 (19)	0	25 (20)	1 (1)
Fatigue	27 (19)	5 (4)	16 (13)	2 (2)
Neuropathy peripheral	20 (14)	3 (2)	20 (16)	2 (2)
Thrombocytopenia	19 (14)	3 (2)	19 (16)	3 (2)
Myalgia	20 (14)	2 (1)	12 (10)	0
Diarrhea	18 (13)	0	23 (19)	2 (2)
Neutropenia	16 (12)	10 (7)	29 (24)	17 (14)
Hypertension	16 (12)	8 (6)	24 (20)	13 (11)
Decreased appetite	17 (12)	0	20 (16)	2 (2)
Epistaxis	17 (12)	0	8 (7)	0
Paresthesia	16 (12)	0	8 (7)	0
Constipation	15 (11)	0	13 (11)	0
Asthenia	13 (9)	3 (2)	13 (11)	2 (2)
Peripheral sensory neuropathy	13 (9)	0	13 (11)	2 (2)
Arthralgia	12 (9)	0	11 (9)	1 (1)
Cough	11 (8)	1 (1)	11 (9)	0
Bone pain	10 (7)	1 (1)	8 (7)	0
Polyneuropathy	10 (7)	1 (1)	5 (4)	0
Weight decreased	9 (6)	0	11 (9)	0
Dyspnea	9 (6)	2 (1)	10 (8)	4 (3)
Vomiting	8 (6)	0	10 (8)	0
Headache	7 (5)	2 (1)	8 (7)	1 (1)
ALT increased	7 (5)	2 (1)	4 (3)	0
Hyponatremia	7 (5)	5 (4)	2 (2)	1 (1)
Leukopenia	6 (4)	0	13 (11)	2 (2)
Pain in extremity	5 (4)	1 (1)	10 (8)	0
Insomnia	5 (4)	0	8 (7)	0
Platelet count decreased	6 (4)	1 (1)	9 (7)	2 (2)
Pneumonia	5 (4)	3 (2)	8 (7)	3 (2)
Proteinuria	5 (4)	1 (1)	9 (7)	1 (1)
Stomatitis	6 (4)	0	7 (6)	0

PT	PF-06439535 N: 139; n (%)		EU-approved bevacizumab N: 122; n (%)	
	All grades	Grade 3-5	All grades	Grade 3-5
Febrile neutropenia	5 (4)	5 (4)	6 (5)	6 (5)
Infusion related reaction	3 (2)	0	11 (9)	2 (2)
Rash	3 (2)	0	9 (7)	0
WBC count decreased	2 (1)	1 (1)	9 (7)	6 (5)
ANC decreased	2 (1)	2 (1)	5 (4)	4 (3)

Although between-arm differences in incidence of $\geq 5\%$ were observed for some AEs (i.e., fatigue, paresthesia, and infusion-related reactions were more frequent in the PF-06439535 arm while diarrhea, leukopenia, and rash were more frequent in the EU-approved bevacizumab arm), there was no pattern indicating meaningful differences between arms. There were no meaningful differences in the incidence of Grade 3-4 events. The most important differences between arms in this population were for the incidence of neutropenia (12% vs. 24% in the PF-06439535 and EU-approved bevacizumab arms respectively, with 7% vs. 14% Grade 3-4 events) and hypertension (12% vs. 20% in the PF-06439535 and EU-approved bevacizumab arms respectively, with 6% vs. 11% Grade 3-4 events). However, these differences appear to be random as the total incidence of decreased ANC in the lab dataset was 1% and there was no difference in the incidence of febrile neutropenia between arms. Although in the older population hypertension was more frequently observed in the EU-approved bevacizumab arm, in the overall study there were no differences between arms and the incidence of Grade 3 hypertension was the same in both arms.

Study B7391001 – safety analyses

Pfizer conducted Study B7391001, a double-blind, randomized, single-dose, 3-arm, comparative pharmacokinetic study of PF-06439535, EU-approved bevacizumab, and US-licensed Avastin. The study enrolled 33, 36, and 33 healthy male volunteers in the PF-06439535, EU-approved bevacizumab, and US-licensed Avastin arms, respectively. One subject (in the EU-approved bevacizumab arm) did not receive medication. All other subjects are evaluable for safety.

All subjects were male; median age was 37 (range 22-53), 42.5 (range 21-55), and 39 (range 21-50) years old in the PF-06439535, EU-approved bevacizumab, and US-licensed Avastin arms, respectively. For the purpose of this analysis, only AEs reported between administration of the bevacizumab product and Day 30 after its administration were analyzed.

AEs were reported in 14 (42%), 19 (54%), and 15 (45%) patients in the PF-06439535, EU-approved bevacizumab, and US-licensed Avastin arms respectively. All AEs were of Grade 1-2. There were no SAEs.

Table 32 - Study B7391001: Most frequently reported AEs (in at least 2 patients)

PT	PF-06439535 N: 33	EU-approved bevacizumab; N: 35	US-licensed Avastin N: 33
Headache	2	3	3
Dyspepsia	2	3	1
Diarrhea	2	1	1
Tooth abscess	2	1	0
Upper respiratory tract infection	1	4	2
Myalgia	1	2	2
Rash macular	1	2	0
Hematuria	0	2	0

In summary, the most common AEs reported appear to be unrelated to the administration of bevacizumab products and are balanced between arms. No meaningful differences were observed.

6 Considerations for Extrapolation

The PF-06439535 application contains clinical data from a study in patients with NSCLC (Study B7391003). 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. Pfizer provided sufficient scientific justification for extrapolation addressing the following issues for the tested and extrapolated conditions of use:

Analytical similarity

Pfizer's analytical similarity program included a comparison of PF-06439535, US-licensed Avastin, and EU-approved bevacizumab. The analytical similarity program had two goals:

- To compare the proposed biosimilar product PF-06439535 to US-licensed Avastin to support a demonstration that PF-06439535 is highly similar to US-licensed Avastin.
- To conduct pairwise comparisons of PF-06439535, US-licensed Avastin, and EU-approved bevacizumab to support the analytical portion of the scientific bridge between the three products. The scientific bridge is needed to justify the relevance of the data generated using EU-approved bevacizumab as the comparator in the NSCLC clinical study to support a demonstration of biosimilarity to US-licensed Avastin.

Multiple quality attributes using multiple lots of PF-06439535, the reference product, and EU-approved bevacizumab were evaluated. Functional assays relative to the mechanism of action were analyzed using a statistical approach, and the results passed the statistical equivalence testing. As expected due to the inherent variability of a biologic, some differences in quality attributes were observed between PF-06439535 and US-licensed Avastin; additional assays or studies to assess biological activity known to be influenced by such differences were conducted and no differences in biological activity between products could be observed in the assays.

The CMC review staff agreed with Pfizer that the totality of the analytical similarity data supports a demonstration that PF-06439535 is highly similar to US-licensed Avastin notwithstanding minor differences in clinically inactive components.

Additionally, the pairwise comparisons of PF-06439535, US-licensed Avastin, and EU-approved bevacizumab support the analytical portion of the scientific bridge between the three products needed to justify the relevance of the data generated using EU-approved bevacizumab in the comparative clinical study.

Mechanism of action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 [VEGFR-1] and KDR [VEGFR-2]) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Neutralizing the biological activity of VEGF regresses the vascularization of tumors, normalizes remaining tumor vasculature, and inhibits 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 (Friedman H, 2009; Hurwitz H, 2004; Sandler A., 2006; Escudier B, 2007; Tewari K., 2014). In all conditions of use, tumor expression of VEGF is increased and this expression correlates with high risk features and lower survival. In a study (Hegde P., 2013) evaluating VEGF levels across multiple clinical studies with bevacizumab either alone or in combination with other agents, 1816 samples from patients with mCRC, NSCLC, and mRCC, high VEGF levels in plasma had an adverse prognostic effect on OS, independent of treatment. In a glioblastoma multiforme (GBM) trial, VEGF expression was increased in glioblastoma cells and nuclear VEGF expression correlated with survival (Clara C., 2014). In a cervical cancer study, VEGF expression was found to be increased in adenocarcinoma as compared to squamous cell carcinoma and high VEGF expression was associated with a poorer prognosis (Gaducci A, 2013).²⁰

There are no data supporting a different mechanism of action in any specific condition.

Pharmacokinetics

In addition to the data characterizing the PK profile of bevacizumab included in the Avastin USPI, bevacizumab exhibits a dose proportional and linear PK profile over the studied dose

range (1–20 mg/kg) and similar PK characteristics across CRC, NSCLC, breast cancer, RCC, GBM, and cervical cancer (Avastin USPI; EMA Avastin SmPC; Lu JF, 2008; Han K., 2016).

The PF-06439535 clinical pharmacology program aimed to support the demonstration of no clinically meaningful differences between PF-06439535 and US-licensed Avastin by

- evaluating the single-dose pharmacokinetic similarity between PF-06439535 and US-licensed Avastin.
- establishing the PK portion of the scientific bridge between PF-06439535, US-licensed Avastin, and EU-approved bevacizumab

In Study B7391001, the pairwise comparisons of PF-06439535 vs. EU-approved bevacizumab and EU-approved bevacizumab vs US-Avastin, the geometric mean ratios and their corresponding 90% confidence intervals for all 3 PK endpoints of AUC zero to infinity, AUC zero to t and Cmax again fell within the pre-defined similarity margin of 0.80 to 1.25. Based on the results from Study B7391001, Pfizer and FDA conclude that PK similarity was demonstrated.

Since similar PK was demonstrated between PF-06439535 and US-licensed Avastin, a similar PK profile would be expected for PF-06439535 in patients across the indications being sought for licensure.

Immunogenicity

As summarized in the Avastin USPI, only 14 of 2233 evaluable subjects (0.63%) tested positive for treatment-emergent anti-bevacizumab antibodies as detected by an electrochemiluminescent-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 B7391001 and B7391003 indicate that immunogenicity was low and that treatment of subjects with NSCLC with either PF-06439535 or bevacizumab results in similar rates of ADAs (1.4% and 1.5% in the PF-06439535 and EU-approved bevacizumab arms respectively in Study B7391003).

Safety

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 the indications of use. While the incidence of specific toxicities may differ across the indications (e.g., fistula is more frequent in patients with cervical cancer 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 PF-06439535 in this application. As analyzed in this review, data from Study B7391003 demonstrated that the type and incidence of treatment-emergent adverse events of special interest were similar for PF-06439535 and EU-approved bevacizumab and that there were no meaningful differences between arms. No new safety signals were identified that would be indicative of new toxicities for the approved bevacizumab indications.

To further address the differences in toxicities between indications and the incidence of these same toxicities in Study B7391003, Table 33Error! Reference source not found. compares data from the Warnings and Precautions section in the Avastin USPI with the results of Study B7391003.

Table 33 - Comparison of the toxicities in the W & P Avastin USPI and Study B7391003

Toxicity	Indication	Avastin USPI	Study B7391003	
		bevacizumab arms	PF-06439535	EU-approved bevacizumab
GI perforations	Across	0.3%- 3.2%	0	0.3%
GI fistulas	Across/cervical cancer	< 2% / 8.3%	0	0
Non-GI fistula	Across/cervical cancer	<1% / 1.8%	0.3%	0
Hemorrhage, ≥ Grade 3	Across	1.2% - 4.6%	1.6%	2.5%
ATE, ≥ Grade 3	Across	< 2.6%	1.7%	0.5%
VTE	Cervical cancer	10.6%	2.8%	1.7%
Hypertension*, Grade 3-4	Across	5% - 18%	6%	6%
Proteinuria, Grade 3-4	mCRC	6.5%	0.3%	0.6%
PRES	Across	<0.5%	0	0

GI: gastrointestinal; ATE: arterial thromboembolic events; VTE: venous thromboembolic events; PRES: posterior reversible leukoencephalopathy

* Hypertension grading must be reviewed with caution as the evolution of the CTCAE dictionary coding changed within years.

As summarized in the safety review, in Study B7391003 the incidence of PF-06439535 toxicities were comparable to the incidence of EU-approved bevacizumab toxicities; in addition, these incidences are within the expected incidences described in the Avastin USPI. The highest historical rate of hypertension occurred in patients with RCC, this is an expected finding, as up to 79% of patients with renal cell cancer are diagnosed with hypertension at the time of tumor diagnosis (Stojanovic, 2009). Similarly, based on the mechanism of action, a comparably high rate of hypertension would be expected following treatment with PF-06439535.

In summary, the data submitted for PF-06439535 demonstrates analytical similarity; the mechanism(s) of action of bevacizumab in each condition of use for which licensure is sought is the same; there are no differences in the PK and biodistribution of bevacizumab across different patient populations; there are no immunogenicity differences across patient populations; differences in the incidence of the expected toxicities in each condition of use and patient

population is predictable and PF-06439535 showed a very similar toxicity profile as bevacizumab.

In conclusion, the totality of the data indicates that the extrapolation of biosimilarity to the indications for which Pfizer is seeking licensure is scientifically justified.

7. Labeling Recommendations

7.1. Proper Name

On March 27, 2019, DMEPA found the proposed suffix -bvzr acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to bevacizumab-bvzr.

7.2. Proprietary Name

On September 25, 2018, FDA issued a letter informing Pfizer of the acceptance of the proposed trade name Zirabev. The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Oncology Products 2 (DOP2) concurred with the findings of OPDP's assessment of the proposed name. DMEPA conducted prescription studies and concluded that Zirabev does not overlap with or sound similar to any currently marketed products or any products in the investigational phase.

7.3. Prescription Drug Labeling

In its draft Guidance for Industry "Labeling for Biosimilar products" (2018), FDA recommends that in the biosimilar product labeling, applicants incorporate relevant data and information from the reference product labeling, with appropriate product specific modifications.

The Pfizer's proposed label follows this recommendation. All preclinical and clinical data for the indications being sought are as in the Avastin USPI. Sections 2, 6, and 16 have been revised to reflect PF-06439535-specific information as well as to comply with current labeling practices.

8. Advisory Committee Meeting and Other External Consultations

The data submitted supports the conclusion of no clinically meaningful differences between PF-06439535 and US-licensed Avastin. No advisory committee was held for this application.

9. Pediatrics

On August 11, 2016, FDA issued an agreement letter to Pfizer's Initial Pediatric Study Plan (iPSP) for PF-06439535 requesting a waiver of pediatric studies. The iPSP was subsequently revised to be consistent with the updated label for US-licensed Avastin and FDA agreed with the revisions. The application contains a request for waiver of the requirements for study of PF-06439535 in pediatric patients, which will be granted.

10. Postmarketing Requirements and Commitments

10.1. Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No clinical postmarketing commitments or requirements are planned.

10.2. Recommendations for Postmarket Requirements and Commitments

Not applicable.

11. Appendices

11.1. References

AVASTIN (bevacizumab) Summary of Product Characteristics (SPC), https://www.ema.europa.eu/documents/product-information/avastin-epar-product-information_en.pdf
AVASTIN (bevacizumab) United States Prescribing Information (USPI), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf .
Botrel TE, Clark O, Clark L, Clark L, Paladini L, Faleiros E, et al. Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): systematic review and meta-analysis. Lung Cancer 2011; 74:89-97.
Chen, H. X., Cleck, J. Adverse effects of anticancer agents that target the VEGF pathway N. Nat. Rev. Clin. Oncol. 2009, 6, 465–477

Clara CA, Marie SKN, de Almeida JRW, et al. Angiogenesis and expression of PDGF-C, VEGF, CD105 and HIF-1 alfa in human glioblastoma. <i>Neuropathology</i> . 2014;34:343-52.
Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon α -2a for treatment of metastatic renal cell carcinoma: A randomised, double-blind phase III trial. <i>Lancet</i> . 2007;370(9605):2103–11.
Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. <i>J Clin Oncol</i> . 2009;27(28):4733–40.
Gadducci A, Guerrieri ME, Greco C. Tissue biomarkers as prognostic variables of cervical cancer. <i>Crit Rev Oncol Hematol</i> . 2013;86:104-29
Han K, Peyret T, Marchand M, et al. Population pharmacokinetics of bevacizumab in cancer patients with external validation. <i>Cancer Chemother Pharmacol</i> . 2016;78:341–51.
He K., Chen H., Gwise T. et al. Statistical Considerations in Evaluating a Biosimilar Product in an Oncology Clinical Study. <i>Clin Cancer Res</i> 2016; 22(20); 1–4.
Hegde PS, Jubb AM, Chen D, et al. Predictive impact of circulating vascular endothelial growth factor in four phase III trials evaluating bevacizumab. <i>Clin Cancer Res</i> . 2013;19(4):929-37.
Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. <i>N Engl J Med</i> . 2004;350(23):2335–42.
Izzedine H., Massard C., Spano JP., Goldwasser F., Khayat D. et al. VEGF signaling inhibition-induced proteinuria: Mechanisms, significance and management. <i>Eur. J. of Cancer</i> 2010, 46:439-448
Johnson D, Feherenbacher L., Novotny W., Herbst R., Nemunaitis J., et al. Randomized trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small cell lung cancer. <i>J Clin Oncol</i> 2004, V22: 2184-2191
Lu J-F, Bruno R, Eppler S, et al. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. <i>Cancer Chemother Pharmacol</i> . 2008;62:779-86.
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. <i>Lung Cancer</i> 2012; 76: 362-7.
Nishio M, Horai T, Kunitoh H, Ichinose Y, Nishiwaki Y, Hida T, et al. Randomized, open-label, multicenter phase II study of bevacizumab in combination with carboplatin and paclitaxel in chemotherapy-naïve Japanese patients with advanced or recurrent non squamous non-small cell lung cancer (NSCLC): JO19907. <i>J Clin Oncol</i> 2009; 27(15s) [Suppl. abstr 8036].
Ranpura V., Pulipati B., Chu D., Zhu X., Wu S. Increased Risk of High-Grade Hypertension with Bevacizumab in Cancer Patients: A Meta-Analysis. <i>American J. of Hypertension</i> , 2010 May V23 N5: 460-468
Reck M., von Powel J., Zatloukai P., Ramlau R, Gorbouna V. et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for non-squamous non-small-cell lung cancer: results from a randomised phase III trial (AVAL). <i>Ann Oncol</i> 2010; 21:1804–9.
Robinson E., Khankin E., Karumanchi A. et al. Hypertension Induced by VEGF Signaling

Pathway Inhibition: Mechanisms and Potential Use as a Biomarker. Semin Nephrol 2010 Nov 30(6):591-601
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.
Scappaticci F., Fehrenbacher L., Cartwright T., Hainsworth J., Heim W. et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J. Surg. Oncol 2005, 3:173-80.
Scappaticci F., Skillings J., Holden S., Gerber H., Miller K. et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J. Natl. Cancer Inst. 2007 Aug 15; 99(16):1232-9.
Stojanovic M1, Goldner B, Ivkovic D. Renal cell carcinoma and arterial hypertension. Clin Exp Nephrol. 2009 Aug;13(4):295-9.
Tewari KS, Sill MW, Long HJ, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370(8):734–43

11.2. Financial Disclosure

Pfizer provided financial disclosure information for Studies B7391001, B7391002, and B7391003. Study B7391002 was a small study of a single dose of EU-approved bevacizumab in healthy volunteers to determine the inter-subject PK variability of bevacizumab; data from this study was used to calculate the sample size of Study B7391001 and therefore not described in this review. There were 801 investigators (data submitted in Form 3454) between all three studies; 798 investigators had no financial conflicts. Three investigators were Pfizer's employees working at the Pfizer Clinical Research Unit in Belgium conducting Study B7391002. As Study B7391002 assessed the PK of commercial Avastin and it is not part of the biosimilarity exercise, it is unlikely that a bias was introduced by a financial conflict.

All but three of the 783 investigators in Study B7391003 provided their financial disclosure information and none received honoraria from Pfizer; there were no reported conflicts of interest. Three investigators that participated in the study disclosed the following information:

- Dr. (b) (6), site # (b) (6) received honoraria from Pfizer for 25,806.99 USD (investigator's fee).
 - Dr. (b) (6), site # (b) (6) held 4,000 Pfizer shares for a value of 131,000 USD as of 2/14/2017. Dr. (b) (6) initially disclosed these shares in 2015 (value of 140,040.00 USD).
 - Dr. (b) (6), site # (b) (6): received honoraria from Pfizer for 32,012.96 USD (consultant and other contributions).
- (b) (6) enrolled in each site.

Pfizer states that during the conduct of these trials, including the processing, analyzing and reporting of data, Pfizer has applied procedures designed to minimize the potential of bias in the data, including conducting the studies according to all applicable laws and regulations,

checking with FDA's Debarment list and the Disqualified/Totally Restricted List for Clinical Investigators as well as the Public Health System Administrative Actions Listing, use of an IWRS for the stratified, blinded assignment to treatment arms, scheduling of procedures and assessments at the same fixed intervals for subjects in all treatment arms, double-blind study design, an external Data Monitoring Committee for safety monitoring, audits to clinical sites, etc.

This reviewer agrees that there no conflict of interest that could bias the results of the studies. Adequate safeguards to minimize bias were in place to protect the integrity of the study from financial conflicts of interest.

Financial Disclosure Form – Study B7391003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>801</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>3</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>none</u> Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: <u>none</u> Significant equity interest held by investigator: <u>1</u> Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>801</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation)

		from Applicant)
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11.3. Appendices – Additional Tables

Table 34 – Study B7391003: Schedule of activities

Protocol Activity/Cycle (1 Cycle = 21 days)	Screening	Treatment Period (Combination Therapy) Blinded bevacizumab with Chemotherapy						Treatment Period (monotherapy) Blinded bevacizumab	Treatment Period (monotherapy) Blinded bevacizumab	End of Treatment/ Withdrawals ²⁶
	≤28 Days Prior to Randomization	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	through Cycle 17 (up to week 52)	Cycle 18+ 1 year post randomization ²⁸	
Study Visit Window (days)	-4	0	±4	±4	±4	±4	±4	±4	±4	±7
Pre-treatment Documentation										
Informed Consent ¹	X									
Demography, Medical /Cancer History, mutation status ²	X									
Complete Physical Exam ³	X									
Brief Physical Exam ⁴		X	X	X	X	X	X	X	Per local SOC	X
Vital signs ⁵	X	X	X	X	X	X	X	X	Per local SOC	X
Baseline Signs and Symptoms ⁶		X							Per local SOC	
ECOG Performance Status (Appendix 1)	X	X	X	X	X	X	X	X	Per local SOC	X
Inclusion/Exclusion Criteria ⁷	X									
Laboratory Studies and Tests										
Hematology ⁸	X	X	X	X	X	X	X	X	Per local SOC	X
Blood Chemistry ⁹	X	X	X	X	X	X	X	X	Per local SOC	X
Coagulation ¹⁰	X								Per local SOC	X
Pregnancy Test ¹¹	(X) ¹¹	X	X	X	X	X	X	X	Per local SOC	X
Urinalysis ¹²	X	X	X	X	X	X	X	X	Per local SOC	X

Protocol Activity/Cycle (1 Cycle = 21 days)	Screening	Treatment Period (Combination Therapy) Blinded bevacizumab with Chemotherapy						Treatment Period (monotherapy) Blinded bevacizumab	Treatment Period (monotherapy) Blinded bevacizumab	End of Treatment/ Withdrawals ²⁶
	≤28 Days Prior to Randomization	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	through Cycle 17 (up to week 52)	Cycle 18+ 1 year post randomization ²⁸	
Study Visit Window (days)	-4	0	±4	±4	±4	±4	±4	±4	±4	±7
Serological Tests ¹³	(X)									
Immunogenicity (ADA/NAb) ¹⁴		X	X	X	X		X	X		X
Pharmacokinetics ¹⁵		X	X	X	X	X	X	X		X
Tumor Assessments										
Brain scan ¹⁶	X	As clinically indicated and at time of confirmatory scan for PR/CR							Per local SOC	
CT or MRI of Chest, Abdomen, and other disease sites, ¹⁶	X	every 6 weeks (±7 days) until Week 25 (based on date of randomization); After Week 25, every 9 weeks (±7 days) until 1 year from randomization							Per local SOC	X
Randomization										
Randomization ¹⁷		X								
Drug Administration										
Paclitaxel and Carboplatin ¹⁸		X	X	X	X	Optional	Optional			
Blinded Bevacizumab ¹⁹		X	X	X	X	X	X	X	X	
Other Clinical Assessments										
12-lead ECG ²⁰	X									X
MUGA or ECHO ²¹	X									X
Contraception check ²²	X	X	X	X	X	X	X	X	Per local SOC	X
Adverse Events ²³	X	Monitored continuously								
Prior Medications/Treatments ²⁴	X									
Concomitant Treatments ²⁵		Monitored continuously								
Survival Follow-up ²⁷		Every 2 months (±14 days) from last study drug administration								

by local approved laboratories, and the results must be reviewed and confirmed as negative for mutations prior to randomization.	
3. Physical Examination:	includes head, ears, eyes, nose, mouth, skin, neck, heart and lung examinations, lymph nodes, abdomen, musculoskeletal, neurological systems, and weight. Height will be recorded at Screening only. Genitourinary examination is only required if directed by signs or symptoms.
4. Brief Physical Examination:	performed as directed by signs and symptoms on Day 1 (pre-dose) of each cycle after Screening.
5. Vital Signs:	Temperature should be taken using the same method throughout the study. Blood pressure, heart rate, and respiratory rate should be taken with the patient in the supine or sitting position after the patient has been resting quietly for at least 5 minutes and prior to dosing on dosing days. Weight should be taken at the beginning of each cycle and will be used for dose calculation in accordance with Section 5.4.1. On days of an infusion, vital signs should be taken within 30 minutes before the first infusion and within 30 minutes of the end of the last infusion.
6. Baseline Signs and Symptoms:	observed after Screening and before Cycle 1, Day 1 pre-dose are recorded as part of Medical History or as Brief Physical Exam findings.
7. Inclusion/Exclusion Criteria:	Eligibility criteria are to be reviewed to confirm eligibility prior to randomization.
8. Hematology:	Tests include hemoglobin, white blood cells, platelets, and absolute neutrophil count. Results of tests must be reviewed prior to each cycle of therapy.
9. Chemistry:	Tests include ALT, AST, alkaline phosphatase, total bilirubin, serum or plasma creatinine, sodium, potassium, total calcium, BUN or urea, magnesium, and albumin, and results must be reviewed prior to each cycle of therapy.
10. Coagulation:	Tests include International Normalized Ratio (INR) for prothrombin time (or prothrombin time if INR is not available) and activated partial thromboplastin time. Tests may be performed more frequently if clinically indicated. Results of tests must be reviewed prior to dosing on Cycle 1 Day 1.
11. Pregnancy Test:	For female patients of childbearing potential, a serum or urine pregnancy test with sensitivity of at least 25 mIU/mL will be performed by the local certified laboratory, and 2 negative tests are required before receiving the first dose of investigational product. The second negative test should be done during the first 5 days of the menstrual period, immediately preceding the first dose of any study treatment. See protocol Section 7.4 for details.
12. Urinalysis:	If the results of the dipstick urine protein indicate $\geq 2+$ proteinuria, follow-up should be performed with a quantitative urine protein analysis according to local standard practices with data captured on the AE CRF if AE criteria are met. The results of the dipstick must be reviewed prior to each cycle of therapy.
13. Serological tests (optional):	See Exclusion criterion #21 for specifications. If testing is performed, samples must be tested by local approved laboratories, and the results must be reviewed and eligibility confirmed prior to randomization.
14. Immunogenicity:	Blood Sampling for ADA/NAb prior to blinded bevacizumab. If adverse events are considered possibly related to ADA formation, an additional sample may be collected at the time of the immunogenicity-related adverse events.
15. PKs:	Blood Sampling for Drug Concentration prior to blinded bevacizumab. Post-dose samples will also be collected at 1 hour (± 0.5 hour) after the end of blinded bevacizumab for Cycles 1 and 5 (if patient received Cycle 5). If ADA/NAb sampling is conducted at the time of immunogenicity-related adverse events, a serum sample for drug concentration will also be collected at that sametime point.
16. Tumor Assessments:	Assessments must include CT with contrast or MRI of head, chest, abdomen (including adrenals) and other disease sites such as pelvis if clinically indicated. Tumor assessments are NOT to be scheduled based on cycle length or number of cycles received. Assessment delay to conform to treatment delays is not permitted. The same method of tumor assessments should be used throughout the trial. A confirmatory scan is required approximately 6 weeks (± 7 days) for a CR/PR.
17. Randomization:	Unless clinically indicated, screening physical examination and laboratory assessments including blood chemistry, hematology, and urinalysis, are not required to be repeated for randomization if they are performed ≤ 7 days prior to Cycle 1, Day 1, and results meet eligibility criteria. Eligibility criteria are to be reviewed and sponsor confirmation of eligibility must be received prior to randomization. Randomization is required on day 1 of first dose (but no more than 1 day prior).
18. Paclitaxel and carboplatin administration:	per dosing algorithm in protocol for a total of at least 4 and no more than 6 cycles. Premedication are to be administered according to the local label or institutional guidelines. Dose delay (up to 2 weeks) and dose reduction will be permitted per local guidelines. See protocol Section 5.4.4 for details.
19. Blinded Bevacizumab:	15 mg/kg by intravenous (IV) infusion on Day 1 of each of the 3-week (21-day) cycles, see See protocol Section 5.4.2 for details
20. ECG:	12-lead ECG will be obtained at Screening, as clinically indicated, and at the End-of-Treatment Visit.
21. MUGA or ECHO:	to assess LVEF (Left ventricular ejection fraction); the original methodology used for each patient must be used throughout the trial.
22. Contraception Check:	Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. See protocol Section 4.4.1 for details.
23. Adverse Events:	Patients must be followed for adverse events from the first day of study treatment through the patient's last visit and at least 28 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later as assessed by the investigator. Serious adverse events should be monitored and reported from the time that the patient provides informed consent, as described in the protocol, through and including 28 calendar days after the last study treatment. Serious adverse events considered related to study treatments are to be reported whenever they occur even after 28 days after the last study treatment.
24. Prior Medication/ Treatments:	Medications and non-drug treatments delivered prior to initial dosing will be recorded from 28 days prior to the start of study treatment.
25. Concomitant Treatments:	recorded from initial dosing and monitored continuously by the investigator until at least 28 days following the last dose of study treatment to coincide with the safety evaluation period. Patients discontinuing the active treatment phase will enter the follow-up phase during which survival and new anti-cancer therapy information will be collected until the study is completed or is terminated early.
26. End-of-Treatment/Withdrawals:	When patients discontinue all study treatment, patients should be evaluated 28 (± 7) days after last dose or prior to the start of new anti-cancer therapy if initiated within 28 days after the last dose.
27. Survival Follow-up:	After discontinuation from treatment, survival status will be collected by telephone contact every 2 months (± 14 days) until death or 1 year from patient randomization.
28. 1 year post-randomization:	Patients who continue to receive study treatment after one year will have assessments performed according to local standard of care (SOC); reduced data collection, although tumor assessment and safety data collection are required.

Table 35 - Study B7391003: Protocol violations

Category - class	Violation	PF-06439535	EU-approved bevacizumab
Prohibited concomitant meds		1	0
Inclusion criteria	Male contraception	15	11
	Prior chemotherapy for metastatic disease	0	1

Category - class	Violation	PF-06439535	EU-approved bevacizumab
	Recurrent disease $\leq$ 6 months	1	0
	Labs or scans $\geq$ 28 days prior to randomization	11	8
	Unhealed wound or bone fracture	1	0
	Infection	0	1
Exclusion criteria	Known CNS metastases	6	3
	Uncontrolled cardiac disease	0	1
	Contraception	3	1
	Tumor compressing/invading major blood vessels	1	0
	Immunocompromised patients	0	1
	Participation in other clinical studies involving investigational drug(s)	2	1
	Sensitizing EGFR mutations	3	2
	Local radiation for bone metastasis in last 4 weeks	1	0
	Hemoptysis, severe bleeding in last 3 months; thrombotic or bleeding disorders; systemic/therapeutic anticoagulation	5	5
	Medically uncontrolled hypertension	1	1
ICD	ICD not dated	0	1
	ICD not signed by Investigator	1	1
	Various	45	34
	Study procedure prior to consent	5	7
	Verbal consent only	0	1
Investigational product	Blind broken	1	2
	Dose modification error	1	9
	Dosing administration deviation	9	1
	Drug administered outside window	42	39
	Infusion duration times	95	103
	Dosing calculation deviation $<$ 10% deviation (over/under) from intended dose of any drug	56	69

Category - class	Violation	PF-06439535	EU-approved bevacizumab
	Dosing calculation deviation > 20% (over/under) from intended dose of any drug	8	14
	Dosing calculation deviation $\geq 10\%$ - $\leq 20\%$ deviation (over/under) from intended dose of any drug	48	41
	Investigational product storage/preparation	32	27
	Lack of chemotherapy	3	4
	Lack of IP / comparator	4	4
	Regimen order not followed per protocol	9	8
Labs	Lab kit/lab reagents unavailable to collect samples	33	36
	Lab partially done	191	161
	Laboratory performed according to local practice and not per protocol	17	23
	Labs lost by courier	1	0
	Labs not done - PK/ADA/Nab	103	102
	Labs not done - Pregnancy test	5	0
	Labs not done - Proteinuria	3	0
	Labs not done – Safety	35	38
	Screening Lab > 7 days old used for randomization	1	3
	Labs not done - Urinalysis	34	26
	Labs performed out of window	20	19
	PK samples collected > 6 hours	62	54
	Other	38	24
Lack of compliance with contraception or checks to be performed at each visit		9	15
Procedures/ tests	Deviation from RECIST criteria	2	3
	Performed outside window	20	18
	Performed outside window - Disease assessments	99	97
	Performed outside window - Vital signs	144	164
	Procedure incomplete	66	63
	Procedure Not Done	3	6

Category - class	Violation	PF-06439535	EU-approved bevacizumab
	Procedure Not Done - ECG	35	22
	Procedure Not Done - ECHO/MUGA	45	40
	Procedure Not done - ECOG	1	2
	Procedure Not Done - Physical Exam	15	7
	Procedure Not Done - Post Baseline disease assessment	39	42
	Procedure Not Done - Vital Signs	24	20
	Other	18	15
Discontinuation criteria	Patient not withdrawn as per protocol.	9	10
Randomization	Incorrect medication /mis-randomization stratification factors incorrect in IMPALA	1	4
	Randomized but not dosed	0	2
Safety reporting	SAE reported late	16	11
Visit schedule	Visit incomplete	1	1
	Visit not done	39	28
	Visit outside protocol window	176	155

Table 36 - Study B7391003: Medication errors (safety dataset analysis)

AEDECOD	PF-06439535	EU-approved bevacizumab
Dose calculation error	17	8
Drug administration error	2	0
Drug dispensing error	1	0
Extravasation	0	1
Inappropriate schedule of drug administration	3	1
Incorrect dose administered	0	5
Incorrect drug administration duration	3	2
Incorrect drug administration rate	1	2
Overdose	14	8
Prescribed overdose	1	0
Prescribed underdose	1	0
Product availability issue	1	0
Underdose	6	6

AEDECOD	PF-06439535	EU-approved bevacizumab
Wrong dose	1	0
Wrong schedule	1	3
Total	52	36

Table 37 - Study B7391003: Summary of response at Week-19 confirmed per applicant's derivation (PP analysis set)

	PF-06439535 N=351	EU-approved bevacizumab N=355
Response at week-19 confirmed, n (%)		
Complete remission (CR)	8 (2)	3 (1)
Partial remission (PR)	153 (44)	157 (44)
Stable disease (SD)	153 (44)	166 (47)
Progressive disease (PD)	14 (4)	13 (4)
Not evaluable (NE)	23 (6)	16 (4)
ORR (CR+PR), % (95% CI)	45.9 (40.6, 51.2)	45.1 (39.8, 50.4)
Treatment comparison (Beva-Pfizer vs -EU)		
Un-stratified ORR risk ratio	0.98	
(90% CI)	(0.86, 1.13)	
Stratified ORR risk ratio	1.03	
(90% CI)	(0.90, 1.17)	

Source: FDA review

Table 38 – Study B7391003: Summary of response at Week-19 confirmed per investigator-assessment (PP analysis set)

	PF-06439535 N=351	EU-approved bevacizumab N=355
Response at week-19 confirmed, n (%)		
Complete remission (CR)	8 (2)	3 (1)
Partial remission (PR)	154 (44)	158 (44)
Stable disease (SD)	154 (44)	166 (47)
Progressive disease (PD)	14 (4)	13 (4)
Not evaluable (NE)	21 (6)	15 (4)
ORR (CR+PR), % (95% CI)	46.2 (40.9, 51.5)	45.4 (40.1, 50.7)
Treatment comparison (Beva-Pfizer vs -EU)		
Un-stratified ORR risk ratio	0.98	

(90% CI)	(0.86, 1.12)
Stratified ORR risk ratio	1.03
(90% CI)	(0.90, 1.18)

Source: FDA review

11.4. Appendix - Study B7391003: Definition and Censoring Rules for Secondary Endpoints

Definitions

DOR was defined as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of PD or to death due to any cause in the absence of documented PD.

PFS was defined as the time from date of randomization to first progression of disease or death due to any cause, whichever occurred first.

Survival (time to death) was defined as the time from date of randomization to death due to any causes.

Censoring Rules:

The DOR endpoint will be censored based on the following algorithms:

- If a Patients last known, 1) to be alive, 2) not to have started new (non-protocol) anti-cancer treatment, and 3) to be progression-free, and who have a baseline and at least one on-study disease assessment, are censored at the date of the last objective disease assessment that verified lack of progressive disease (even if there is unacceptably long interval between the assessments).
- If no assessment of tumor progression is identified by the investigator assessment and the patient does not die, the endpoint will be censored on the date of the last available tumor assessment.
- If radiotherapy or surgery is used to manage any target lesion or the patient starts a new anti-cancer therapy prior to the documented PD, the endpoint will be censored on the date of the last available tumor assessment prior to the start of the new anti-cancer therapy.

The PFS endpoint will be censored based on the following algorithms:

- If a Patients last known, 1) to be alive, 2) not to have started new (non-protocol) anti-cancer treatment, and 3) to be progression-free, and who have a baseline and at

least one on-study disease assessment, are censored at the date of the last objective disease assessment that verified lack of disease progression (even if there is unacceptably long interval between the assessments).

- If no assessment of tumor progression is identified by the investigator assessment and the patient does not die, the endpoint will be censored on the date of the last available tumor assessment.
- If no evaluation of disease is performed after randomization, the endpoint will be censored on the date of randomization with duration of 1 day. (If patient died prior to the first scheduled disease assessment, death will be considered as an event).
- If radiotherapy or surgery is used to manage any target lesion or the patient starts a new anti-cancer therapy prior to the documented PD, the endpoint will be censored on the date of the last available tumor assessment prior to the start of the new therapy.
- Patients with documentation of progression or death after an unacceptably long interval (> 14 weeks) since the last tumor assessment will be censored at the time of last objective assessment verifying lack of disease progression prior to the event.
- If no adequate disease assessment at baseline, the endpoint will be censored on the date of randomization with duration of 1 day.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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