13 December 2018
EMA/97237/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zirabev

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/004697/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Ab	Antibody
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse events of special interest
ALK	Anaplastic lymphoma receptor tyrosine kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATE	Arterial thromboembolic events
AUC	Area under the curve
AUC_T	Area under the serum concentration time profile from time 0 to the time of the last quantifiable concentration
AUC0-∞	AUC measured from the time of dosing and extrapolated to infinity
BOR	Best overall response
CNS	Central nervous system
CI	Confidence interval
Cmax	Measured maximum serum concentration after administration
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Observed pre-dose trough serum drug concentration
CV%	Coefficient of variation as percentage
DOR	Duration of response
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
eNCA	Electronic noncompartmental analysis
EOS	End of Study
EOT	End of treatment
GLP	Good Laboratory Practice
GM	Geometric mean
ITT	Intent-to-Treat
IV	Intravenous/intravenously
MAA	Marketing Authorisation Application
MoA	Mechanism of action
NAb	Neutralizing antibody
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package leaflet
PP	Per protocol
PR	Partial response
RD	Risk difference
RECIST	Response evaluation criteria in solid tumours
RR	Risk ratio
SAE	Serious adverse event
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System organ class

$t_{½}$	Terminal half-life
T_{max}	The time point when C_{max} occurred
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic
VEGF	Vascular endothelial growth factor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 1 February 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Zirabev, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Zirabev in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.

Zirabev in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status, please refer to section 5.1.

Zirabev, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.

Zirabev in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer.

Zirabev in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see Section 5.1).

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant indicated the active substance bevacizumab contained in the above medicinal product to be considered as a known active substance.

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	Date	Area
EMA/CHMP/SAWP/430458/2014	24 July 2014	the SA pertained to non-clinical, clinical
EMA/CHMP/SAWP/238092/2015	24 April 2015	the SA pertained to non-clinical, clinical
EMA/CHMP/SAWP/667247/2015	22 October 2015	the SA pertained to non-clinical, clinical

1.1. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bjorg Bolstad Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	1 February 2018
The procedure started on	1 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	22 May 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	22 May 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	5 June 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 June 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 September 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	22 October 2018

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	15 November 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 November 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	28 December 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zirabev on	13 December 2018

2. Scientific discussion

About the product

Zirabev (PF-06439535) is a recombinant humanised immunoglobulin G1 kappa (IgG1k) monoclonal antibody (mAb). PF-06439535 is composed of 2 heavy chains (gamma 1) and 2 light chains (kappa), linked by disulfide bonds and has the same primary amino acid sequence as bevacizumab-EU. PF-06439535 is produced by recombinant technology in a Chinese hamster ovary (CHO) cell line.

Type of Application and aspects on development

This application concerns a centralised procedure for marketing authorisation of Zirabev (PF-06439535) bevacizumab concentrate for solution for infusion for intravenous administration of 25 mg/mL, as a biosimilar product to the European reference product Avastin (EU/1/04/300/001-002).

The development programme is in general compliance with CHMP guidance/scientific advice.

Non-clinical

In a formal scientific advice from 2015, the CHMP agreed that the proposed preclinical and pharmacological similarity approach seemed to be sufficient to evaluate preclinical and pharmacological similarity of the biosimilar compared to the reference product, and adequate to permit submission and review of a Bevacizumab (PF-06439535) MAA for Zirabev as a proposed biosimilar to Avastin.

The two studies performed in animals were conducted in accordance with Good Laboratory Practice (GLP) Regulations.

Clinical

Formal scientific advice(s) given by EMA for this medicinal product:

- EMA/CHMP/SAWP/430458/2014, 27.07.2014
  Initial advice on the data generated to date and the proposed phase 3 development
- EMA/CHMP/SAWP/238092/2015, 24.04.2015
  EMA/CHMP/SAWP/667247/2015, 22.10.2015 (follow-up)
  Feedback on statistical aspects of design and sample analysis for immunogenicity assessment

Scientific advice(s) given by Member State(s) for this medicinal product:

Presenting the overall development program and seek advice on the clinical data filing strategy and dossier development

- Denmark, 16.09.2016
- Finland, 19.09.2016
- Austria, 21.09.2016

2.1. Quality aspects

2.1.1. Introduction

Zirabev is presented as a similar biological application to the reference medicinal product Avastin.

The finished product (FP) is presented as a concentrate for solution for infusion containing 25 mg/ml of bevacizumab as active substance (AS).

Other ingredients are sucrose, succinic acid, disodium edetate, polysorbate 80, sodium hydroxide (for pH adjustment) and water for injections.

The product is available as a 4 ml or 16 ml solution in a vial (Type I glass) with a stopper (butyl rubber) containing 100 mg of bevacizumab or 400 mg of bevacizumab, respectively. The finished product comes in a pack size of 1 vial.

Prior to administration the concentrate for solution for infusion should be diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection to a concentration of the final bevacizumab solution between 1.4 mg/ml to 16.5 mg/ml.

2.1.2. Active Substance

General information

Bevacizumab (also referred to as PF-06439535 by the Applicant) is a humanised IgG1κ mAb with two identical heavy chains (HC) and two identical light chains (LC), covalently linked with four inter-chain disulphide bonds. The monoclonal antibody (mAb) is produced in a Chinese Hamster Ovary (CHO) cell line, the same cell line used for manufacturing of the reference product Avastin. The confirmed amino acid sequence, the molecular mass (theoretical and experimental) for the deglycosylated molecule and experimental molecular mass including glycosylation, the molecular formula of the light and heavy chains of PF-06439535 number of cysteines, the number of intra and inter disulphide bonds and the general properties are provided.

The N-linked glycosylation consensus sequence in the CH2 region is essentially fully occupied with asialo, core-fucosylated, complex-type biantennary oligosaccharides, predominately with structures containing zero and one terminal galactose residues. The molecular mass is approximately 149 kilodaltons (kDa).

Manufacture, characterisation and process controls

Bevacizumab active substance (AS) is manufactured according to current Good Manufacturing Practices (GMP) at Wyeth BioPharma Division, One Burtt Road, Andover, MA 01810, USA. The site is covered by a valid GMP certificate.

Description of the manufacturing process and process controls

The manufacturing process of the AS has been well described by the Applicant.

The manufacturing process for PF-06439535 active substance uses a recombinant CHO cell line. Cells are grown in suspension culture using chemically-defined (CD), animal-derived component-free (ACF) media. The main steps of the manufacturing process are cell culture, recovery and purification. The process begins with the thawing of cells from the working cell bank (WCB) followed by expansion. The purification of PF-06439535 comprises several chromatography steps and orthogonal dedicated virus clearance steps.

The cell culture process starts with the thawing of a working cell bank (WCB) vial which is progressively expanded. During culture expansion and maintenance critical process parameters and critical material attributes are identified and justified with acceptable ranges (alert and termination limits). Inoculum culture from a seed bioreactor is added to production medium in the production bioreactor to a pre-defined target seed density. The production bioreactor culture is harvested and clarified by centrifugation and depth filtration to remove cells and debris. After this harvest step, the product is purified by an affinity chromatography step, a virus inactivation step, and ion exchange chromatography steps. The product is then processed through a virus retaining filter (VRF) followed by concentration and solution exchange in an ultrafiltration/diafiltration (UF/DF) step. Lastly, the excipients are added to the product to achieve the final formulation of active substance, followed by final filtration and freezing.

The process controls include a combination of critical process parameters (CPP), non-critical process parameters (non-CPP), critical material attributes (CMA), and in-process tests. The filtered PF-06439535 active substance is filled into a suitable container closure system, labelled, frozen, and shipped frozen to the finished product manufacturing site.

Control of materials

Raw materials are sufficiently described and controlled.

With the exception of CloneDetect (Human IgG (H+L) Specific, Fluorescein-conjugated) derived from sheep and used in the development of the recombinant cell line, no materials of animal or human origin are used during the production of the active substance.

The fermentation growth medium is a proprietary dry powder medium. It is a protein-free, chemically-defined medium and contains no proteins or peptide components of animal or plant origin and no undefined lysates or hydrolysates.

The details regarding the origin of materials, pharmacopoeial reference or internal specification, and the stage of the manufacturing process, where the material is used, are provided.

Details on the coding sequence and generation of the expression vector to code for bevacizumab amino acid sequence have been provided and are consistent with Pfizer-generated mass spectrometry and biochemical data for the reference product bevacizumab-US and bevacizumab-EU.

A two-tiered cell banking system, consisting of a master cell bank (MCB) and a working cell bank (WCB), was established for commercial production. The MCB and WCB were characterised according to ICH requirements, e.g. Q5A (R1), Q5B and Q5D. The adventitious agents assays test results indicate that the cell bank is sterile and free of detectable mycoplasma and viruses. During routine production, cell culture age is controlled to less than the limit of in vitro cell age (LIVCA). The provided data support the proposed PF-06439535 LIVCA. The LIVCA is supported by several assays demonstrating phenotypic and genotypic stability. Data have been provided to indicate that the cell line is robust with respect to critical parameters. MCB and WCB stability under the defined storage conditions will be monitored. All newly prepared WCBs will also be manufactured in accordance with a pre-specified protocol and cGMP guideline and qualified, complying with ICH Q5D and Q5A (R1). The protocol for establishment of a new WCB is provided. If the protocol to establish a new WCB differs from the current protocol, a variation procedure shall be submitted.

Control of critical steps and intermediates

The Applicant has presented critical and non-critical quality attributes (QAs) of bevacizumab, their relevance to the similarity assessment, and the justification for the criticality and similarity assignment. For QAs that have been ranked as CQAs, most are controlled through release and stability testing. The in-process controls including process parameters and material attributes with ranges and in-process tests with control limits have also been provided.

The PF-06439535 manufacturing process is built upon the Applicant's CHO cell-derived mAb platform process. Principles outlined in ICH Q8-ICH Q11 are applied. The control strategy was defined using a holistic approach. The understanding of the PF-06439535 manufacturing process has been obtained by performing manufacturing-scale runs and process characterisation studies, including design of experiments (DOE) studies, and by using scale-down models of individual unit operations. In alignment with ICH Q10, quality systems are in place to support continuous quality/process verification and change management post approval.

Process validation

The validation of the PF-06439535 active substance manufacturing process included three process performance qualification (PPQ) batches from three independent consecutive thaws of the WCB. Process parameters (inputs) were maintained within pre-defined limits. The process validation was demonstrated by meeting pre-determined acceptance criteria for product quality and performance parameters.

Process validation was conducted on a number of consecutive batches from consecutive thaws of the WCB. Manufacturing-scale runs and process characterisation studies were performed, which include DOE studies using scale-down models of individual unit operations representative of the commercial process and univariate and multivariate experiments.

All process validation batches met acceptance criteria and conform to the commercial specifications. In addition, process parameter and in-process test data from the process validation campaign are within committed control limits for the commercial process. Process validation results demonstrate control, effectiveness and consistency of the AS manufacturing process.

The final container closure system has been appropriately validated. The two sizes of container were considered during the process validation studies and process manufacture development studies. Container integrity is confirmed visually at the time of use.

Manufacturing process development

Only minor modifications were made during the process development history, and all batches used for nonclinical and clinical studies were manufactured at the intended commercial launch site using the intended commercial process. Some process parameters were tightened as the program progressed to process validation to optimize process performance and consistency, while remaining within prior established target ranges. Overall, the process changes have no significant impact on process performance or product.

In order to reduce the sparger clogging, which was observed during the development phase of the process a different sparger configuration and a new impeller configuration was used thereafter.

Characterisation

All characterisation and elucidation studies were conducted on PF-06439535 manufactured by the commercial manufacturing process. The analytical techniques and methodologies applied to the characterisation of PF-06439535 are capable of evaluating primary structure, molecular mass, posttranslational modifications, charge and size heterogeneity, extinction coefficient, higher order structure, aggregation and fragmentation, biological activity and degradation pathways. The results demonstrated that PF-06439535 has the expected structure and functional properties.

Specification

Adequate active substance specifications have been provided. The list of test parameters for the active substance specification includes tests of identity, purity and impurities, potency and other general tests. The acceptance criteria are applicable to batch release and end of shelf-life unless specified.

In-house method numbers for the analytical procedures used for active substance release are specified in the dossier. Stated impurities have been studied in non-clinical studies.

Analytical methods

The analytical methods used for active substance testing have been described in detail. The majority of analytical procedures are common to both AS and FP. Compendial analytical procedures used for batch release and stability studies are clarity, coloration, pH, bioburden and endotoxin. Non-compendial analytical procedures used for batch release and stability studies were demonstrated to be suitable for the intended use.

The validation of the analytical methods was described in detail. The results are deemed sufficient and acceptable and the methods are considered appropriately validated.

Batch analysis

Batch data from several PF-06439535 active substance batches which demonstrate that manufacturing generates a consistent active substance have been provided. All batches comply with the commercial acceptance criteria with the exception of colouration since the colour standard was only specified for appearance testing for the process validation batches.

Reference standard

The reference standard used for analysis of finished product is the same as that used for active substance. PF-06439535 reference standards were generated as follows: a clinical reference material, primary reference material (PRM) and a working reference material (WRM). A two tiered system for in-house PF-06439535 reference material has been implemented to support the commercial product. The existing primary reference

material (PRM) and working reference material (WRM) have been suitably manufactured and characterised for their purpose.

A protocol for the qualification of future reference standard is provided, which is acceptable.

Stability

A suitable shelf life is proposed for active substance stored at the intended storage conditions. This shelf life claim is based on an ICH compliant stability programme, including long term and accelerated conditions and under stressed conditions (thermal stress and photostability stress). Based on the data presented, the proposed active substance shelf life is supported. The proposed stability protocol containing adequate stability-indicating test parameters is considered appropriate.

2.1.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as a liquid concentrate for solution for infusion as a 100 mg/4 mL presentation and a 400 mg/16 mL presentation.

Zirabev finished product, 100 mg/4 mL presentation, is supplied in a 5 mL Type I clear glass vial sealed with a stopper and an aluminum seal with flip-off plastic cap. To ensure that a 4 mL nominal volume can be withdrawn from the vial, there is an overfill of approximately 0.3 mL.

Zirabev finished product, 400 mg/16 mL presentation, is supplied in a 20 mL Type I clear glass vial sealed with a stopper and an aluminum seal with flip-off plastic cap. To ensure that a 16 mL nominal volume can be withdrawn from the vial, there is an overfill of approximately 0.5 mL.

For both presentations there is no manufacturing overage. The two presentations are comparable and representative of one another in that the AS and formulated bulk FP used to make the Zirabev are identical for the two presentations.

Zirabev finished product is formulated in succinate (buffer), sucrose (tonicifier), edetate disodium dihydrate (EDTA) (chelator), polysorbate 80 (surfactant), and water for injections (solvent) pH 5.5. The selected formulation for PF-06439535 is different from the licensed bevacizumab.

Pharmaceutical development

The formulation development program for Zirabev evaluated the effects of buffer type, pH and excipient selection on the chemical and physical stability of the active molecule. The composition of the final formulation is different from the reference product.

There are two presentations for Zirabev intended to match the presentations in markets where the corresponding presentation of the Avastin licensed product is registered: 100 mg and 400 mg single-dose vials (100 mg/4 mL and 400 mg/16 mL). The formulation composition has remained the same throughout development. Only the 400 mg Zirabev presentation was used in clinical studies. Zirabev has been manufactured at the intended commercial manufacturing facility for the entirety of the clinical development program. No significant changes have been made to the overall process for Zirabev manufacturing throughout the product history.

Manufacture of the product and process controls

Zirabev 400 mg/16 mL and 100 mg/4 mL (both 25 mg/mL) presentations are manufactured using the same process steps and controls. The only differences between the presentations are the fill volume and the container closure system. All other manufacturing steps and process parameters are the same.

The batch formula for Zirabev presentations 400 mg/16 mL and 100 mg/4 mL consists of the same bulk Zirabev formulation including 25 mg/mL PF-06439535, 85 mg/mL sucrose, 0.05 mg/mL edetate disodium dihydrate (EDTA), 0.2 mg/mL polysorbate 80, in 20 mM succinate buffer at pH 5.5.

Frozen PF-06439535 active substance is shipped in appropriate containers. The active substance is thawed and transferred to a manufacturing vessel. Dilution buffer is prepared and the active substance is diluted with the buffer to the target protein concentration. The bulk finished product is then sterile filtered, aseptically filled into vials, stoppered and capped with a crimp seal. Following the capping operation, the vials are visually inspected.

Validation

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Process controls with their control limits for the finished product manufacturing process have been provided and are acceptable.

Sufficient information is provided on filter validation and shipping validation.

There is no excipient of human or animal origin and no novel excipient. An adequate elemental impurities risk assessment is presented in accordance with ICH Q3D.

Product specification

The list of test parameters for the finished product specification contains tests for control of identity, purity and impurities, potency and other general tests. The acceptance criteria are applicable from lot release to end of shelf-life. The specification for the finished product release has been set in accordance with Ph. Eur. Requirements and ICH Q6B.

Reference standard

The reference standard used for analysis of Zirabev FP is the same as that used for the AS.

Batch analysis

Batch analysis data are presented for FP lots for both presentations 100 mg and 400 mg used for clinical trials, stability and process validation. The results demonstrate consistency of the manufacturing process capabilities. All lots comply with the commercial acceptance criteria.

Stability of the product

The proposed shelf-life for the unopened vial is 3 years when stored at the recommended temperature of 2 – 8 °C. The FP should not be frozen and the vial should be kept in the outer carton in order to protect from light. The stability program followed the relevant ICH guidelines for stability of the finished product and data is provided for both 100mg/4mL and 400mg/16mL presentations.

Stability data were provided for primary and supportive FP batches for both 100mg/4mL and 400mg/16mL presentations stored under the recommended long term conditions of 5 ± 3 °C, the accelerated condition of 25

± 2 °C/60 ± 5% relative humidity (RH). In addition data from thermal stress and photostability conditions were included. Additional long term stability data are provided for FP batches, which is considered representative and support the 3-year shelf-life at 2°C - 8°C.

Based on the stability results an appropriate recommendation is made in the SPC.

Zirabev FP is formulated as a concentrate for solution for infusion. Prior to administration Zirabev needs to be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection. Studies were performed to evaluate the physicochemical stability and compatibility of PF-06439535 in 0.9% sodium chloride with commercially available administration components that are commonly used during preparation and storage of the dosing solution and/or during infusion. These studies were completed using several lots of FP including an aged FP lot near the end of its shelf life.

Adventitious agents

The approach for adventitious agents testing is described. The MCB and WCB testing is reviewed as part of the active substance control as well as the control of raw materials.

The only material of animal origin identified is an antiserum used in clone selection, which is derived from sheep and stabilized in bovine serum albumin. A CEP is not available for this reagent and bovine serum albumin (BSA). However, the information on the origin of the serum indicates low risk of viral contamination and testing performed to qualify the cell line could be expected to have detected adventitious agents from these species.

Viral clearance studies were performed with a suitable panel of model viruses on qualified small scale models. The total process clearance determined by summation of orthogonal removal/inactivation methods.

Comparability exercise for finished medicinal product

The Applicant has performed an extensive comparability analysis to demonstrate biosimilarity to the reference product Avastin (Avastin bevacizumab-EU and Avastin bevacizumab-US).

The comparability assessment consists of a comparison of PF-06439535 to bevacizumab-EU, PF-06439535 to bevacizumab-US, and bevacizumab-EU to bevacizumab-US. Formulation differences were not considered to influence the analytical studies. Details of methods used in the characterisation and forced degradation studies, including method qualification or validation, are presented.

A summary of the analytical similarity assessment is provided in **Error! Reference source not found.**. In general, the biosimilarity assessment performed by the Applicant is considered adequate to confirm the analytical similarity between PF-06439535 and EU-approved Avastin.

Table 1 Summary of the methods used to analyse PF-06439535, bevacizumab-US and bevacizumab-EU

Quality attribute	Criteria for similarity	Analytical procedure	Similarity conclusion
Primary Structure and Posttranslational Modifications	Identical amino acid sequence	LC/MS/MS – Peptide Mapping with specialized bioinformatics	Identical primary sequence.

		Peptide Mapping/ Edman Degradation	
	Similar molecular mass and size	nanoElectrospray Ionization Mass Spectrometry	Comparable results.
	Similar posttranslational modifications	nanoElectrospray Ionization Mass Spectrometry	Comparable profiles.
		LC/MS – Subunit Analysis	
		LC/MS and LC/UV – Peptide Mapping (Trypsin)	
VEGF binding to Fab Domain	Similar range of inhibition of VEGF response and binding to VEGF	Inhibition of Cell Growth Assay	Slightly lower inhibition of cell growth activity observed for PF-06439535 batches as compared to bevacizumab-EU. However, the statistical quality range for relative potency of bevacizumab-EU covers the range for PF-06439535.
		Binding to VEGF165 Target Antigen by ELISA	Comparable binding.
	Similar binding to other VEGF isoforms	Binding to other VEGF isoforms (VEGF121, VEGF189, VEGF206) by ELISA	Comparable binding.
ADCC Activity	Similar lack of ADCC activity	PBMC ADCC assay	Similar lack of ability to induce ADCC.
Fcɣ Receptor Binding	Similar binding kinetics	Binding to FcɣRI, FcɣRIIa, FcɣRIIb, FcɣRIIIa and FcɣRIIIb by SPR	Comparable binding. Minor differences in relative KD (% KD) values for FcγRIIIa 158F are considered not significant. SPR response results demonstrate similar binding to FcγRIIIa 158F.
FcRn Binding	Similar range of binding to FcRn	Binding to FcRn by SPR	Comparable binding. Minor differences in relative KD (% KD) values for FcRn are considered not significant. SPR response results demonstrate similar binding to FcRn. Not considered to have an impact on PK.
CDC Activity	Similar lack of CDC activity	CDC assay	Similar lack of CDC activity.
	Similar dose-dependent response curves	C1q binding assay	Comparable binding to C1q.
N-Linked Glycan Profile	Similar N-linked glycan distribution profile, structure, composition, glycosidic linkages, and sialic acid levels	HILIC/MS	Predominant N-linked glycans contents (G0F and G1F) similar. Slightly higher Man5 levels are not considered to have impact on PK.
		Exoglycosidase Digestion/HILIC	
Charge Heterogeneity: Species	Similar range for levels of acidic species	iCE	Slightly lower acidic and main species and largely higher basic species observed for PF-06439535 as compared to bevacizumab EU batches. Difference for basic species attributed to PF-06439535 (all batches) having a higher proportion of species containing one or two C-terminal lysine residues in the heavy chain are not clinically relevant.
Charge Heterogeneity: Basic Species	Similar range for levels of basic species		
Charge Heterogeneity: Main Species	Similar range for levels of main species		

Charge Heterogeneity	Similar identity of major and minor charge isoforms	Cation Exchange-HPLC profile characterized by MS	Similar identity of charge isoforms present for PF-06439535, bevacizumab-EU batches.
		Carboxypeptidase B/iCE	Comparable levels of charge species.
Product Purity	Similar range for levels of monomer	SE-HPLC	Increase in purity profile: higher monomer content and lower levels of HMMS leading to a better safety profile.
	Similar range for levels of HMMS		
	Similar range for levels of HC + LC and fragment content	CGE (reducing)	Increase in purity profile: higher HC+LC content and lower levels of fragments leading to a better safety profile.
	Similar range for levels of Intact IgG	CGE (Non-reducing)	Higher level of intact IgG leading to a better safety profile.
	Similar banding pattern	SDS-PAGE (Total protein staining and Western blotting)	Similar banding pattern.
Disulfide Bonds	Similar state of cysteines and disulfide bonds	Sulfhydryl Analysis	Comparable results.
		LC/MS – Non-reduced Peptide Mapping (Lys-C)	
Higher Order Structure	Similar secondary structure	Far-UV Circular Dichroism (CD) Spectroscopy	Similar graphical profiles.
		Fourier Transform Infrared (FTIR) Spectroscopy	
	Similar tertiary structure	Near-UV CD Spectroscopy	
		Fluorescence Spectroscopy	
	Similar thermal stability	Differential Scanning Calorimetry (DSC)	
Forced degradation	Similar degradation profiles under forced degradation conditions (elevated temperature, light exposure, and forced deamidation) and demonstrate there are no new degradation products	SE-HPLC, iCE, CGE (reducing and nonreducing), cell based bioassay, UV spectroscopy, LC/MS –Peptide mapping (Trypsin), HIAC (elevated temperature studies only)	Similar degradation pathways. No new degraded species.

GMO

Not applicable.

2.1.4. Discussion on chemical, pharmaceutical and biological aspects

Module 3 of the dossier for PF-06439535 is of good quality and the information provided is sufficiently detailed.

No major objection was raised by CHMP. Other concerns were raised in relation to several issues. The Applicant was requested to justify and explain the rationale behind their proposed control strategy and provide particular examples of expected critical process parameters (CPP) (e.g. pH, oxygen, density, temperature etc.).

The Applicant provided additional data and explanations and was able to resolve all concerns. Two recommendations for post-authorisation follow-up related to the compound-specific toxicological risk assessment in case of any unexpected leachable and the ultrafiltration monitoring protocol for all parameters and scale down model viral clearance studies have been listed. One recommendation for pre-authorisation follow-up, relates to the provision of final protocols for the monitoring of chromatography resins and ultrafiltration membrane process steps.

During the procedure a concern was raised in relation to differences observed in biological activity by the cell growth assay between PF-06439535 and the EU reference product. The Applicant justified the differences on the basis of assay variability. In conclusion based on the totality of evidence it was considered that sufficient reassurance on the conclusion of biosimilarity of bevacizumab versus the EU reference product was obtained. The Applicant has committed to re-evaluate the acceptance criterion for potency/biological activity after manufacture of recommended number of commercial batches as a post-authorisation recommendation.

The analytical similarity between PF-06439535 and the reference products, Avastin bevacizumab-EU and Avastin bevacizumab-US, has been addressed in an extensive comparability exercise. The similarity between PF-06439535 and EU-approved Avastin can be confirmed.

In conclusion, from a quality point of view, the MAA of PF-06439535 is approvable as a biosimilar to Avastin bevacizumab-EU.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

The analytical similarity between PF-06439535 and the reference products, Avastin bevacizumab-EU and Avastin bevacizumab-US, has been confirmed in an extensive comparability exercise.

In conclusion, from a quality point of view, the MAA of PF-06439535 is approvable as a biosimilar to Avastin bevacizumab-EU.

2.1.6. Recommendation(s) for future quality development

In the context of the obligation of the Marketing Authorisation Holder (MAH) to take due account of technical and scientific progress, the CHMP recommended additional following points for further investigation, where the Applicant commits to:

- notify authorities if an increase of a particular impurity of any unexpected leachable compound is observed at future time points of the on-going leachables study and provide the associated compound specific toxicological risk assessment.
- provide final protocols for the monitoring of chromatography resins and ultrafiltration membranes process steps.
- perform additional scale down model viral clearance studies in alignment with the manufacturing process.
- re-evaluate the acceptance criterion for potency/biological activity for active substance and finished product for this assay after manufacture of the recommended number of commercial batches.

2.2. Non-clinical aspects

2.2.1. Introduction

The known mechanism of action (MoA) of bevacizumab is to bind VEGF, thereby inhibiting the interaction of VEGF and its receptors (VEGFR-1 and VEGFR-2 (Ellis, 2006)).

VEGF is a major mediator of tumour angiogenesis and signals through VEGFR-2, the major VEGF signalling receptor (Kerbel, 2008). VEGF binds to VEGFR-2 on the surface of endothelial cells, leading to receptor dimerization and autophosphorylation, and activation of intracellular signalling pathways, including PI3K, Src, Akt, and ERK (Matsumoto & Claesson-Welsh, 2001). Activation of multiple signalling pathways eventually leads to biological responses which include cell activation, proliferation, differentiation, migration, survival, and vascular permeability. All of these activities mediate the formation of new blood vessels. The applicant did not perform any own pharmacodynamics studies with PF-06439535.

Physicochemical and functional characterization of PF-06439535, bevacizumab-US, and bevacizumab-EU was undertaken.

2.2.2. Pharmacology

Primary pharmacodynamic studies

To assess the similarity of pharmacologic response for PF-06439535 compared with bevacizumab, PF-06439535 was tested in a panel of *in vitro* functional and binding assays that are reflective of the Mechanism of Action (MoA) of bevacizumab. In all of these assays, PF-06439535 was compared to bevacizumab-US and bevacizumab-EU, and bevacizumab-US was compared to bevacizumab-EU.

The known MoA for bevacizumab involves the binding of the Fab domain of the monoclonal antibody to the VEGF target antigen in the extracellular matrix and preventing it from binding to its receptors (VEGFR-1 and VEGFR-2) on the surface of endothelial cells, thereby inhibiting VEGF activities. A functional assay was developed to measure inhibition of VEGF-induced cell proliferation in human endothelial umbilical vein cells (HUVEC). In addition, the binding of bevacizumab to the target antigen human VEGF was assessed with a binding enzyme-linked immunosorbent assay (ELISA).

In compliance with Guideline on similar biological medicinal products containing monoclonal antibodies, following *in vitro* non-clinical studies have been performed:

- Binding to targets antigen: binding of bevacizumab to the target antigen human VEGF (VEGF165, VEGF121, VEGF189, and VEGF206)

- Binding of PF-06439535, bevacizumab-US, bevacizumab-EU to representative isoforms of the relevant three Fc gamma receptors (FcγRI, FcγRII and FcγRIII), FcRn and complement (C1q)

- Fab-associated functions (Inhibition of VEGF binding to its receptors and cell proliferation)

- Fc-associated functions of PF-06439535, bevacizumab-US, bevacizumab- EU: Lack of ADCC and CDC activity in VEGF expressing cells

Together these assays broadly cover the functional aspects of PF-06439535.

Secondary pharmacodynamic studies

No secondary pharmacodynamics study with PF-06439535 was conducted.

Safety pharmacology programme

No stand-alone safety pharmacology study has been conducted. Information on cardiovascular and respiratory endpoints was collected in the repeat dose toxicity study in young male *Cynomolgus* monkeys (see section 2.2.4 Toxicology).

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions study has been conducted.

2.2.3. Pharmacokinetics

Toxicokinetic (TK) and anti-drug antibody (ADA) evaluations were conducted in support of a 1-month repeat-dose toxicity study in young male *Cynomolgus* monkeys with PF-06439535 and bevacizumab-EU (Study 13GR179) and a 2-week repeat-dose toxicity study of PF-06439535 in Sprague-Dawley rats (Study 8305590 [14MA078]). Validated assays were used for the TK and ADA evaluations.

Exposure to PF-06439535 was confirmed in both rat and monkey, and mean systemic exposure (as assessed by Cmax and AUC72) for PF-06439535 and bevacizumab-EU was similar in monkeys. The mean Cmax and AUC72 exposure ratios of PF-06439535 relative to bevacizumab (EU) on Day 1 and 25 ranged from 0.8 to 1.0. Antibodies to PF-06439535 or bevacizumab were not detected in any animals treated with PF-06439535 or bevacizumab (EU).

No studies on distribution, metabolism, excretion, or pharmacokinetic drug interaction have been conducted with PF-06439535.

2.2.4. Toxicology

Single dose toxicity

No single-dose toxicity studies were conducted with PF-06439535.

Repeat dose toxicity

Comparative study in monkey, PF-06439535 vs bevacizumab–EU (Study 13GR179, GLP)

PF-06439535 and bevacizumab–EU were each administered by IV bolus injection to young male *Cynomolgus* monkeys (4/group) at 10 mg/kg/dose twice weekly for 1 month (Days 1, 4, 8, 11, 15, 18, 22, 25, and 29). A separate group of monkeys (4 males) received the vehicle control article/diluent 1 used with PF-06439535 (20 mM succinate, 85 mg/mL sucrose, 0.05 mg/mL EDTA, 0.2 mg/mL polysorbate-80, pH 5.5). Another group of 4 males received the vehicle control article/diluent 2 used with bevacizumab-EU (60 mg/mL trehalose, 5.8 mg/mL sodium phosphate [monobasic], 1.2 mg/mL sodium phosphate [dibasic], 0.4 mg/mL polysorbate-20, pH 6.2). A 10 mg/kg twice weekly dose was justified on the basis of the Originator's toxicity studies in which physeal dysplasia was observed.

Assessments included mortality, clinical signs, body weights, food intake, ophthalmic examinations, heart rate, electrocardiograms, respiration rate, haematology, coagulation, clinical chemistry, and urinalysis parameters. Blood samples were collected from all animals for measurement of PF-06439535 or bevacizumab-EU serum concentrations and determination of TK parameters. Blood samples were also collected from all animals for evaluation of ADA induction. At the end of the dosing phase, a complete necropsy was conducted, organs were weighed, and tissues were collected for microscopic evaluation.

Administration of PF-06439535 or bevacizumab-EU was well tolerated. There were no PF-06439535 or bevacizumab-EU-related findings in clinical signs, body weight, food intake, ophthalmology examinations, respiration rate, electrocardiograms, haematology, coagulation, clinical chemistry, or urinalysis parameters. All animals survived to their scheduled euthanasia and there were no PF-06439535 or bevacizumab-EU-related changes in organ weights or macroscopic findings.

All animals were sexually immature based on the microscopic appearance of the male reproductive tract tissues. All animals were skeletally immature based on the presence of active (open) growth plates observed microscopically in the distal femur. PF-06439535 or bevacizumab-EU-related microscopic findings were limited to the expected pharmacologically-mediated response of physeal dysplasia of the growth plate of the distal femur, with apparent similarity in incidence and severity (minimal to moderate) in all animals dosed with PF-06439535- or bevacizumab-EU. This finding was considered to be adverse for growing animals. There were no findings of physeal dysplasia in the two concurrent vehicle control groups.

Non-comparative study in rat, PF-06439535 (study 8305590, GLP)

A 2-week IV bolus repeat-dose study was conducted in SD rats (13-14/sex/group) administered PF-06439535 at 0, 15, or 150 mg/kg IV twice weekly for 2 weeks (5 doses, Days 1, 4, 8, 11, and 15). Assessment of toxicity was based on mortality, clinical observations, body weight, food consumption, ophthalmic examinations, and clinical and anatomic pathology. Blood samples were collected from toxicokinetic animals for toxicokinetic evaluations and ADA analysis.

PF-06439535 had no effect on survival, clinical observations, food consumption, or ophthalmic examinations or clinical pathology parameters. PF-06439535 was associated with a non-adverse, statistically significantly minimally higher mean body weight gain in males administered 150 mg/kg/dose. This finding was not considered adverse because it was small in magnitude, did not correlate with other findings, and was within the range observed for this strain at this age.

No direct PF-06439535-related changes were present in the haematology, coagulation, clinical chemistry, or urinalysis test results. On Day 16 of the dosing phase, the male group administered 150 mg/kg/dose had minimally higher mean serum total protein concentration, and male and female groups administered 150 mg/kg/dose had minimally to mildly higher serum globulin concentrations with concurrent minimally lower albumin:globulin ratios. Comparison of serum globulin concentrations to the plasma concentration of the test article (an immunoglobulin) indicated that higher serum globulin concentrations and changes in other serum protein parameters were due to the physical presence of the test article and not to a biological effect of test article administration.

PF-06439535 was associated with minimal sinusoidal cell hyperplasia in the liver of males and females administered 150 mg/kg/dose. In males, this finding correlated with higher absolute and relative group mean liver weights (1.14 to 1.31x control) and was not adverse because of the minimal severity, lack of correlating clinical pathology findings, and absence of clinically observed detrimental effects on the health of the animals.

Genotoxicity

No genotoxicity study with PF-06439535 was conducted.

Carcinogenicity

No carcinogenicity study with PF-06439535 was conducted.

Reproduction Toxicity

No reproduction and development study with PF-06439535 was conducted.

Toxicokinetic data

Repeat-dose toxicokinetics of PF-06439535 in SD rats (Study 8305590, GLP)

After twice-weekly IV dosing of PF-06439535 at 15 or 150 mg/kg/dose in SD rats for 2 weeks, systemic exposure (as assessed by Cmax and AUC72) was similar in males and females across dose groups (**Error! Reference source not found.**). Mean systemic exposure increased with increasing dose in a slightly less than dose-proportional manner on Days 1 and 11. Based on mean AUC72 values, mean accumulation ratios (AUC72, Day 11/Day 1) ranged from 2.3 to 2.6 in males and from 2.7 to 3.0 in females across all dose groups. ADAs were not detected in animals dosed with vehicle or PF-06439535.

Table 2: Mean ± SD toxicokinetic parameters for PF-06439535 in SD rats (n = 4/sex/group) after twice-weekly administration of PF-06439535

Dose (mg/kg/dose)	Study Day	Sex	Cmax (µg/mL)	AUC_{72} (µg•h/mL)
15	1	Male	308 ± 34.2	12200 ± 904
		Female	308 ± 8.54	12000 ± 624
	11	Male	659 ± 53.9	31600 ± 2360
		Female	720 ± 56.3	35800 ± 2720
150	1	Male	2740 ± 341	110000 ± 7760
		Female	2780 ± 1170	96800 ± 20000
	11	Male	6260 ± 394	250000 ± 34100

		Female	6660 ± 400	258000 ± 12400

AUC_{72} = Area under the serum drug concentration-time curve for 0-72 hours; C_{max} = Highest drug concentration observed in serum.

Repeat-dose toxicokinetics of PF-06439535 and bevacizumab-EU in *Cynomolgus* monkeys (Study 13GR179, GLP)

After twice-weekly IV dosing of PF-06439535 or bevacizumab-EU at 10 mg/kg/dose in young male *Cynomolgus* monkeys for 1 month there were no quantifiable concentrations of PF-06439535 or bevacizumab-EU in samples collected and analysed prior to dosing on Day 1, or in samples analysed from vehicle control groups. Quantifiable concentrations of PF-06439535 or bevacizumab-EU at all time points collected and analysed from day 1 through day 30 (day 29, 24 hours post-dose) confirmed exposure to PF-06439535 or bevacizumab-EU over the duration of the study. Mean systemic exposure (as assessed by Cmax and AUC72) for PF-06439535 and bevacizumab-EU was similar. The mean Cmax and AUC72 exposure ratios of PF-06439535 relative to bevacizumab-EU on Day 1 and 25 ranged from 0.8 to 1.0. ADAs were not detected in animals dosed with PF-06439535 or bevacizumab-EU.

Table 3: Mean ± SD toxicokinetic parameters for PF-06439535 and bevacizumab-EU in male *Cynomolgus* monkeys (n = 4/group) after twice-weekly administration of PF-06439535 or bevacizumab-EU at 10 mg/kg/dose

	Study Day	Cmax (µg/mL)	Cmax Ratio[a]	AUC_{72} (µg•h/mL)	AUC_{72} Ratio[a]
PF-06439535	1	241 ± 37.2	0.809	12100 ± 876	0.823
Bevacizumab-EU		298 ± 29.6		14700 ± 2260	
PF-06439535	25	789 ± 54.7	0.925	45500 ± 5420	1.01
Bevacizumab-EU		853 ± 91.5		45100 ± 3670	

AUC_{72} = Area under the serum drug concentration-time curve for 0-72 hours; C_{max} = Highest drug concentration observed in serum. [a]. PF-06439535: bevacizumab-EU ratio.

Local Tolerance

No separate local tolerance studies have been conducted with PF-06439535. Compared with their respective vehicle controls, there were no adverse findings suggestive of injection site toxicity observed with PF-06439535 or bevacizumab-EU in monkey (Study 13GR179). In the 2 week study in rat (Study 8305590), minimal to mild perivascular haemorrhage and/or mixed cell inflammation was observed at the intravenous injection site. The findings were considered unrelated to the test article because they were distributed randomly among groups, including the control group, and were considered secondary to the mechanical trauma associated with the injection procedure.

Other toxicity studies

Immunogenicity of PF-06439535 in comparison with bevacizumab (EU) was assessed as part of the 1-month toxicology study in monkeys (Study 13GR179), and for PF-06439535 in the 2 week study in rat (Study 8305590). No antidrug antibodies (ADA) were detected in the PF-06439535 or bevacizumab (EU) treated groups.

2.2.5. Ecotoxicity/environmental risk assessment

Bevacizumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for

Human Use" (EMEA/CHMP/SWP/4447/00), bevacizumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.2.6. Discussion on non-clinical aspects

Pharmacology

The comparability exercise indicates that PF-06439535, bevacizumab-US, bevacizumab- EU can be considered biosimilar except for the binding affinity to the FcɣRIIIa 158 F isoform and the FcRn SPR Binding Activity for which some differences were observed. During the assessment procedure, the applicant discussed specific concerns related to this in accordance with the current knowledge on different FcgRIII variants (e.g. ADCC mediation, proinflammatory cytokines production, potential link of some phenotypes of FcgRIII to neutropenia, Ab-Ag complex mediated damage or Lupus-like reactions). Bevacizumab does not have ADCC function and there is no pro-inflammatory cytokine production expected. Binding of bevacizumab to FcgRIII variants were concluded to be of no concern at the clinical level with respect to neutropenia, lupus-like reactions or antigen-antibody complex mediated damage.

In conclusion, the small differences in bevacizumab FcgRIIIa 158F binding parameters or differences in patient FcgRIIIa genotype are considered unlikely to have clinical consequences.

Based on the results from the similarity assessment, the lack of *in vivo* pharmacology studies with PF-06439535 is acceptable and in line with guidance documents.

Dedicated studies on secondary pharmacodynamics, safety pharmacology, and pharmacodynamics drug interactions were not conducted. This is considered acceptable for a biosimilar product, and is also in accordance with Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

Pharmacokinetic

Sensitive analytical procedures for quantification of PF-06439535 and bevacizumab (ELISA and ligand binding assay), and ADAs against bevacizumab (ECL), have been developed and validated for rat and monkey serum. The analytical methods are of adequate quality and are considered acceptable.

Systemic exposure (as assessed by C_{max} and AUC_{72}) for PF-06439535 and bevacizumab (EU) was comparable in monkey. ADAs were not detected neither in rats, nor monkeys dosed with PF-06439535 or bevacizumab-EU. However, quantifiable concentrations of PF-06439535 or bevacizumab (EU) present in samples may have interfered with the detection of ADA.

The lack of studies on distribution, metabolism, excretion, or pharmacokinetic drug interaction for PF-06439535 is acceptable and in line with EMA/CHMP/BMWP/403543/2010.

Toxicology

Repeated dose toxicity studies in non-human primates are usually not recommended for similar biological products (EMA/CHMP/BMWP/403543/2010). Nevertheless, a 4-week repeat-dose toxicity study was conducted with PF-06439535 and bevacizumab (EU) in young *Cynomolgus* monkeys. In addition, and on the request of a regulatory authority outside Europe, the applicant performed a 2-week toxicology study in rat to detect potential adverse effects related to the formulation. From a 3R perspective and with reference to the European guidance document EMA/CHMP/BMWP/403543/2010, neither the study in monkey, nor the study in rat were warranted.

At 10 mg/kg twice per week, both PF-06439535 and bevacizumab (EU) were well tolerated in the 4-week repeat dose toxicity study in sexually and skeletally immature *Cynomolgus* monkeys, with similar incidence and severity of findings related to the pharmacological effect (physeal dysplasia) in both treatment groups. The study design included only one dose level (10 mg/kg twice per week). This was selected based on original study results with bevacizumab, allowing for comparison of effects on physeal dysplasia, the most sensitive finding in the original 4-week toxicity study in monkeys with bevacizumab. Overall, results indicate comparable toxicity, immunogenicity and exposure levels, between PF-06439535 and bevacizumab (EU) at a dose level of 10 mg/kg twice per week.

In the rat study the NOAEL was established at the highest dose level (150 mg/kg/dose twice weekly for 2 weeks). Given the lack of reactivity between PF-06439535 and VEGF in rat, the high NOAEL is as expected.

The formulation for PF-06439535 is different from Avastin with respect to excipients used. The excipients are however well known and not expected to trigger adverse effects at the site of administration. No separate local tolerance studies have been conducted with PF-06439535. Compared with their respective vehicle controls, there were no adverse findings suggestive of injection site toxicity observed with PF-06439535 or bevacizumab-EU in monkey, or with PF-06439535 in rat.

No ADAs to PF-06439535 of bevacizumab (EU) were detected in either study. However, high levels of circulating drug could possibly have interfered with the ability to detect antibodies in the drug safety studies. In monkeys, a pharmacological response was observed in all animals dosed with PF-06439535 or bevacizumab-EU. This finding supports that any theoretical formation of ADAs did not neutralise the effect of the mAb. In line with this, the animals' plasma concentration of PF-06439535 and bevacizumab (EU) increased from day 1 towards the end of study.

Overall, the results add to the totality of evidence to support the demonstration of PF-06439535 as a biosimilar product to bevacizumab (EU).

Studies on genotoxicity, carcinogenicity, and reproduction and developmental toxicity were not conducted. This is considered acceptable, and in accordance with EMA/CHMP/BMWP/403543/2010. Sections 4.6 and 5.3 of the proposed SmPC are in line with the approved product information for Avastin.

PF-06439535 is not expected to pose a risk to the environment.

2.2.7. Conclusion on the non-clinical aspects

PF-06439535 can be considered similar to the reference product Avastin in terms of *in vitro* functionality (except for the binding affinity to the FcɣRIIIa 158 F isoform and the FcRn SPR binding activity for which some not clinically relevant differences were observed), *in vivo* toxicological, toxicokinetic and immunogenicity profiles. The Summary table in Module SII of the RMP adequately reflects the important non-clinical findings with bevacizumab. The non-clinical findings with PF-06439535 were similar to findings reported for the reference product Avastin. Consequently, no additional measures are required.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 4.Summary of Clinical Studies Included in This Submission

Study Identifier (Country/Region)/ Status	Study Design	Treatment	Study Population	Number of Subjects/Patients Randomized	Objectives
B7391002[a] (EU, single center)/Completed	Single-arm, single-dose, open-label, pilot PK variability study	A single dose of bevacizumab-EU was administered at a dose of 5 mg/kg as a 90 minute IV infusion.	Healthy male subjects between 18 to 55 years of age	N=21 Bevacizumab-EU=21	Primary • To assess the inter-subject variability in single dose PKs of bevacizumab in healthy subjects Secondary • To assess single dose safety (including immunogenicity) and tolerability of bevacizumab in healthy subjects • To assess the PK after single dose
B7391001[a] (US, single center)/Completed	Double-blind (sponsor unblinded), randomized (1:1:1), parallel-group, single-dose, 3-arm, comparative PK study	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.	Healthy male subjects between 21 to 55 years of age	N=102 PF-06439535=33 Bevacizumab-US=33 Bevacizumab-EU=36	PK Similarity • To compare the PK of PF-06439535 to bevacizumab-EU and PF-06439535 to bevacizumab-US PK Bridging • To compare the PK of bevacizumab-EU to bevacizumab-US Safety • To evaluate the single-dose safety, tolerability, and immunogenicity

Table 4.Summary of Clinical Studies Included in This Submission

Study Identifier (Country/Region)/ Status	Study Design	Treatment	Study Population	Number of Subjects/Patients Randomized	Objectives
B7391003 (WW)/Completed	Randomized (1:1), Double-blind Study	Patients receive at least 4 cycles and no more than 6 cycles of either PF-06439535 plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin, followed by the previously assigned blinded bevacizumab monotherapy. Bevacizumab: 15 mg/kg by IV infusion on Day 1 of each of the 3-week (21-day) cycles. The initial dose was 15 mg/kg over 90 minutes as an IV infusion. If the first infusion was well tolerated, the second infusion may have been administered over 60 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions may have been administered over 30 minutes. Paclitaxel: administered as the first drug when chemotherapy was administered. 200 mg/m^2 by IV infusion over 3 hours on Day 1 in 21-day cycles. Carboplatin: administered as the second drug when chemotherapy was administered. IV infusion dosing was based on the use of	Patients ≥ 18 years of age with newly diagnosed Stage IIIB or IV non-squamous NSCLC or recurrent non-squamous NSCLC who have not received previous chemotherapy for metastatic disease	N=719 PF-06439535 plus paclitaxel and carboplatin=358 Bevacizumab-EU plus paclitaxel and carboplatin=361	Primary To compare the confirmed ORR by Week 19 following treatment with PF-06439535 in combination with paclitaxel and carboplatin to bevacizumab-EU plus paclitaxel and carboplatin in patients who had not received previous treatment for advanced non-squamous NSCLC Secondary • To evaluate the safety of PF-06439535 plus paclitaxel and carboplatin and bevacizumab-EU plus paclitaxel and carboplatin; • To evaluate secondary measures of tumour control; • To evaluate the population PK of PF-06439535 and bevacizumab-EU; • To evaluate the immunogenicity of PF-06439535 and bevacizumab-EU

Table 4.Summary of Clinical Studies Included in This Submission

Study Identifier (Country/Region)/ Status	Study Design	Treatment	Study Population	Number of Subjects/Patients Randomized	Objectives
		mathematical formula, based upon a patient's GFR in mL/min and carboplatin AUC in mg/mL•min) over a minimum of 15 minutes.			

Abbreviations: AUC=area under the concentration versus time curve; EU=European Union; GFR=glomerular filtration rate; IV=intravenous; N=total number of subjects/patients randomized; NSCLC=non-squamous non-small cell lung cancer; ORR=objective response rate; PK=pharmacokinetics; US=United States; WW=worldwide.
a. Efficacy was not assessed in this study.

2.3.2. Pharmacokinetics

The pharmacokinetic properties of PF-06439535 were studied and compared to those of both EU- and US-sourced bevacizumab (Avastin) in the clinical program:

- The first study (Study B7391002) was a single-dose, single-arm pilot pharmacokinetic (PK) variability study conducted with the reference EU product bevacizumab (not the test product PF-06439535) in healthy male subjects (n= 21). The Study was conducted to characterize inter-subject PK variability and safety profiles including immunogenicity of bevacizumab-EU following IV administration to healthy male subjects. The inter-subject variability, as indicated by the %CV, were 16%, 12%, and 15% for C_{max}, AUC_t, and AUC_{inf}, respectively.
- The phase I clinical study B7391001 in healthy male subjects: the primary objective was to demonstrate the PK similarity of PF-06439535 relative to the EU and US reference bevacizumab, and of bevacizumab-EU to bevacizumab-US, following a single 5 mg/kg dose intravenously (IV) infusion. A complete blood sampling for PK assessment were collected from pre-dose and at specified times up to day 100 of study visits.
- The phase III clinical study B7391003 in patients: the secondary objectives of the study included evaluation of serum trough bevacizumab concentrations at selected cycles. Blood sampling for predose (C_{max}) PK assessment were collected prior to bevacizumab infusion at every cycle through cycle 17, and at end of treatment/Withdrawals. In addition, post-dose samples (apparent C_{max}) were collected at 1 hour after the end of the IV infusion for Cycle 1 and 5 (if the patient received Cycle 5).

The same enzyme linked immunosorbent assay (ELISA) bioanalytical method was used for the phase I study (B7391001) and the phase III study (B7391003). PF-06439535 and bevacizumab-EU were determined by electrochemiluminescence (ECL) following an antibody capture procedure. Description and validation reports were provided with satisfactory results regarding precision, accuracy, selectivity and sensitivity, short and long-term stability and incurred sample reanalysis.

In the Phase I PK study B7391001, the PK data were analysed using standard NCA approach with an internally validated electronic noncompartmental analysis (eNCA, version 2.2.4) software system. Pharmacokinetic parameters, e.g. AUC_t, AUC_{inf}, C_{max}, CL, Vss, and $t_{1/2}$ were calculated according to standard procedures.

Standard summary statistics (*means, median, SD, CV etc…*) have been used. Point estimates and 90% confidence interval (CIs) for the ratios of the geometric means (GMs) for AUC_{last}, AUC_{inf}, and C_{max} were estimated using an ANOVA model for comparisons between PF-06439535 and bevacizumab-EU.

To establish bioequivalence, the 90% CI for the test-to-reference ratio of GM for AUC_t, AUC_{inf}, and C_{max} was to fall within the protocol-specified bioequivalence criteria of 0.80 and 1.25.

Absorption

- **Bioavailability**

The drug product is for intravenous use.

- **Bioequivalence**

Phase I study (b7391001)

This study was a double blind, single centre, randomised, parallel-group, single-dose, 3-arm, phase I study.

The Primary objective was to demonstrate the PK similarity of PF-06439535 to bevacizumab-US and bevacizumab-EU following 5 mg/kg single IV dose administration of the three products. The primary PK endpoints were: Cmax, AUCinf and AUClast based on PK samples collected through Day 71. Ad hoc PK analysis was also conducted based on PK samples collected through Day 100.

Test product was PF-06439535 (batch number 13-110832). Reference products were EU-sourced bevacizumab (batch 13-111567 and 13-111286) and US-sourced bevacizumab (batch 13-110446).

The PK bridging objective was to compare the PK of bevacizumab-EU to bevacizumab-US. The safety objective was to evaluate the single-dose safety, tolerability, and immunogenicity.

A total of 97 subjects of 101 (who received the assigned drug) in 3 parallel groups (32, 33, and 32 subjects, respectively) were included in the PK data analysis. Exclusions from the per-protocol population for the primary PK analysis (4 subjects) are properly discussed and justified.

To note, a sample size of 29 subjects per arm was calculated (based on the pilot PK study using the bevacizumab-EU) to provide at least 85% power for comparison in AUC and C_{max} for the similarity objective between PF-06439535 and bevacizumab-EU. Thus, the available PK data are considered sufficiently sensitive to draw valid conclusions from the study.

Demographic data (age, race, ethnicity, weight, height and BMI) were comparable among the 3 treatment groups.

Blood samples (5 mL) for PK assessment were collected at pre-dose, 1.5 (end of infusion), 4 and 24 hours after the start of dosing, at days 3, 5, 8, 15, 22, 29, 43, 57, 64, 71 and 100 of study visits.

Serum concentration-time data for bevacizumab (Pfizer), bevacizumab (US), and bevacizumab (EU) are summarised by treatment and time point in Table 5 . Median serum concentration-time profiles for PF-06439535, bevacizumab-EU, and bevacizumab-US are presented in Figure 2. The mean standard deviation (±SD) PK parameters for bevacizumab-Pfizer, bevacizumab-EU, and bevacizumab-US are summarized in Table 6.

Table 5: **Serum Bevacizumab-Pfzier, Bevacizumab-EU concentration (ng/mL) versus time Summary (Per-Protocol Population)**

Treatment Group=Bevacizumab-Pfizer

Dosing Day *	Planned Time Post Dose	N	NALQ	Mean	SD	CV (%)	Median	Min	Max
1	0 H	33	0						
	1 H 30 MIN	33	33	140700	21154	15	142000	95400	193000
	4 H	33	33	137700	20935	15	140000	89000	180000
	24 H	33	33	113000	16066	14	115000	79800	143000
	48 H	33	33	93670	16023	17	95300	64800	121000
	96 H	33	33	71700	11842	17	71700	49500	103000
	168 H	33	33	54710	11477	21	54300	36100	96700
	336 H	32	32	37380	7644.9	20	36850	22500	63700
	504 H	32	32	27130	5361.3	20	26850	15600	37700
	672 H	32	32	20960	5302.4	25	20650	4220	28000
	1008 H	30	30	12220	2800.6	23	12100	5990	17000
	1344 H	31	31	6846	1974.1	29	6780	2870	10500
	1512 H	32	32	4964	1574.6	32	4720	2110	8490
	1680 H	30	30	3719	1314.9	35	3470	1410	6440
	2376 H	30	29	833.9	419.78	50	827.5	0.000	1790

Treatment Group=Bevacizumab-EU

Dosing Day *	Planned Time Post Dose	N	NALQ	Mean	SD	CV (%)	Median	Min	Max
1	0 H	35	0						
	1 H 30 MIN	35	35	138500	22962	17	140000	96200	205000
	4 H	35	35	134000	20272	15	135000	92300	180000
	24 H	35	35	107600	16750	16	107000	75600	146000
	48 H	35	35	88090	14862	17	87900	58800	131000
	96 H	35	35	67630	9697.3	14	66900	47000	94500
	168 H	35	35	53190	7403.7	14	53600	35900	73000
	336 H	34	34	37590	6930.4	18	36850	25400	54100
	504 H	34	34	27740	5488.3	20	27400	17800	39900
	672 H	34	34	22630	5496.7	24	21050	14100	43000
	1008 H	33	33	13120	4020.4	31	13000	5460	22900
	1344 H	32	32	7557	2702.8	36	7455	2060	13900
	1512 H	31	31	5742	2588.8	45	5480	609	13700
	1680 H	33	33	4330	2372.5	55	4010	290	11700
	2376 H	32	31	1216	937.63	77	976.5	0.000	4790

Treatment Group=Bevacizumab-US

Dosing Day *	Planned Time Post Dose	N	NALQ	Mean	SD	CV (%)	Median	Min	Max
1	0 H	33	0						
	1 H 30 MIN	33	33	127400	17961	14	128000	93200	187000
	4 H	33	33	126500	17957	14	123000	101000	191000
	24 H	33	33	103400	11445	11	103000	80300	130000
	48 H	33	33	82970	11225	14	82100	62900	114000
	96 H	33	33	64650	8229.4	13	63600	45600	87200
	168 H	33	33	50170	4997.8	10	51400	37900	57400
	336 H	32	32	35450	4683.3	13	35350	28000	49500
	504 H	32	32	26200	3332.1	13	25400	20700	33300
	672 H	32	32	21070	2799.6	13	20150	16000	26000
	1008 H	31	31	12250	2522.3	21	11700	8450	18900
	1344 H	32	32	7027	1738.6	25	6655	3740	11400
	1512 H	32	32	5582	2374.2	43	5320	2350	15300
	1680 H	31	31	4014	1352.6	34	3850	2040	7420
	2376 H	27	27	970.9	612.58	63	811.0	266	2780

'N' = Number of observations (non-missing concentrations)

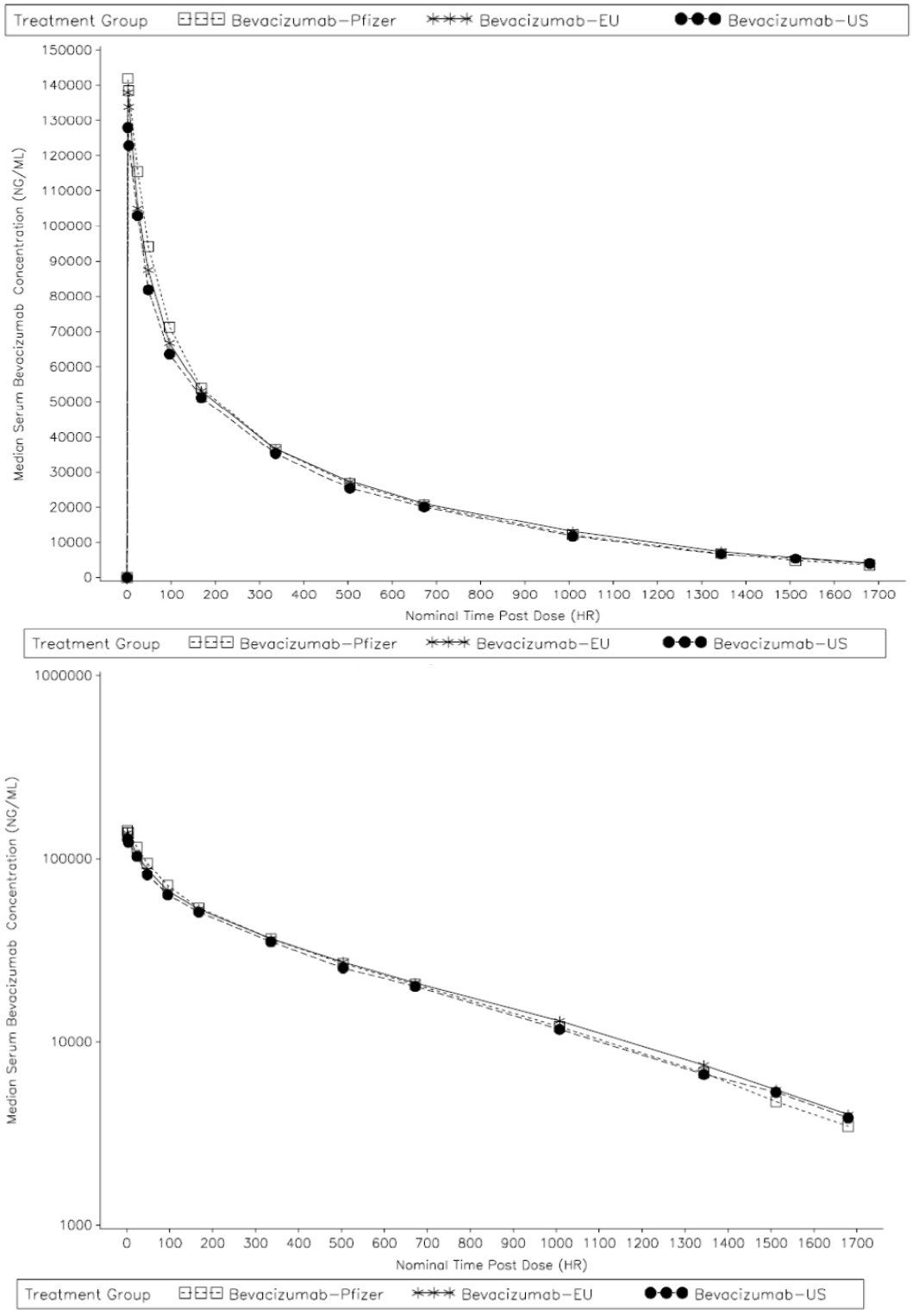


Figure 1: **Median Serum concentration time profiles of PF-06439535 ("Bevacizumab-Pfizer"), Bevacizumab-US, and Bevacizumab-EU following a single intravenous dose to healthy subjects at 5 mg/kg**

Table 6: Mean (±SD) Pharmacokinetic Parameter Estimates of Bevacizumab-Pfizer, Bevacizumab-EU, and Bevacizumab-US (Ad-hoc analysis - up to day 100)

Parameters (units)	PF-06439535	Bevacizumab-EU	Bevacizumab-US
N, n	32, 32	33, 33	32, 32
C_{max} (µg/mL)	142.9 ± 20.278	137.0 ± 20.473	130.0± 18.189
AUC_t (µg•hr/mL)	41990 ± 6827.9	42550 ± 7524.1	40070 ± 4881.7
AUC_{inf} (µg•hr/mL)	42580 ± 6764.8	43320 ± 8085.9	41050 ± 5252.3
CL (mL/hr/kg)	0.1196 ± 0.021	0.1185 ± 0.021791	0.1228 ± 0.015463
V_{ss} (mL/kg)	60.53 ± 10.716	62.93 ± 8.9201	66.83 ± 7.2737
$t_{½}$ (hr)	334.9 ± 55.310	359.0 ± 75.979	363.4 ± 55.977

Source: Table 14.4.3.1.1

Table 7. Summary of Statistical Comparisons of Pharmacokinetic Exposure Parameters (C_{max}, AUC_T, and $AUC_{0-\infty}$) between Test and Reference Products (Ad-hoc analysis -up to day 100)

		Adjusted Geometric Means			
Parameter (Units)	Comparison (Test vs. Reference)	Test	Reference	Ratio (Test/ Reference) of Adjusted Means[a]	90% CI (%) For Ratio[a]
AUC_t – D100 (µg•hr/mL)	PF-06439535 versus Bevacizumab-EU	41430	41930	98.79	(92.61, 105.38)
	PF-06439535 versus Bevacizumab-US	41430	39790	104.11	(97.55, 111.11)
	Bevacizumab-EU versus Bevacizumab-US	41930	39790	105.39	(98.80, 112.42)
AUC_{inf}- D100 (µg•hr/mL)	PF-06439535 versus. Bevacizumab-EU	42030	42620	98.62	(92.33 105.33)
	PF-06439535 versus Bevacizumab-US	42030	40730	103.21	(96.58, 110.29)
	Bevacizumab-EU versus Bevacizumab-US	42620	40730	104.65	(97.98, 111.78)
C_{max} – D100 (µg/mL)	PF-06439535 versus Bevacizumab-EU	141.5	135.5	104.42	(98.36, 110.84)
	PF-06439535 versus Bevacizumab-US	141.5	128.9	109.79	(103.38, 116.60)
	Bevacizumab-EU versus Bevacizumab-US	135.5	128.9	105.15	(99.05, 111.62)

Source: Table 14.4.3.3.1

Median serum concentration-time profiles for PF-06439535 and bevacizumab-EU appear to be very similar. Consistently, the mean standard deviation (±SD) PK parameters (C_{max}, AUCs, CL, V_{ss}, $t_{1/2}$) for PF-06439535 and bevacizumab-EU were very similar, with similar inter-subject variability (CV% around 15 to 20%) for each of the PK parameters.

For the purpose of PK similarity, the geometric LS means ratios from the primary PK analysis (based on up to Day 71 data) for the comparison of PF-06439535 and the reference beavcizumab-EU for C_{max}, AUC_{last}, AUC_{inf} were 1.04, 1.00 and 0.99 and the corresponding 90%CIs were [98.36-110.84], [93.69-105.93], [92.16-105.44], respectively. Similarly, the geometric LS means ratios from the ad hoc PK analysis (based on up to 100 data) for the comparison of PF-06439535 and the reference beavcizumab-EU for C_{max}, AUC_{last}, AUC_{inf} were 1.04, 0.99 and 0.99 and the corresponding 90%CIs were [98.36-110.84], [92.61-105.38], [92.33-105.33], respectively. Thus, the primary endpoints (i.e. C_{max}, AUC_{last}, AUC_{inf}) with their 90% confidence intervals are well within the predefined acceptance range of 80-125%.

Additionally to investigation following single-dose administration in healthy volunteers (n=32), PK of PF-06439535 has been characterised under repeated doses in patients with non-squamous NSCLC.

Phase III study (B7391003)

This is a completed multinational, randomised, double-blind, active-controlled, multiple dose study in adult subjects with non-squamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel. Paclitaxel and carboplatin were administered per dosing algorithm in the protocol. Bevacizumab (in combination or as monotherapy) was administered at the start of every 21-Day cycle (Q3W) at a dose of 15 mg/kg by IV infusion over 90 minutes.

A total of 719 patients at 216 centers were enrolled and randomized with 358 patients to the PF-06439535 group and 361 patients to the bevacizumab-EU group. Of these, 714 patients received at least 1 dose of study therapy, 356 patients were assigned to the PF-06439535 group, and 358 patients were assigned to the bevacizumab-EU group.

Blood samples for PK measurement were collected prior to bevacizumab infusion at every cycle through Cycle 17, and at End of Treatment (EOT)/Withdrawals, and post-dose samples were collected at 1 hour (± 0.5 hour) after the end of the infusion of bevacizumab for Cycle 1 and 5 (if the patient received Cycle 5).

The current PK data include all serum PF-06439535 and bevacizumab-EU concentration, available up to and inclusive of the data cutoff date of 08 May 2017. At this date, all the randomized patients had either completed the Week 25 visit or discontinued. Approximately 20% of patients had not reached the Week 55 visit.

Serum concentrations of PF-06439535 and bevacizumab-EU versus time are summarized descriptively in Table 8.

Mean standard deviation (SD), and median serum concentration-time profiles for PF-06439535 and bevacizumab-EU are presented in **Error! Reference source not found.**.

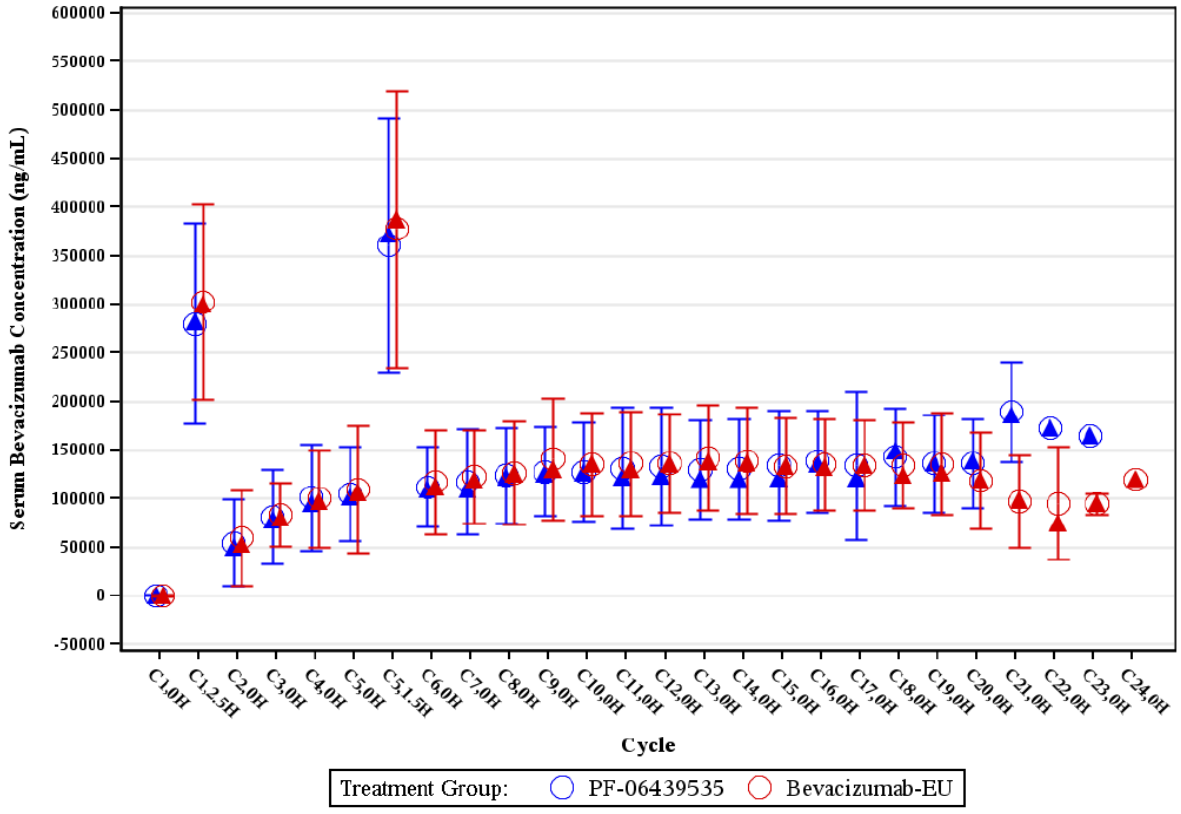


Figure 2: Mean and Median Plot of Serum Bevacizumab Concentration with standard deviation - PK Population – Study B7391003

Table 8: Summary of serum concentration of PF-06439535 and bevacizumab-EU versus time – PK Population – Study B7391003.

Treatment Group = PF-06439535

Visit	Planned Time Post Dose	N	NALQ	Mean	SD	CV (%)	Median	Min	Max
CYCLE 1	0 H	333	6	68.08	705.53	1036	0.0000	0.000	11300
	2 H 30 MIN	319	309	280000	103260	37	282000	0.000	546000
CYCLE 2	0 H	310	308	54350	44479	82	49050	0.000	460000
CYCLE 3	0 H	206	206	81090	48671	60	77450	4040	495000
CYCLE 4	0 H	277	277	100900	54979	54	94700	1000	475000
CYCLE 5	0 H	257	256	105300	48469	46	101000	0.000	494000
	1 H 30 MIN	192	192	360700	131170	36	372500	19700	636000
CYCLE 6	0 H	244	244	112000	40825	36	109000	10300	247000
CYCLE 7	0 H	192	192	117300	53844	46	109000	10600	566000
CYCLE 8	0 H	195	195	123600	48893	40	122000	28100	376000
CYCLE 9	0 H	184	184	127200	46200	36	124000	14600	259000
CYCLE 10	0 H	170	169	125700	50769	40	124000	0.000	269000
CYCLE 11	0 H	170	169	129500	61329	47	121500	0.000	568000
CYCLE 12	0 H	141	141	135200	64560	48	125000	22300	500000
CYCLE 13	0 H	136	136	130900	58093	44	120000	10700	389000
CYCLE 14	0 H	131	131	128000	50840	40	119000	41700	294000
CYCLE 15	0 H	103	103	134000	55933	42	122000	39100	315000
CYCLE 16	0 H	92	92	137000	54813	40	131000	38900	278000
CYCLE 17	0 H	90	90	134800	86847	64	112000	26800	648000
CYCLE 18	0 H	15	15	142700	50144	35	149000	50500	243000
CYCLE 19	0 H	13	13	135800	49717	37	136000	52000	237000
CYCLE 20	0 H	10	10	135800	45205	33	138500	49900	221000
CYCLE 21	0 H	5	5	189000	51098	27	186000	146000	272000
CYCLE 22	0 H	2	2	190500	26163	14	190500	172000	209000
CYCLE 23	0 H	2	2	193500	40305	21	193500	165000	222000
CYCLE 24	0 H	1	1	242000			242000	242000	242000

Treatment Group = Bevacizumab-EU

Visit	Planned Time Post Dose	N	NALQ	Mean	SD	CV (%)	Median	Min	Max
CYCLE 1	0 H	338	7	116.4	1032.1	886	0.0000	0.000	12300
	2 H 30 MIN	326	321	302200	100360	33	300000	0.000	525000
CYCLE 2	0 H	326	324	58930	49452	84	52650	0.000	522000
CYCLE 3	0 H	211	211	83350	32384	39	79700	5270	259000
CYCLE 4	0 H	299	298	99750	50531	51	96500	0.000	697000
CYCLE 5	0 H	271	271	110000	65416	59	106000	5610	723000
	1 H 30 MIN	201	201	377200	142250	38	387000	28700	1010000
CYCLE 6	0 H	268	267	116700	53844	46	111500	0.000	469000
CYCLE 7	0 H	214	214	122100	47793	39	118000	8440	273000
CYCLE 8	0 H	208	207	126400	52985	42	125000	0.000	426000
CYCLE 9	0 H	193	192	140900	62548	44	131000	0.000	558000
CYCLE 10	0 H	179	178	135900	53975	40	138000	0.000	287000
CYCLE 11	0 H	169	169	135600	54531	40	130000	6980	289000
CYCLE 12	0 H	138	138	136300	51312	38	136000	29000	263000
CYCLE 13	0 H	121	121	139700	53750	38	138000	31400	257000
CYCLE 14	0 H	117	117	136200	53439	39	136000	28000	292000
CYCLE 15	0 H	104	104	134000	49663	37	134000	36300	249000
CYCLE 16	0 H	95	95	128600	49742	39	127000	13100	258000
CYCLE 17	0 H	92	92	127500	52784	41	125000	3000	280000
CYCLE 18	0 H	23	23	130400	46741	36	122000	48700	233000
CYCLE 19	0 H	18	18	135400	52368	39	126000	53300	227000
CYCLE 20	0 H	15	15	118000	49551	42	118000	46300	234000
CYCLE 21	0 H	8	8	96450	47311	49	98500	17800	155000
CYCLE 22	0 H	5	5	95180	57797	61	74200	46000	195000
CYCLE 23	0 H	2	2	94300	10889	12	94300	86600	102000
CYCLE 24	0 H	1	1	119000			119000	119000	119000
CYCLE 25	0 H	1	1	123000			123000	123000	123000
CYCLE 26	0 H	1	1	118000			118000	118000	118000
CYCLE 27	0 H	1	1	104000			104000	104000	104000

N = Number of observations (non-missing concentrations)

Mean and median trough (pre-dose) and apparent peak (1 hour post end of infusion at Cycle 1 and cycle 5) concentrations appear to be comparable across the 2 treatment groups for all time points measured from baseline (time 0) through Cycle 18. Moreover, large but similar variance in each group (CV of 40 to 60%) was observed.

The mean and median bevacizumab C_{trough} values increase steadily up to Cycle 9. This finding was observed for the two treatment groups (test and reference) but not consistent with the half-live (between 18 and 20 days) of bevacizumab and the Q3W dosing regimen.

- **Influence of food**

Not applicable for I.V. administration.

Distribution

Not applicable.

Elimination

Clearance and terminal half-life of PF-06439535, Bevacizumab-US, and Bevacizumab-EU were estimated in the phase I study b7391001. CL was 0.119 ml/hr/kg for PF-06439535, 0.122 ml/hr/kg for Bevacizumab-US, and 0.117 ml/hr/kg for Bevacizumab-EU. $t_{½}$ was 397 hr for PF-06439535, 413 hr for Bevacizumab-US, and 417 h for Bevacizumab-EU. No statistically significant difference was found between the treatments for any of the parameters.

Special populations

No studies were performed in patients with hepatic or renal impairment.

2.3.3. Pharmacodynamics

No new pharmacodynamic data has been submitted as part of this application.

No validated PD markers considered relevant to predicting efficacy of bevacizumab in patients do so far exist. Therefore, no PD markers were included in the PK study, and clinical endpoints were utilised in the phase 3 study in NSCLC patients.

As the mechanism of action of bevacizumab, inhibition of tumour vessel growth, is expected to be similar across all approved cancer indications, extrapolation to other cancer indications of the reference product than advanced NSCLC is considered acceptable provided that similarity of PF-06439535 to the bevacizumab reference product has been convincingly demonstrated through comparability studies both at the quality, non-clinical and clinical level.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics of PF-06439535 following a 5 mg/kg bodyweight single i.v. injection in healthy male volunteers has been determined in a pivotal PK similarity study (b7391001).

The study design (number of subjects and sampling scheme) was chosen based on the assessment of inter-subject variability in a single dose pharmacokinetics study of bevacizumab in healthy male subjects (b7391002), and appears to be adequate. To support the PK findings of the pivotal phase I study, trough and apparent peak serum levels were determined during the repeat dose phase III clinical study. The primary endpoints of the phase I clinical study (i.e. $AUC_{inf,}$ $AUCl_{ast}$ and C_{max}) with their 90% confidence intervals are well within the predefined acceptance range of 80-125%.

In the phase III study (B7391003), the observation that steady-state is achieved only around cycle 9 was explained by a decrease in number of patients evaluated for PK post cycle 6, and in addition a potential reduction in clearance of bevacizumab/ PF-06439535 in patients with therapeutic response. The basis for the latter explanation is not substantial, and is considered a postulation. However, the finding of slight increase of bevacizumab concentrations between Cycle 5 and Cycle 9 was reported for both test and reference treatments. Thus, PK similarity (the pivotal issue for this dossier) is not questioned. No formal investigations in subjects with impaired hepatic or renal function were performed. According to the originator´s product SmPC, PK of bevacizumab has not been investigated in patients with impaired renal or hepatic function. Thus, no study is required in the context of this biosimilar application.

The results indicate that PF-06439535 is comparable to Avastin at the PK level.

No new pharmacodynamic data has been submitted as part of this application. No validated PD markers considered relevant to predicting efficacy of bevacizumab in patients do so far exist. Therefore, no PD markers were included in the PK study, and clinical endpoints were utilised in the phase 3 study in NSCLC patients.

As the mechanism of action of bevacizumab, inhibition of tumour vessel growth, is expected to be similar across all approved cancer indications, extrapolation to other cancer indications of the reference product than advanced NSCLC is considered acceptable provided that similarity of PF-06439535 to the bevacizumab reference product has been convincingly demonstrated through comparability studies both at the quality, non-clinical and clinical level.

2.3.5. Conclusions on clinical pharmacology

The available PK/PD data support biosimilarity of PF-06439535 versus the EU reference product Avastin.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response study was conducted.

2.4.2. Main study

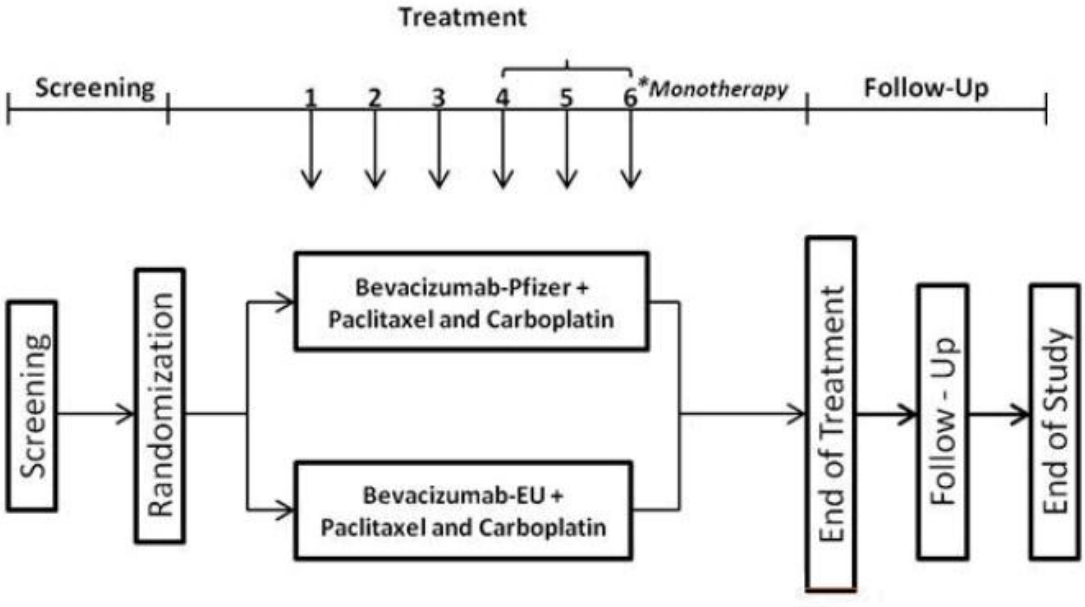
A Phase 3 randomized, double-blind study of PF-06439535 plus Paclitaxel-Carboplatin and Bevacizumab plus Paclitaxel-Carboplatin for the first-line treatment of patients with advanced non-squamous non-small cell lung cancer

Methods

The main study B7391003 is a multinational, double-blind, randomised, parallel-group Phase 3 clinical trial comparing the efficacy and safety of PF-06439535 plus paclitaxel and carboplatin versus bevacizumab-EU plus paclitaxel and carboplatin as first-line treatment for patients with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC. A summary of study B7291003 is provided in Figure 3. The ITT population was comprised of 719 patients who were randomised to double-blind treatment, 358 patients to the PF-06439535 group and 361 patients to the bevacizumab-EU group. Randomisation was stratified by region (according to the location of the drug depot supplying the site), sex (male/female) and smoking history (never/ever). Two populations were defined for the efficacy analyses: ITT population and PP population. The ITT population was the primary efficacy analysis population. The PP population was used for sensitivity analyses of

the primary and secondary efficacy endpoints. The estimated duration of study participation was approximately one year. Last subject last visit (LSLV) is defined as up to one year from randomisation of the last patient (End of Treatment) plus 28-day follow-up. The study was considered completed (End of Study) when the last patient completed the LSLV. See study scheme (Figure 3) for details.

Figure 3: Study scheme



Study Participants

Main inclusion criteria:

1. Male and female patients ≥18 years of age, or ≥age of consent in the region.

2. Newly diagnosed Stage IIIB or IV NSCLC (according to Revised International System for Staging Lung Cancer Criteria of 2010) or recurrent NSCLC.

3. Histologically or cytologically confirmed diagnosis of predominately non-squamous NSCLC.

4. At least one measurable lesion as defined by RECIST version 1.1

5. For patients with recurrent disease, at least 6 months must have had elapsed since completing adjuvant or neoadjuvant treatment.

6. Screening scan (computed tomography [CT] or magnetic resonance imaging [MRI]) of the head, chest, abdomen (with adrenal glands), and other disease sites as clinically indicated, to assess disease burden.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Main exclusion criteria:

1. Small cell lung cancer (SCLC) or combination of SCLC and NSCLC. Squamous-cell tumours and mixed adenosquamous carcinomas of predominantly squamous nature.

2. Evidence of a tumour that compressed or invaded major blood vessels or tumour cavitation that was likely to bleed.

3. Known sensitising epidermal growth factor receptor (EGFR) mutations (for example, exon 19 deletion or exon 21 L858R) or echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) translocation positive mutations. If mutation testing was performed, the results must have been reviewed and confirmed as negative for mutations prior to randomisation.

4. History of other cancer within 5 years prior to screening for this study, with the exception of adequately treated ductal carcinoma in situ of the breast, cervical carcinoma in situ, or basal or squamous cell skin cancer.

5. Prior systemic therapy for NSCLC; prior neoadjuvant or adjuvant therapy was allowed if surgical resection for primary disease was performed.

6. History of local radiation for painful bone metastases in the last 2 weeks. Patients with bone metastases were eligible, however those with symptomatic or painful bone metastases should not have received palliative local radiation for at least 2 weeks prior to randomisation.

Treatments

Premedication for administration

On treatment days when both bevacizumab and paclitaxel-carboplatin were administered, the order of administration was: 1) paclitaxel, 2) carboplatin, 3) bevacizumab. Bevacizumab monotherapy was administered following completion of at least four cycles and no more than six cycles of chemotherapy.

Premedication to ameliorate the toxicities associated with the chemotherapy were to be administered according to the local label or institutional guidelines.

Study drug administration

Paclitaxel

Following premedication, paclitaxel was administered as the first drug when chemotherapy was administered. Paclitaxel at a dose of 200 mg/m^2 was administered by IV infusion over 3 hours on Day 1 in each cycle (21-day cycle). In the absence of progressive disease (PD), patients received paclitaxel treatment for at least 4 cycles but no more than 6 cycles. Dose reduction for toxicity was allowed.

Carboplatin

Carboplatin was administered by IV infusion over a minimum of 15 minutes, and could be administered immediately after the paclitaxel infusion had completed. Patients were administered carboplatin for at least 4 cycles and no more than 6 cycles. Dose reduction for toxicity was allowed.

Bevacizumab

Blinded bevacizumab was administered once at the start of every 21-day cycle. The initial dose was 15 mg/kg delivered over 90 minutes as an IV infusion. The concentration of bevacizumab solution was required to be kept within the range of 1.4 mg/mL to 16.50 mg/mL. Infusions were not allowed to be administered as an IV push or bolus injection. Infusions were not allowed to be administered or mixed with dextrose solutions.

Patients received therapy until RECIST version 1.1 defined disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred, or End of Treatment whichever came first.

Objectives

Primary objective: To compare the efficacy of PF-06439535 versus Avastin (EU)

Secondary objective: To assess and compare the immunogenicity and safety profile of PF06439535 versus Avastin (EU)

Outcomes/endpoints

Primary Endpoint

- ORR - the percent of patients within each treatment group that achieved complete response (CR) or partial response (PR) by Week 19 of the study and subsequently confirmed on a follow-up tumour assessment by Week 25, based on the pre-specified equivalence margins required by EMA (-13% to 13%).

Secondary Endpoints

- Progression-free survival (PFS) at 1 year: Time from the date of randomization to first documentation of PD, or death due to any cause in the absence of documented PD
- Survival at 1 year: Time from date of randomisation to death due to any cause while the patient is in the study
- Duration of response (DOR): Time from date of the first documentation of objective tumour response (CR or PR) to the first documentation of PD, or to death due to any cause in the absence of documented PD

Sample size

Based on the results of a meta-analysis combining Sandler (2006), Johnson (2004), and Niho (2012), the objective response rate (ORR) to bevacizumab + chemotherapy combination therapy was estimated to be approximately 40%, and the response rate to chemotherapy alone was estimated to be 21%. The relative risk (RR) of response for bevacizumab + chemotherapy versus chemotherapy alone was estimated to be 2.17 with 95% CI (1.74, 2.70).

Equivalence will be considered established if the 95% confidence interval of the risk difference falls into the margins (-0.13, 0.13).

A sample size of 656 patients (328 per treatment arm) provides approximately 86% power for achieving equivalence in risk difference (RD) under specified margin of (-13%, 13%) with 2.5% type I error rate assuming an ORR of 38% in both treatment arms. This target sample size of 656 patients will provide approximately a power of 84% given above assumptions and assuming ORR=41%.

Considering a possible ~7.5% attrition rate for patients reaching evaluation for ORR, a total sample size of approximately 710 patients (355 per treatment arm) were randomized to achieve the target sample size of 656.

Randomisation

After screening and sponsor approval patients were randomised through an online Interactive Web Response System (IWRS), and received a unique patient identification number (ID) retained throughout the study. Patients were randomised (1:1) to receive at least 4 cycles and no more than 6 cycles of either PF-06439535 plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin, followed by the assigned blinded bevacizumab monotherapy. Randomisation was stratified by region (according to the location of the drug depot supplying the site), sex (male/female) and smoking history (never/ever). Randomisation was according to a randomisation schedule generated by the Sponsor, and to which the Sponsor's personnel directly involved in the study conduct were blinded. The only exception was in the event of an emerging safety issue which may have required breaking the blind.

Blinding (masking)

Treatment assignments for this study were blinded to the patients, investigator/study staff and Sponsor's study team conducting the trial. The study pharmacists (or qualified designee) preparing treatment infusions were unblinded, and pharmacy records were monitored by a Sponsor appointed unblinded monitor.

Statistical methods

This was a comparative study aiming at demonstrating clinical equivalence of PF-06439535 and bevacizumab reference product by comparing the confirmed ORR by Week 19 following treatment.

Hypothesis

Two one-sided hypothesis tests was carried out in the study for ORR in order to show that bevacizumab-Pfizer is equivalent to bevacizumab-EU.

TEST 1: H_{0a}: $\theta_1 - \theta_2 > R_{ub}$ vs. H_{1a}: $\theta_1 - \theta_2 \leq R_{ub}$

TEST 2: H_{0b}: $\theta_1 - \theta_2 < R_{lb}$ vs. H_{1b}: $\theta_1 - \theta_2 \geq R_{lb}$

Where R_{ub} is the largest acceptable difference for equivalence, and R_{lb} is the smallest acceptable difference for equivalence. Note: $R_{lb} = -R_{ub}$=-0.13.

Populations

The Intent-to-Treat (ITT) population was defined as all patients who were randomized to study treatment, and was used for patient accountability and all efficacy analyses. The Safety population was defined as all subjects who received at least one dose of study treatment inclusive of chemotherapy. Patients were assigned to treatment groups "as randomized" for efficacy analyses, but "as treated" for all other analyses (if receiving both treatments, assigned to treatment initially given). The Per-Protocol (PP) population was defined as all patients who were randomized and received the study treatment (PF-06439535 or bevacizumab-EU) as planned and had no major protocol deviations. The PP population was used for sensitivity analyses of the primary and secondary endpoints.

Statistical method of analysis

The primary efficacy endpoint of the study was ORR defined as the percent of patients within each treatment group who achieved a BOR of CR or PR by Week 19 in accordance with RECIST version 1.1, and subsequently confirmed on a follow-up tumour assessment by Week 25, based on the Sponsor's derived best overall

assessment using tumour measurements reported by the investigator in the CRF. The two 1-sided hypotheses were tested in this study for ORR in order to show that PF-06439535 was equivalent to bevacizumab-EU. For the EU, equivalence was considered established if the 95% CI of the risk difference falls into the margins (-13%, 13%).

The primary efficacy analysis for the primary endpoint in the ITT population was based on the Miettinen and Nurminen (1985) method without strata. Estimated risk ratio and risk difference and the asymptotic 95% and 90% CI in ORR between PF-06439535 and bevacizumab-EU were computed. These values were used to determine equivalence based on the criteria defined above.

The same analysis based on PP population was also performed as a sensitivity analysis. The Miettinen and Nurminen method was also carried out with additional stratification variables (region, gender and smoking history), to assess whether these variables would affect the risk ratio/risk difference of ORR between the 2 treatment groups. This analysis was performed based on both ITT and PP population as secondary analyses.

Results

Participant flow

Table 9: Summary of the screened patients

Number (%) of Patients	n (%)
Total number of patients screened	1095 (100.0)
Number of patients randomized	719 (65.7)
Number of screen failure patients	376 (34.3)

Table 10: Summary of the reasons for screen failure patients

Number (%) of Patients	Total N=376
Subject died	2 (0.5)
Lost to follow-up	1 (0.3)
Other	11 (2.9)
Does not meet entrance criteria	343 (91.2)
No longer willing to participate in study	18 (4.8)
Study terminated by Sponsor	1 (0.3)

Table 11: Patient Disposition

Number (%) of Patients	PF-06439535	Bevacizumab-EU	Total
Randomized[a]	358	361	719
Treated	356 (99.4)	358 (99.2)	714 (99.3)
Study			
Discontinued	356 (99.4)	358 (99.2)	714 (99.3)
Randomized not treated	2 (0.6)	3 (0.8)	5 (0.7)
Treatment			
Discontinued[b]	356 (99.4)	358 (99.2)	714 (99.3)
Analyzed for efficacy			
ITT population	358 (100.0)	361 (100.0)	719 (100.0)
PP population[c]	351 (98.0)	355 (98.3)	706 (98.2)
PK population	351 (98.0)	354 (98.1)	705 (98.1)
Analyzed for safety			
Safety population[d]	356 (99.4)	358 (99.2)	714 (99.3)
AEs	356 (100.0)	358 (100.0)	714 (100.0)
Laboratory data	342 (96.1)	348 (97.2)	690 (96.6)

Source: Table 14.1.1.1
Patient 10941004 received paclitaxel and carboplatin but withdrew prior to receiving PF-06439535 so had no End of Treatment page for bevacizumab.
Patient 10621017 had no CRF AE page but had been confirmed to have had experienced no AEs.
Abbreviations: AE=adverse event, CRF=case report form, EU=European Union, ITT=Intent-to-Treat, PK=pharmacokinetic, PP=Per-Protocol.

a. The number of randomized patients was used as the denominator for percentages except for safety data.
b. Treatment was defined as all 3 agents (blinded bevacizumab, paclitaxel and carboplatin).
c. PP population was not reevaluated in Week 55 analyses and remained the same.
d. The number of safety population was used as the denominator for percentages of AEs and laboratory data.

Of the 719 randomised, 714 patients were included in the safety population and received at least one dose of study therapy inclusive of chemotherapy. Five patients did not receive any blinded bevacizumab or paclitaxel/carboplatin, including two patients randomised to the PF-06439535 group, and three patients randomised to the bevacizumab-EU group. Of these five randomised patients who did not receive any randomised treatment, two patients were mistakenly unblinded by Principal Investigators on Cycle 1 Day 1 and discontinued from the study, one patient discontinued as per the decision of the Sponsor and the Principal Investigator due to exacerbation of chronic obstructive pulmonary disease (COPD) condition, one patient withdrew consent after randomisation but before receiving any study drug, and one patient met exclusion criterion 15 (CNS metastases). One additional patient in the PF-06439535 group did not receive blinded bevacizumab due to hypertension after the administration of paclitaxel and carboplatin. This patient was included in the safety population.

There were 714 (100.0%) patients who completed or discontinued from paclitaxel and carboplatin treatments (356 [100.0%] patients in the PF-06439535 group and 358 [100.0%] patients in the bevacizumab EU group). The majority of patients completed the protocol defined number of cycles (4-6 cycles) of chemotherapy. The most frequent reason for discontinuation from the study, including the survival follow up period, was death (136[38.2%] patients and 138 [38.5%] patients in the PF-06439535 and bevacizumab-EU groups, respectively).

Recruitment

The study was conducted at 216 centers in Australia, Brazil, Bulgaria, Chile, Croatia, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, India, Italy, Japan, Korea, Malaysia, Netherlands, Philippines, Poland, Romania, Russian Federation, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, and United States (US).

First Subject First Visit (FSFV): 20 April 2015

Primary completion date: 08 May 2017

Study Completion Date: 22 December 2017

Conduct of the study

Protocol amendments

The original protocol (version date: 04 November 2014) was amended 3 times. The main changes are summarised below:

Amendment 1 (version date: 05 May 2015):

- Addition of inclusion criteria to require that patients be eligible to receive study treatment of bevacizumab, paclitaxel, and carboplatin for the treatment of advanced or metastatic non-squamous NSCLC.
- Clarification of mutation testing language.
- Clarification of bevacizumab dose reductions.
- Clarification of CHF and IRR guidelines.

Amendment 2 (version date: 06 July 2015); Changes incorporated feedback from investigators, regulatory agencies, and protocol template updates:

- Clarification of study design language.
- Updated to global sample size, statistical considerations, and addition of Japan specific statistical analysis.
- Addition of maximum allowed doses for carboplatin.
- Addition of exclusion criteria regarding local radiation for painful bone metastases within the past 4 weeks.
- Addition of inclusion criteria to require that patients be eligible to receive study treatment of bevacizumab, paclitaxel, and carboplatin for the treatment of advanced or metastatic non-squamous NSCLC.
- Addition of toxicity information.
- Addition of required discontinuation of bevacizumab due to severe or life threatening infusion reaction that is considered to be secondary to bevacizumab and not paclitaxel and/or carboplatin.
- Addition of blood sample collection time points for ADA/NAb and corresponding drug concentrations, as well as the plan to analyze the samples, according to the Scientific Advice from the European Medicines Authority (EMA).

Amendment 3 (version date: 10 June 2016):

- For EU, changed primary analysis from risk ratio to risk difference
- Inclusion Criterion 6: window around baseline scan removed; specified in SOA.

- Inclusion Criterion 8: addition of plasma creatinine and UPC ratio.
- Exclusion Criterion 3: added language that was previously in body of protocol, to require review of mutation testing results prior to randomization, if testing is performed.
- Exclusion Criterion 6: reduced window for prior radiotherapy from four weeks to two weeks.
- Exclusion Criterion 12: language revised to exclude active infections and remove window for prior anti-infective agents.
- Exclusion Criterion 15: language added to define and allow treated and stable brain metastases.
- Exclusion Criterion 21: clarification to exclude active hepatitis B and C infection instead of past infection.
- Exclusion Criterion 25: added prior immunotherapy and bevacizumab.

Removed language regarding investigator's judgment in the following criterion: Exclusion Criterion 2 (tumour involving major blood vessels): "in the opinion of the investigator"; 13 (comorbidities) "as per the investigator's discretion"; 21 (hepatitis infection) "based on investigator clinical judgment".

Protocol Deviations

Table 12: **Summary of Important Protocol Deviations - ITT Population**

Number (%) of Patients	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Number of patients with important protocol deviations	3 (0.8)	7 (1.9)	10 (1.4)
Inclusion/exclusion	3 (0.8)	5 (1.4)	8 (1.1)
Did not meet inclusion criterion 2: newly diagnosed Stage IIIB or IV NSCLC or recurrent NSCLC for which they had not received chemotherapy for metastatic disease.	2 (0.6)	2 (0.6)	4 (0.6)
Did not meet inclusion criterion 4: at least 1 measurable lesion as defined by RECIST version 1.1	1 (0.3)	2 (0.6)	3 (0.4)
Met exclusion criterion 5: prior systemic therapy for metastatic disease	0	1 (0.3)	1 (0.1)
Investigational product	0	1 (0.3)	1 (0.1)
Blind broken - inadvertent unblinded before the patient reached Week 19 or End of Treatment milestone visit	0	1 (0.3)	1 (0.1)
Randomization	0	1 (0.3)	1 (0.1)
Randomized but not dosed	0	1 (0.3)	1 (0.1)

Source: Table 14.1.1.6.2

Abbreviations: EU=European Union, ITT=Intent-to-Treat, N=number of patients randomized to the study, NSCLC=non-small cell lung cancer, RECIST=Response Evaluation Criteria in Solid Tumors.

Baseline data

Table 13: Demographic Characteristics – ITT Population

	PF-06439535	Bevacizumab-EU	Total
Number (%) of Patients	358	361	719
Gender			
Male	237	230	467
Female	121	131	252
Age (years)			
<18	0	0	0
18-44	19 (5.3)	17 (4.7)	36 (5.0)
45-64	198 (55.3)	222 (61.5)	420 (58.4)
≥65	141 (39.4)	122 (33.8)	263 (36.6)
Mean	61.7	60.9	61.3
SD	9.5	8.9	9.2
Range	25-87	31-83	25-87
Race			
White	319 (89.1)	319 (88.4)	638 (88.7)
Black	3 (0.8)	1 (0.3)	4 (0.6)
Asian	36 (10.1)	40 (11.1)	76 (10.6)
Other	0	1 (0.3)	1 (0.1)
Ethnicity			
Hispanic/Latino	13 (3.6)	16 (4.4)	29 (4.0)
Not Hispanic/Latino	345 (96.4)	345 (95.6)	690 (96.0)
Weight (kg)			
Mean	71.8	72.2	72.0
SD	15.1	15.6	15.4
Range	40.0-127.0	28.3-135.0	28.3-135.0
Body Mass Index[a] (kg/m^2)			
Mean	25.3	25.6	25.5
SD	4.7	5.1	4.9
Range	15.6-51.5	12.5-41.9	12.5-51.5
Height (cm)			
Mean	168.4	167.6	168.0
SD	9.0	9.3	9.2
Range	146.0-196.0	144.0-195.0	144.0-196.0

Source Data: Module 5.3.5.1 Study B7391003 Table 14.1.2.1

Baseline was defined as the value recorded at Cycle 1, Day 1. If this value was missing, the value recorded at Screening was used.

Abbreviations: EU= European Union; ITT=Intent-to-Treat; SD=standard deviation.

a. Body mass index was defined as $weight/(height \times 0.01)^2$.

Table 14: Primary Diagnoses - ITT Population

Number (%) of Patients	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Histopathological classification			
Mixed adenocarcinoma	3 (0.8)	4 (1.1)	7 (1.0)
Adenocarcinoma	348 (97.2)	351 (97.2)	699 (97.2)
Large cell carcinoma	6 (1.7)	5 (1.4)	11 (1.5)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Recurrence type			
Newly diagnosed Stage IIIB	48 (13.4)	29 (8.0)	77 (10.7)
Newly diagnosed Stage IV	265 (74.0)	282 (78.1)	547 (76.1)
Recurrent	45 (12.6)	50 (13.9)	95 (13.2)
Prior surgeries for primary diagnoses			
No	298 (83.2)	293 (81.2)	591 (82.2)
Yes	60 (16.8)	68 (18.8)	128 (17.8)
Prior systemic therapies for primary diagnoses			
No	343 (95.8)	341 (94.5)	684 (95.1)
Yes	15 (4.2)	20 (5.5)	35 (4.9)
Prior radiation therapies for primary diagnoses			
No	333 (93.0)	338 (93.6)	671 (93.3)
Yes	24 (6.7)	23 (6.4)	47 (6.5)
Not reported	1 (0.3)	0	1 (0.1)

Source Data: Module 5.3.5.1 Study B7391003 Table 14.1.2.2.1; 14.1.2.2.3
Recurrence: Patients whose cancer had returned following an initial treatment with surgery, radiation therapy, and/or chemotherapy administered for curative intent.
Prior surgeries: Only included primary tumor resection.
Abbreviations: EU=European Union; ITT= Intent-to-Treat; N=number of patients randomized to the study.

Numbers analysed

A total of 719 patients were randomized in this study and were included in the efficacy analyses (ITT population), 358 patients to the PF-06439535 group and 361 patients to the bevacizumab-EU group. Sensitivity analyses of the efficacy endpoints were performed in the per-protocol population.

Table 15: Per-protocol (PP) Population - Summary of Exclusions from ITT Population

Number (%) of Patients	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Total patients excluded	7 (2.0)	6 (1.7)	13 (1.8)
Incorrect histopathological NSCLC[a]	1 (0.3)	0	1 (0.1)
Randomized but never bevacizumab dosed	3 (0.8)	3 (0.8)	6 (0.8)
Prior systemic anti-cancer therapy for Stage IIIB or IV disease	1 (0.3)	2 (0.6)	3 (0.4)
Inadvertent unblinding of study therapy for reasons other than safety reasons before Week 19[b]	1 (0.3)	1 (0.3)	2 (0.3)
Screening tumor assessment greater than 42 days prior to randomization	1 (0.3)	1 (0.3)	2 (0.3)

Source Data: Module 5.3.5.1 Study B7391003 Table 14.1.1.5

Abbreviations: EU=European Union; ITT=Intent-to-Treat; IV=intravenous; N=number of patients randomized to the study; NSCLC=non-small cell lung cancer; PP=per protocol

a. Intended histopathological subtype: predominately non-squamous NSCLC.

b. One (1) patient (Patient 10251001) also received the incorrect blinded bevacizumab study treatment (wrong kit used) for Cycle 1. An additional two patients not included in this category (10251002 and 11911003) were inadvertently unblinded on D1 prior to administration of study medication and were never dosed.

Outcomes and estimation

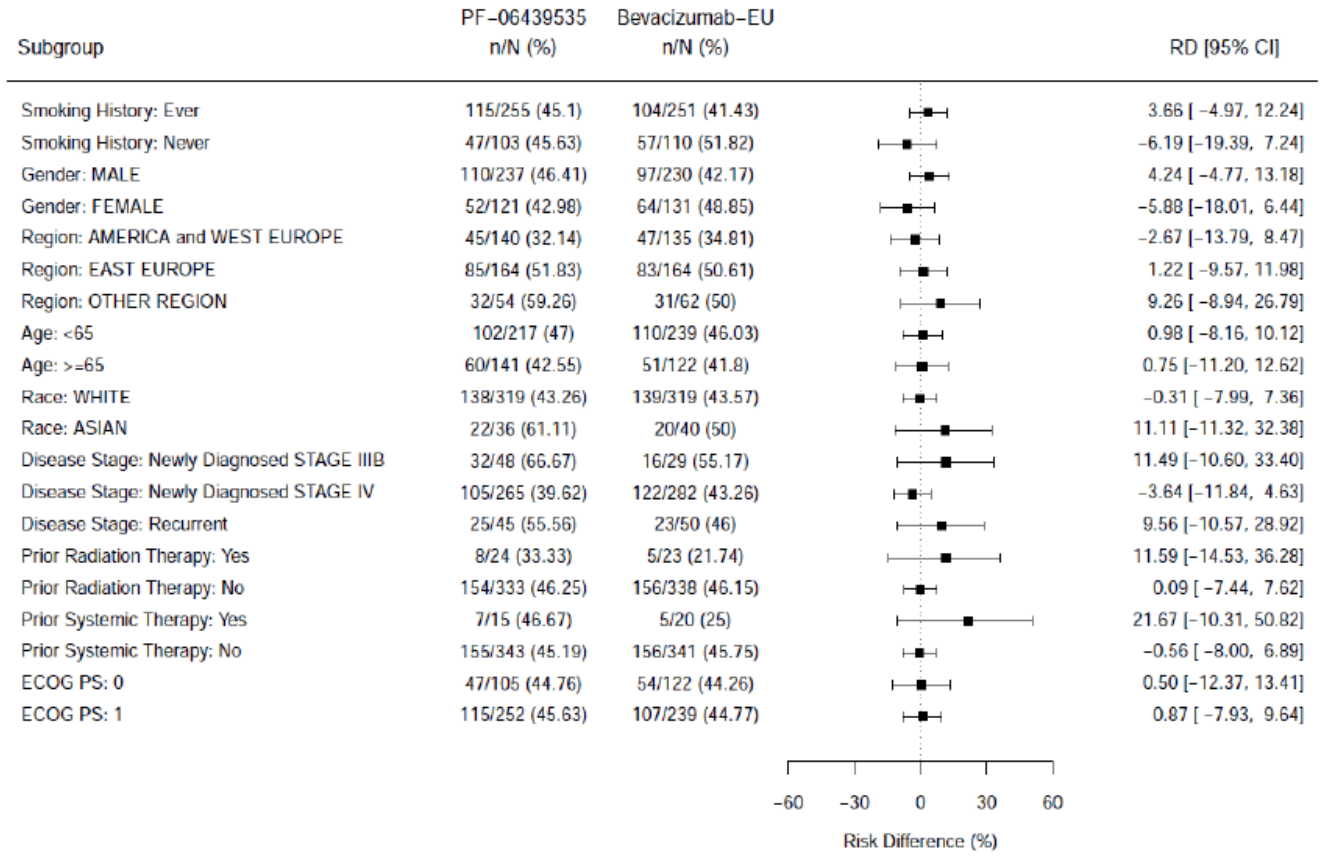
Primary endpoint: ORR

Table 16: Summary of Best Overall Response and ORR (Week 19) - ITT

	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Best overall response, n (%)			
Complete response (CR)	9 (2.5)	4 (1.1)	13 (1.8)
Partial response (PR)	153 (42.7)	157 (43.5)	310 (43.1)
Stable disease	154 (43.0)	166 (46.0)	320 (44.5)
Objective progression	15 (4.2)	14 (3.9)	29 (4.0)
Indeterminate[a]	27 (7.5)	20 (5.5)	47 (6.5)
Objective response rate (CR + PR), n (%)	162 (45.3)	161 (44.6)	323 (44.9)
95% exact CI[b]	[40.01, 50.57]	[39.40, 49.89]	[41.25, 48.64]
Treatment comparison (versus bevacizumab-EU)			
Un-stratified risk difference in ORR (%)[c]	0.6531		
95% CI of difference[c]	[-6.6080, 7.9082]		
Treatment comparison (versus bevacizumab-EU)			
Un-stratified risk ratio[d]	1.0146		
95% CI of risk ratio[d]	[0.8628, 1.1933]		
90% CI of risk ratio[d]	[0.8856, 1.1625]		

ORR was defined as the percentage of patients within each treatment group who achieved complete response or partial response by Week 19 of the study in accordance with RECIST version 1.1 which was subsequently confirmed by Week 25.
Abbreviations: CI=confidence interval, CR=complete response, EU=European Union, ITT=Intent-to-Treat, n/N=number of patients with observation/total number of patients, ORR=objective response rate, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors, US=United States.
[a] Indeterminate: Early death, unevaluable tumour assessment, and early study discontinuations.
[b] Exact method based on F-distribution was used.
[c] Calculated based on 2-sided Miettinen and Nurminen method without strata for risk difference for confirmed response. EU equivalence margins (95% CI in -13% to 13%).
[d] Calculated based on 2-sided Miettinen and Nurminen method without strata for risk ratio for confirmed response. US equivalence margins (90% CI in 0.73 to 1.37) and Japan equivalence margins (95% CI in 0.729 to 1.371).

Table 17: Forest plot of risk differences in ORR (PF-06439535 versus Bevacizumab-EU) with 95% CIs (Week 19) by strata-ITT population



Abbreviations: BOR=best overall response, CI=confidence interval, CR=complete response, ECOG PS=Eastern Cooperative Oncology Group performance status, EU=European Union, ITT=Intent-to-Treat, N=total number of patients in the specified subgroup, n=number of patients who achieved a BOR of CR or PR by Week 19 in the specified subgroup, ORR=objective response rate, PR=partial response, RD=risk difference.

Table 18: Summary of Best Overall Response and ORR (Week 19) – PP Population

	PF-06439535 (N=351) n (%)	Bevacizumab-EU (N=355) n (%)	Total (N=706) n (%)
Best Overall Response			
Complete Response	8 (2.3)	3 (0.8)	11 (1.6)
Partial Response	153 (43.6)	157 (44.2)	310 (43.9)
Stable Disease	153 (43.6)	165 (46.5)	318 (45.0)
Objective Progression	14 (4.0)	13 (3.7)	27 (3.8)
Indeterminate	23 (6.6)	17 (4.8)	40 (5.7)
Objective Response Rate (CR+PR)	161 (45.9)	160 (45.1)	321 (45.5)
95% Exact CI [1]	[40.57, 51.24]	[39.81, 50.41]	[41.75, 49.22]
SD Duration (weeks) [2]			
0 - <6 weeks	7 (4.6)	15 (9.1)	22 (6.9)
6 - <12 weeks	37 (24.2)	23 (13.9)	60 (18.9)
12 - <18 weeks	28 (18.3)	28 (17.0)	56 (17.6)
18 - <24 weeks	30 (19.6)	45 (27.3)	75 (23.6)
>=24 weeks	51 (33.3)	54 (32.7)	105 (33.0)
Treatment Comparison (vs Bevacizumab-EU)			
Un-Stratified Risk Difference in ORR (%) [3]	0.7985		
95% CI of Difference (%) [3]	[-6.5371, 8.1267]		
Stratified Risk Difference in ORR (%) [4]	1.1922		
95% CI of Difference (%) [4]	[-6.1023, 8.4738]		
Treatment Comparison (vs Bevacizumab-EU)			
Un-Stratified Risk Ratio [5]	1.0177		
95% CI of Risk Ratio [5]	[0.8656, 1.1966]		
90% CI of Risk Ratio [5]	[0.8885, 1.1658]		
Stratified Risk Ratio [6]	1.0266		
95% CI of Risk Ratio [6]	[0.8740, 1.2057]		
90% CI of Risk Ratio [6]	[0.8970, 1.1748]		

Analysis of the primary efficacy endpoint of ORR was repeated on the final data as a sensitivity analysis. The analysis of ORR showed an un-stratified risk ratio of 1.0146 (PF-06439535 versus bevacizumab-EU), with a 95% CI of (0.8628, 1.1933) and a 90% CI of (0.8856, 1.1625), and an un-stratified risk difference of 0.6531% (PF-06439535 versus bevacizumab-EU), with a 95% CI of (-6.6080%, 7.9082%). The results were consistent with those from the analysis performed previously at Week 25.

Secondary endpoints

<u>One year progression-free survival rate</u>

There were 228 (63.7%) and 255 (70.6%) patients who had objective progression or had died without objective progression in the PF-06439535 group and the bevacizumab-EU group, respectively. The probability of being progression free at Week 55 was 32.3% (95% CI: 26.9%, 37.8%) in the PF-06439535 group and 30.5% (95% CI: 25.3%, 35.8%) in the bevacizumab-EU group (**Table 19**). A total of 236 patients (130 [36.3%] patients in the PF-06439535 and 106 [29.4%] patients in the bevacizumab-EU treatment groups) were censored (**Table 20**).

Table 19: Summary of progression-free survival (Week 55) - ITT Population

Number (%) of Patients	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Number with event	228 (63.7)	255 (70.6)	483 (67.2)
Type of event			
Objective progression	192 (53.6)	219 (60.7)	411 (57.2)
Death without objective progression	36 (10.1)	36 (10.0)	72 (10.0)
Number censored	130 (36.3)	106 (29.4)	236 (32.8)
Probability of being event free at Week 55[a] [95% CI[b]]	32.3 [26.9, 37.8]	30.5 [25.3, 35.8]	31.4 [27.6, 35.2]
Kaplan-Meier estimates of time to event (week) quartiles [95% CI][c]			
25%	23.4 [18.9, 24.3]	24.0 [19.3, 24.3]	24.0 [20.3, 24.3]
50%	41.3 [33.1, 42.3]	33.6 [33.0, 37.0]	34.4 [33.1, 41.1]
75%	71.9 [59.7, 88.3]	68.9 [56.9, 75.0]	69.0 [60.9, 75.0]
Versus bevacizumab-EU			
Hazard ratio[d]	0.930		
95% CI of hazard ratio	0.776-1.114		
P-value[e]	0.4388		

A hazard ratio=1 indicated no difference in PD/death between PF-06439535 and bevacizumab-EU;
>1 indicated an increase in PD/death in PF-06439535;
<1 indicated an increase in PD/death in bevacizumab-EU.
Abbreviations: CI=confidence interval, EU=European Union, ITT=Intent-to-Treat, N=total number of patients, PD=progressive disease.
a. Estimated from the Kaplan-Meier curve.
b. Calculated based on the product-limit method.
c. Based on the Brookmeyer and Crowley method.
d. Based on the Cox proportional hazards model stratified by smoking, gender, and region.
e. 2-sided p-value from the log-rank test stratified by smoking, gender, and region.

Table 20: Censorship reasons for analysis of progression-free survival (Week 55) - ITT population

Number (%) of Patients	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Number censored	130 (36.3)	106 (29.4)	236 (32.8)
Reasons for censorship			
No adequate baseline assessments	2 (<1.0)	3 (<1.0)	5 (<1.0)
No on-study disease assessments	18 (5.0)	10 (2.8)	28 (3.9)
Given new anti-cancer treatment prior to tumour progression	12 (3.4)	17 (4.7)	29 (4.0)
Withdrew consent for follow-up	5 (1.4)	6 (1.7)	11 (1.5)
Lost to follow-up	4 (1.1)	7 (1.9)	11 (1.5)
Unacceptable gap (>14 weeks) between PD or death to the most recent prior adequate assessment	19 (5.3)	16 (4.4)	35 (4.9)
In follow-up for progression	70 (19.6)	47 (13.0)	117 (16.3)

Abbreviations: EU=European Union, ITT=Intent-to-Treat, N=total number of patients, PD=progressive disease.

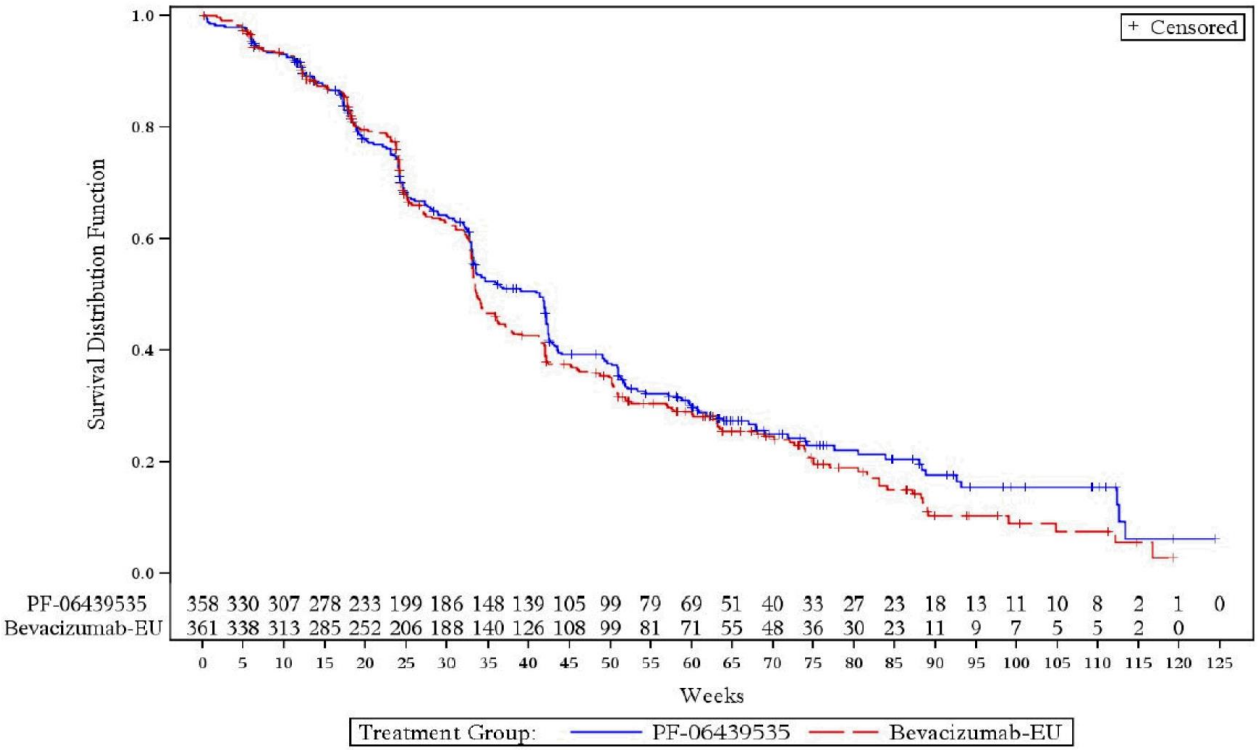


Figure 4: Kaplan-Meier plot of progression-free survival - ITT population

The analysis of PFS for patients in the PP population showed results consistent with the primary ITT population. The hazard ratio when comparing PFS between PF-06439535 and bevacizumab-EU was 0.931, with a 95% CI of (0.777, 1.117). The stratified log-rank test resulted in a 2-sided p-value of 0.4511. The Kaplan-Meier curves of PFS for the PP population in the two treatment groups were comparable.

Duration of response

Table 21: Duration of objective response (Week 55) - Patients in ITT population who had an objective response achieved by Week 19

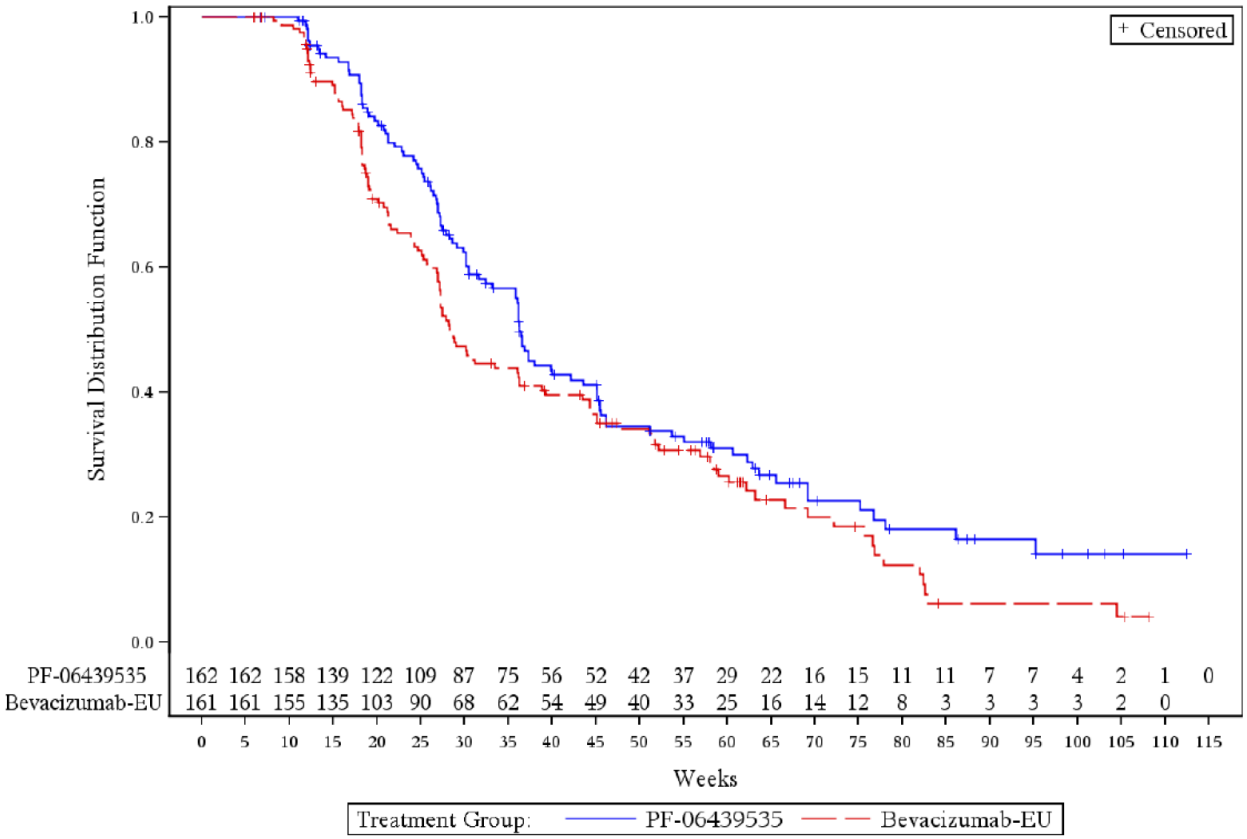
Number (%) of Patients	PF-06439535 (N=162)	Bevacizumab-EU (N=161)	Total (N=323)
Number with event	107 (66.0)	119 (73.9)	226 (70.0)
Type of event			
Objective progression	101 (62.3)	110 (68.3)	211 (65.3)
Death without objective progression	6 (3.7)	9 (5.6)	15 (4.6)
Number censored	55 (34.0)	42 (26.1)	97 (30.0)
Probability of being event free at Week 55[a] [95% CI[b]]	32.0 [24.2, 40.1]	30.8 [23.3, 38.6]	31.5 [26.1, 37.2]
Kaplan-Meier estimates of time to event (week) quartiles [95% CI][c]			
25%	25.3 [20.7, 27.1]	18.9 [17.9, 21.3]	21.3 [18.9, 24.4]
50%	36.3 [31.6, 43.6]	28.7 [27.0, 36.3]	35.9 [28.9, 36.6]
75%	69.1 [55.0, 86.1]	62.1 [51.3, 76.6]	63.6 [58.1, 75.6]
Versus bevacizumab-EU			
Hazard ratio[d]	0.790		
95% CI of hazard ratio	0.600-1.039		
P-value[e]	0.0906		

A hazard ratio=1 indicated no difference in PD/death between PF-06439535 and bevacizumab-EU;
>1 indicated an increase in PD/death in PF-06439535;
<1 indicated an increase in PD/death in bevacizumab-EU.
Abbreviations: CI=confidence interval, CR=complete response, EU=European Union, ITT=intent-to-treat, N=number of patients who achieved confirmed objective response (CR or PR) by Week 19, PD=progressive disease, PR=partial response.
a. Estimated from the Kaplan-Meier curve.
b. Calculated based on the product-limit method.
c. Based on the Brookmeyer and Crowley method.
d. Based on the Cox proportional hazards model stratified by smoking, gender, and region.
e. 2-sided p-value from the log-rank test stratified by smoking, gender, and region.

Table 22: Censorship Reasons for Analysis of Duration of Objective Response (Week 55) - Patients in ITT Population Who Had an Objective Response Achieved by Week 19

Number (%) of Patients	PF-06439535 (N=162)	Bevacizumab-EU (N=161)	Total (N=323)
Number censored	55 (34.0)	42 (26.1)	97 (30.0)
Reasons for censorship			
Given new anti-cancer treatment prior to tumor progression	4 (2.5)	7 (4.3)	11 (3.4)
Withdrew consent for follow-up	1 (<1.0)	4 (2.5)	5 (1.5)
Lost to follow-up	4 (2.5)	3 (1.9)	7 (2.2)
Unacceptable gap (>14 weeks) between PD or death to the most recent prior adequate assessment	6 (3.7)	5 (3.1)	11 (3.4)
In follow-up for progression	40 (24.7)	23 (14.3)	63 (19.5)

Abbreviations: CR=complete response, EU=European Union, ITT=intent-to-treat, N=number of patients who achieved confirmed objective response (CR or PR) by Week 19, PD=progressive disease, PR=partial response.



Abbreviations: EU=European Union, ITT=intent-to-treat.

Figure 5 Kaplan-Meier Plot of Duration of Objective Response (Week 55) – Patients in ITT Population Who Had a Confirmed Objective Response Achieved by Week 19

One year survival rate

Table 23: Summary of overall survival (Week 55) - ITT Population

Number (%) of Patients	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Number of deaths	144 (40.2)	149 (41.3)	293 (40.8)
Number censored	214 (59.8)	212 (58.7)	426 (59.2)
Survival probability at Week 55[a] [95% CI[b]]	65.8 [60.5, 70.6]	64.1 [58.6, 69.0]	65.0 [61.2, 68.4]
Kaplan-Meier estimates of time to event (week) quartiles [95% CI][c]			
25%	40.3 [34.0, 49.0]	42.9 [36.3, 47.9]	41.1 [37.4, 46.0]
50%	84.4 [71.7, -]	77.4 [69.3, 102.1]	83.0 [73.4, 98.7]
75%	-	-	-
Versus bevacizumab-EU			
Hazard ratio[d]	0.918		
95% CI of hazard ratio	0.729-1.157		
P-value[e]	0.4726		

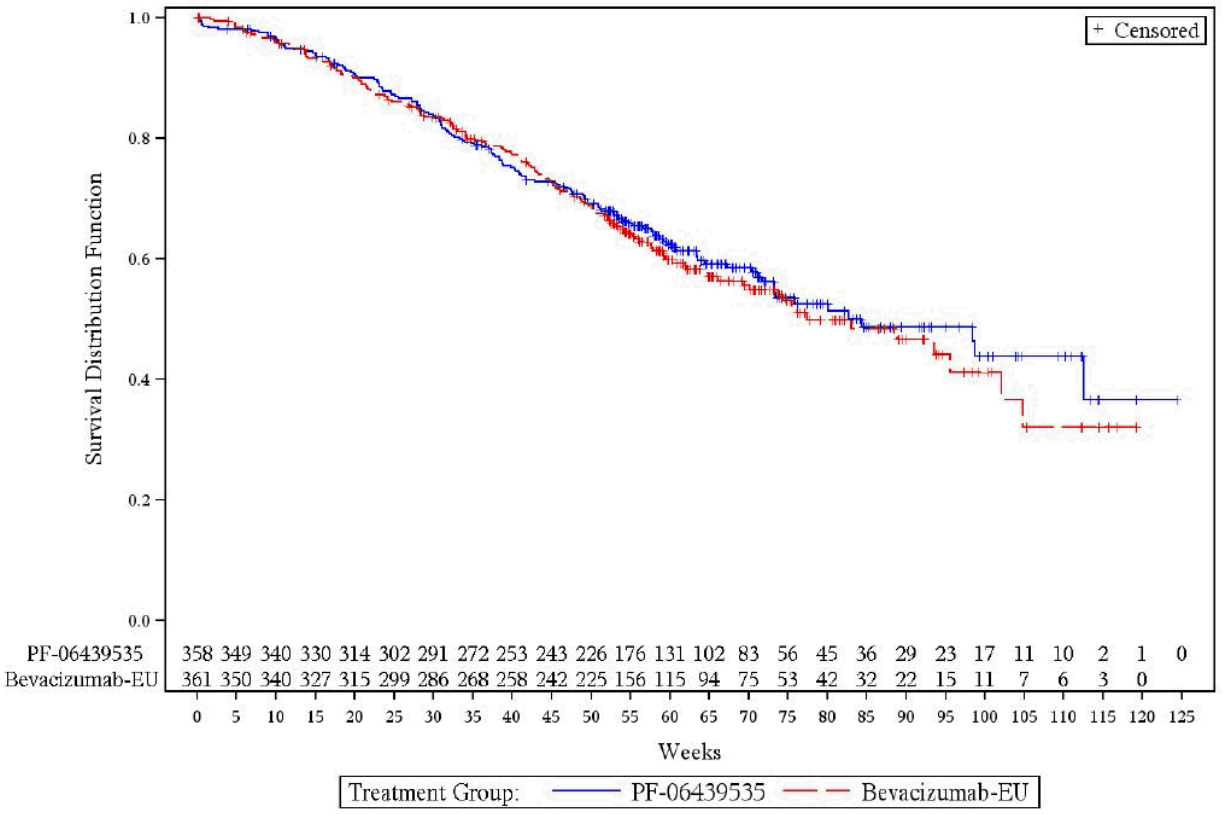
A hazard ratio=1 indicated no difference in death between PF-06439535 and bevacizumab-EU;
>1 indicated an increase in death in PF-06439535;
<1 indicated an increase in death in bevacizumab-EU.
Abbreviations: CI=confidence interval, EU=European Union, ITT=intent-to-treat, N=total number of patients.

a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley method.
d. Based on the Cox proportional hazards model stratified by smoking, gender, and region.
e. 2-sided p-value from the log-rank test stratified by smoking, gender, and region.

Table 24: Censorship Reasons for Analysis of Overall Survival (Week 55) – ITT Population

Number (%) of Patients	PF-06439535 (N=358)	Bevacizumab-EU (N=361)	Total (N=719)
Number censored	214 (59.8)	212 (58.7)	426 (59.2)
Reasons for censorship			
Alive	146 (40.8)	142 (39.3)	288 (40.1)
Patient no longer willing to participate	59 (16.5)	57 (15.8)	116 (16.1)
Lost to follow-up	9 (2.5)	13 (3.6)	22 (3.1)

Abbreviations: EU=European Union, ITT=intent-to-treat, N=total number of patients.



Abbreviations: EU=European Union, ITT=intent-to-treat.
Figure 6: Kaplan-Meier plot of overall survival - ITT population

Summary of main study(ies)

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk

assessment (see later sections).

Table 25: Summary of Efficacy for trial B7193003 (including secondary endpoints at week 55)

Title: A Phase 3 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			
Study identifier	B7391003		
Design	Multinational, double-blind, randomized, parallel-group Phase 3 clinical trial.		
	Duration of main phase:		55 weeks of treatment and follow-up for disease progression, and overall survival until unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred, or end of treatment (EOT).
Hypothesis	Equivalence		
Treatments groups	PF-06439535		-Chemotherapy: Carboplatin (AUC 6) + Paclitaxel 200 mg/m2 Q3W for at least 4 and not more than 6 cycles. -PF-06439535: 15 mg/kg intravenous (IV) infusion Q3W for at least 4 and not more than 6 cycle with chemotherapy followed by the assigned blinded bevacizumab monotherapy. N=358 subjects randomized
	Bevacizumab-EU		-Chemotherapy: Carboplatin (AUC 6) + Paclitaxel 200 mg/m2 Q3W for at least 4 and not more than 6 cycles -bevacizumab 15 mg/kg intravenous (IV) infusion Q3W Q3W for at least 4 and not more than 6 cycle with chemotherapy followed by the assigned blinded bevacizumab monotherapy for 6 cycles N=361 subjects randomized
Endpoints and definitions	Primary endpoint	Objective response rate (ORR)	ORR defined as the percent of patients within each treatment group who achieved a BOR of CR or PR by Week 19, in accordance with RECIST version 1.1, and subsequently confirmed on a follow-up tumour assessment by Week 25. The primary endpoint of ORR was based on the Sponsor's derived BOR using tumour measurements reported by the investigator in the CRF
	Secondary endpoint	Duration of objective response (DOR)	DOR was defined as the time from date of the first documentation of objective tumour response (CR or PR) to the first documentation of PD or to death due to any cause in the absence of documented PD in patients who achieved PR or CR by Week 19 subsequently confirmed by Week 25.

	Secondary endpoint	One year progression free survival rate (PFS)	PFS was defined as the time from date of randomization to first progression of disease or death due to any cause, whichever occurred first. The tumour assessment was based on investigator assessment in accordance with RECIST version 1.1
	Secondary endpoint	One year survival rate (OS)	Survival (time to death) was defined as the time from date of randomization to death due to any causes.
Database lock for primary endpoints	08 May 2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat population consists of all randomized subjects. All data during study are included in the analyses (Final data set).		
Descriptive statistics and estimate variability	Treatment group	PF-06439535	Bevacizumab-EU
	Number of subject	358	361
	ORR (CR+PR), n (%)	162 (45.3%)	161 (44.6%)
	95% exact CI (%)	[40.01, 50.57]	[39.40, 49.89]
	PFS (% event free at week 55)	32.3	30.5
	95%CI (%)	[26.9, 37.8]	[25.3, 35.8]
	DOR (% event free at week 55 after confirmed objective response)	32.0	30.8
	95% CI	[24.2, 40.1]	[23.3, 38.6]
	OS (% survival at week 55)	65.8	64.1
	95% CI	[60.5, 70.6]	[58.6, 69.0]
Effect estimate per comparison	Primary endpoint **ORR**	Comparison groups	PF-06439535 versus Bevacizumab-EU
		Un-stratified risk difference in ORR (%)	0.6531
		95% CI of difference*	[-6.6080, 7.9082]
		Un-stratified risk ratio	1.0146
		95% CI of risk ratio 90% CI of risk ratio	[0.8628, 1.1933] [0.8856, 1.1625]

	Secondary endpoint **PFS**	Comparison groups	PF-06439535 versus Bevacizumab-EU
		Hazard ratio	0.930
		95% CI of hazard ratio	0.776-1.114
		P-value	0.4388
	Secondary endpoint **DOR**	Comparison groups	PF-06439535 versus Bevacizumab-EU
		Hazard ratio	0.790
		95% CI of hazard ratio	0.600-1.039
		P-value	0.0906
	Secondary endpoint **OS**	Comparison groups	PF-06439535 versus Bevacizumab-EU
		Hazard ratio	0.918
		95% CI of hazard ratio	0.729-1.157
		P-value	0.4726
Notes	*Calculated based on 2-sided Miettinen and Nurminen method without strata for risk difference for confirmed response. EU equivalence margins (95% CI in -13% to 13%).		

2.4.3. Discussion on clinical efficacy

Study B7391003 is a multinational, double-blind, randomised (1:1), parallel-group, multiple dose study evaluating the efficacy, safety, PK, and immunogenicity of PF-06439535 plus paclitaxel and carboplatin versus bevacizumab-EU plus paclitaxel and carboplatin for the first-line treatment for patients with advanced non-squamous NSCLC.

Design and conduct of clinical studies

Randomisation was stratified by region, gender (male/female) and smoking history (never/ever). A total of 719 subjects were enrolled to receive either treatment of PF-06439535 plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin for at least 4 and no more than 6 cycles, followed by bevacizumab monotherapy.

All clinical studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and were consistent with International Conference on Harmonisation (ICH) "Guideline for Good Clinical Practice (GCP)" (ICH E6). GCP inspections were conducted at two centres by Ukraine Ministry of Health in the study and no major deviations were observed.

The chosen patient population of histologically or cytologically confirmed diagnosis of non-squamous NSCLC with the presence of newly diagnosed stage IIIB or IV NSCLC (according to Revised International System for Staging Lung Cancer Criteria of 2010) or recurrent NSCLC with at least one measurable lesion as defined by RECIST version 1.1, is considered acceptable for the purpose to establishing clinical similarity between PF-06439535 plus paclitaxel-carboplatin versus reference bevacizumab plus paclitaxel-carboplatin. NSCLC is regarded as a representative indication for the reference product. Exclusion of patients with known sensitising EGFR mutations (exon 19 deletion or exon 21 L858R) or EML4-ALK translocation positive mutations, is considered appropriate.

The drug was administered intravenously at hospitals and the regimen was according to the Avastin product labelling. The primary efficacy endpoint of Study B7391003 was ORR defined as the percent of patients within

each treatment group who achieved a BOR of CR or PR by Week 19 in accordance with RECIST 1.1 and subsequently confirmed on a follow-up tumour assessment by Week 25.

The inclusion and exclusion criteria used in the Phase 3 study were also according to the Avastin labelling and therefore considered adequate. Sample size calculations, randomisation and blinding procedures are also considered adequately performed.

ORR is considered acceptable as primary endpoint since ORR in NSCLC patients have been observed to be the most sensitive endpoint observed through the bevacizumab reference product trials.

The selected primary and secondary outcomes, their measurement time points as well as the pre-selected criteria for biosimilarity are in general according to the CHMP scientific advice provided, as well as according to relevant CHMP guidelines for biosimilar clinical development. RD of ORR at week 19 in the PP population with 95% CIs has also been provided, confirming the conclusion on similarity of efficacy in the ITT population.

The equivalence study design with the type I error rate controlled at 2.5% has previously been accepted by CHMP (EMA/CHMP/SAWP/667247/2015), and the planning of a trial based on the operating characteristic of an equivalence margin of about ± 12-13% points on the RD scale is considered feasible. The same advice pointed out that the chosen RD margin may be justified statistically by being lower than the lower bound of a 95% confidence interval from a meta-analysis. It was also pointed out that there is a need to justify the margin from a clinical perspective. There should be a clinical discussion of the irrelevance of the margin, which may lead to a smaller margin if the clinical irrelevance of the statistically derived margin cannot be justified. However, it is reasonable to assume that the margin would have been in the range of 10-13% regardless, and the result of the trial is well within these limits.

Efficacy data and additional analyses

Overall, 719 subjects with non-squamous NSCLC were randomised; 358 in the PF-06439535 arm vs. 361 in the bevacizumab-EU arm. Intent to treat was the main protocol specified population for analysis. There were no protocol deviations that were likely to significantly impact on study findings.

Results from the analysis of the primary endpoint, ORR, met the pre-specified equivalence criterion in both populations. In the ITT population, the ORR was similar for the treatment groups (45.3% in the PF-06439535 group and 44.6% in the -EU group). The analysis of ORR provided an un-stratified risk difference of 0.6531% (PF-06439535 versus bevacizumab-EU), with a 95% CI of (-6.6080%, 7.9082%), which fell entirely within the pre-determined equivalence margin (-13% to 13%). Further analysis of the PP population (both RD and RR) supports the conclusion. Sub-population analyses were conducted for ORR, and overall, no marked differences in the treatment comparisons were observed across subgroup categories.

In the ITT population, the percentages of patients who progressed/died or were censored, were comparable between the two treatment groups.

The probability of being progression free at Week 55 was 32.3% (95% CI: 26.9%, 37.8%) in the PF-06439535 group and 30.5% (95% CI: 25.3%, 35.8%) in the bevacizumab-EU group. The probability of not having subsequent progression or death at Week 55 after a confirmed objective response was 32.0% (95% CI: 24.2%, 40.1%) in the PF-06439535 group, and 30.8% (95% CI: 23.3%, 38.6%) in the bevacizumab-EU group.

Analysis of the primary efficacy endpoint of ORR was repeated at week 55 as a sensitivity analysis. The results were consistent with those from the analysis performed previously at Week 25.

2.4.4. Conclusions on the clinical efficacy

Similarity between PF-06439535 and EU-licensed bevacizumab reference product was demonstrated in the ITT-population, with RD of ORR at week 19 within the pre-specified equivalence margin (-13% to 13%). Equivalence between PF-06439535 and reference bevacizumab was also shown by RD of ORR in the PP population.

From the statistical point of view, the choice of the margin using the 95-95 rule seems reasonable. Since the treatment effect attributable to bevacizumab is small, the applicant should have provided clinical justification for the equivalence margin obtained in the study, in addition to the statistical considerations in the report. However, based on similar studies it is likely that the confidence interval for the difference obtained in the study would have been within a clinically justifiable margin.

The secondary outcomes (PFS, duration of response, OS) as well as the different sensitivity analyses were in line with the primary outcome, supporting the biosimilarity claim between PF-06439535 and the bevacizumab reference product.

In conclusion, from an efficacy point of view, the MAA of PF-06439535 is approvable as a biosimilar to Avastin (bevacizumab-EU). Since the mechanism of action of bevacizumab is the same independent of indication, extrapolation to all other indications labelled for the reference product bevacizumab is considered acceptable.

2.5. Clinical safety

Comparative safety data of PF-06439535 was derived from two clinical studies:

- Study B7391001 was a, double blind, randomized, parallel-group, single-dose, 3-arm, comparative PK study of PF-06439535 and bevacizumab sourced from the US and EU administered to healthy males.
- Study B7391003 was a multinational, parallel arm, randomized, double-blind, multiple dose study to compare the safety and efficacy of PF-06439535 plus paclitaxel and carboplatin with bevacizumab-EU plus paclitaxel and carboplatin in first-line treatment of advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous-non-small cell lung cancer (NSCLC).

The safety population consists of a total of 815 subjects who received at least 1 dose of study medication in studies B7391001 (101 subjects) and B7391003 (714 subjects) of which 388 subjects received PF-06439535. The safety data represent the final data when all patients have completed the week 55 visit.

Patient exposure

Study B7391001

The subjects were randomized to one of the three arms to receive a single IV dose of 5 mg/kg of PF-06439535 or bevacizumab-EU or bevacizumab-US. Exposure to investigational product was comparable across the treatment groups; 33 subjects in the PF-06439535 arm, 35 subjects in the bevacizumab-EU arm and 33 subjects in the bevacizumab US arm.

Study B7391003

Patients were randomized in a 1:1 ratio to receive a IV dose of 15 mg/kg of PF-06439535 plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin for at least four and no more than six cycles (1 Cycle=21 days [3 week] ± 4 days), followed by the assigned blinded bevacizumab monotherapy. A total of 356

patients received study treatment in the PF-06439535 treatment arm and 358 in the bevacizumab-EU treatment arm.

Table 26: Summary of treatment exposure for Bevacizumab, Paclitaxel, and Carboplatin – Safety population study B7391003

	PF-06439535 (N=356)			Bevacizumab-EU (N=358)			Total (N=714)		
	Bevacizumab	Paclitaxel	Carboplatin	Bevacizumab	Paclitaxel	Carboplatin	Bevacizumab	Paclitaxel	Carboplatin
Summary of duration (cycles):									
Number of patients	355	356	356	358	358	358	713	714	714
Mean	10.7	4.9	4.9	10.7	5.0	5.0	10.7	4.9	5.0
SD	6.77	1.52	1.52	6.67	1.45	1.41	6.72	1.49	1.47
Median	10.0	6.0	6.0	10.0	6.0	6.0	10.0	6.0	6.0
Range	1-32	1-6	1-6	1-30	1-6	1-6	1-32	1-6	1-6
Number (%) of patients in treated cycle:									
≥1	355 (99.7)	356 (100.0)	356 (100.0)	358 (100.0)	358 (100.0)	358 (100.0)	713 (99.9)	714 (100.0)	714 (100.0)
≥2	336 (94.4)	335 (94.1)	335 (94.1)	344 (96.1)	344 (96.1)	345 (96.4)	680 (95.2)	679 (95.1)	680 (95.2)
≥3	318 (89.3)	317 (89.0)	317 (89.0)	325 (90.8)	323 (90.2)	327 (91.3)	643 (90.1)	640 (89.6)	644 (90.2)
≥4	302 (84.8)	303 (85.1)	304 (85.4)	312 (87.2)	308 (86.0)	313 (87.4)	614 (86.0)	611 (85.6)	617 (86.4)
≥5	280 (78.7)	228 (64.0)	230 (64.6)	290 (81.0)	234 (65.4)	238 (66.5)	570 (79.8)	462 (64.7)	468 (65.5)
≥6	265 (74.4)	201 (56.5)	204 (57.3)	278 (77.7)	207 (57.8)	211 (58.9)	543 (76.1)	408 (57.1)	415 (58.1)
≥7	241 (67.7)	0	0	253 (70.7)	0	0	494 (69.2)	0	0

The number of patients in each treated cycles (up to ≥cycle 35) for the monotherapy setting is similar in the two treatment groups.

Adverse events

Study B7391001

Of the 101 subjects that received study drug, 55 subjects (54.5%) experienced 107 AEs. The majority of these were Grade 1 or Grade 2. The most common all-causality TEAEs (reported in >3 subjects) were upper respiratory tract infection, headache, dyspepsia, myalgia and diarrhoea.

Table 27: Summary of Treatment-Emergent Adverse Events (All Causalities) – Safety Population, Study B7391001

	PF-06439535	Bevacizumab		Total
		-EU	-US	
Subjects Evaluable for AEs	**N=33 (%)**	**N=35 (%)**	**N=33 (%)**	**N=101 (%)**
Number of adverse events	30	45	32	107
Subjects with adverse events	16 (48.5)	22 (62.9)	17 (51.5)	55 (54.5)
Subjects with serious adverse events	0	1 (2.9)	0	1 (1.0)
Subjects with grade 3 or 4 adverse e	0	1 (2.9)	0	1 (1.0)
Subjects with grade 5 adverse events	0	0	0	0
Subjects discontinued due to adverse events	0	0	0	0
Subjects with dose reduced due to adverse events	0	0	0	0
Subjects with temporary discontinuation due to adverse events	0	0	0	0

Treatment related AEs

Twenty (19.8%) subjects experienced 31 treatment-related AEs. The majority of the treatment related AEs were Grade 1 or Grade 2. The most common treatment-related AEs (reported in >2 subjects) were Dyspepsia (1 in the PF-06439535 arm, 2 in the bevacizumab-EU arm and 1 in the bevacizumab-US arm) and Rash macular (1 in the PF-06439535 arm and 2 in the bevacizumab-EU arm).

Study B7391003

Table 28: Treatment-emergent adverse events occurring in ⩾10% of patients in any treatment group (All-Causalities) by combination therapy and monotherapy (Study B7391003)

System Organ Class and Preferred Term	PF-06439535		Bevacizumab-EU		Total	
	Combination Therapy (N=356) n (%)	Bevacizumab Monotherapy (N=254) n (%)	Combination Therapy (N=358) n (%)	Bevacizumab Monotherapy (N=262) n (%)	Combination Therapy (N=714) n (%)	Bevacizuma Monotherap (N=516) n (%)
Total	310 (87.1)	161 (63.4)	311 (86.9)	167 (63.7)	621 (87.0)	328 (63.6)
Blood and lymphatic system disorders						
Anaemia	85 (23.9)	39 (15.4)	97 (27.1)	24 (9.2)	182 (25.5)	63 (12.2)
Neutropenia	54 (15.2)	17 (6.7)	58 (16.2)	16 (6.1)	112 (15.7)	33 (6.4)
Thrombocytopenia	53 (14.9)	19 (7.5)	59 (16.5)	21 (8.0)	112 (15.7)	40 (7.8)
Gastrointestinal disorders						
Constipation	35 (9.8)	4 (1.6)	26 (7.3)	5 (1.9)	61 (8.5)	9 (1.7)
Diarrhoea	38 (10.7)	11 (4.3)	45 (12.6)	8 (3.1)	83 (11.6)	19 (3.7)
Nausea	64 (18.0)	11 (4.3)	66 (18.4)	7 (2.7)	130 (18.2)	18 (3.5)
Vomiting	34 (9.6)	9 (3.5)	26 (7.3)	10 (3.8)	60 (8.4)	19 (3.7)
General disorders and administration site conditions						
Asthenia	36 (10.1)	14 (5.5)	33 (9.2)	13 (5.0)	69 (9.7)	27 (5.2)
Fatigue	56 (15.7)	26 (10.2)	49 (13.7)	28 (10.7)	105 (14.7)	54 (10.5)
Investigations						
Alanine aminotransferase increased	30 (8.4)	27 (10.6)	20 (5.6)	23 (8.8)	50 (7.0)	50 (9.7)
Aspartate aminotransferase increased	23 (6.5)	30 (11.8)	19 (5.3)	24 (9.2)	42 (5.9)	54 (10.5)
Weight decreased	19 (5.3)	18 (7.1)	20 (5.6)	14 (5.3)	39 (5.5)	32 (6.2)
Metabolism and nutrition disorders						
Decreased appetite	36 (10.1)	15 (5.9)	38 (10.6)	10 (3.8)	74 (10.4)	25 (4.8)
Musculoskeletal and connective tissue disorders						
Arthralgia	36 (10.1)	6 (2.4)	41 (11.5)	2 (0.8)	77 (10.8)	8 (1.6)
Myalgia	53 (14.9)	4 (1.6)	47 (13.1)	6 (2.3)	100 (14.0)	10 (1.9)
Nervous system disorders						
Headache	18 (5.1)	14 (5.5)	24 (6.7)	17 (6.5)	42 (5.9)	31 (6.0)
Neuropathy peripheral	49 (13.8)	7 (2.8)	58 (16.2)	13 (5.0)	107 (15.0)	20 (3.9)
Paraesthesia	38 (10.7)	12 (4.7)	31 (8.7)	2 (0.8)	69 (9.7)	14 (2.7)
Peripheral sensory neuropathy	33 (9.3)	4 (1.6)	43 (12.0)	8 (3.1)	76 (10.6)	12 (2.3)
Respiratory, thoracic and mediastinal disorders						
Cough	28 (7.9)	18 (7.1)	31 (8.7)	20 (7.6)	59 (8.3)	38 (7.4)
Dyspnoea	22 (6.2)	14 (5.5)	26 (7.3)	13 (5.0)	48 (6.7)	27 (5.2)
Epistaxis	36 (10.1)	9 (3.5)	26 (7.3)	9 (3.4)	62 (8.7)	18 (3.5)
Skin and subcutaneous tissue disorders						
Alopecia	165 (46.3)	10 (3.9)	163 (45.5)	16 (6.1)	328 (45.9)	26 (5.0)
Vascular disorders						
Hypertension	40 (11.2)	26 (10.2)	45 (12.6)	26 (9.9)	85 (11.9)	52 (10.1)

Combination therapy includes chemotherapy-only cycles.
For one patient, the 7th cycle of chemotherapy which was recorded on Concomitant Medication was excluded from this summary
Abbreviations: EU=European Union; N=number of patients evaluable for AEs; n=number of patients that met the criteria.

TEAEs of grade 3 or higher

A total of 343 (48%) patients that had a TEAE reported a Grade 3 or higher, 171 [48%] and 172 [48%] patients in the PF-06439535 and bevacizumab-EU group, respectively. The most frequently reported (≥5%) Grade 3 or higher TEAEs were hypertension, with 33 (9.3%) patients in the PF-06439535 group and 31 (8.7%) patients in the bevacizumab-EU group followed by neutropenia with 26 (7.3%) patients in the PF-06439535 group and 32 (8.9%) patients in the bevacizumab-EU group and anaemia with 19 (5.3%) patients in the PF-06439535 group

and 18 (5.0%) patients in the bevacizumab-EU group. Grade 3 or higher febrile neutropenia was reported in a total of 18 patients (nine [2.5%] patients in each arm).

Table 29: Treatment-Emergent Adverse Events of Grade 3 or Higher by MedDRA Preferred Term in ≥5% of Patients in Either Treatment Group (All Causalities) - Safety Population, Study B7391003

Number (%) of Patients with AEs by MedDRA[a] Preferred Term	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Any AEs	**171 (48.0)**	**172 (48.0)**	**343 (48.0)**
Hypertension	33 (9.3)	31 (8.7)	64 (9.0)
Neutropenia	26 (7.3)	32 (8.9)	58 (8.1)
Anaemia	19 (5.3)	18 (5.0)	37 (5.2)

Source: Table 14.3.1.2.4.2
Included data up to 28 days after the last dose of study drug or to start of subsequent anti-cancer therapy (whichever came first).
Abbreviations: AE=adverse event, EU=European Union, MedDRA=Medical Dictionary for Regulatory Activities, N=number of patients evaluable for AEs.
a. MedDRA version 20.1 coding dictionary applied.

Bevacizumab related TEAEs

Bevacizumab-related TEAEs were those AEs considered related to bevacizumab with or without causal relationship to chemotherapy in accordance to the investigator's assessment.

Table 30: Treatment-Emergent Adverse Events (Bevacizumab-Related)[a] – Safety Population, Study B7391003

Number (%) of Patients	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Number of adverse events	625	574	1199
Patients with adverse events	190 (53.4)	199 (55.6)	389 (54.5)
Patients with serious adverse events	23 (6.5)	17 (4.7)	40 (5.6)
Patients with Grade 3 or 4 adverse events	60 (16.9)	49 (13.7)	109 (15.3)
Patients with Grade 5 adverse events	6 (1.7)	1 (0.3)	7 (1.0)
Patients discontinued any treatment due to adverse events	33 (9.3)	25 (7.0)	58 (8.1)
Patients discontinued bevacizumab only due to adverse events	16 (4.5)	12 (3.4)	28 (3.9)
Patients discontinued bevacizumab and chemotherapy due to adverse events	13 (3.7)	9 (2.5)	22 (3.1)
Patients discontinued paclitaxel due to adverse events	17 (4.8)	13 (3.6)	30 (4.2)
Patients discontinued carboplatin due to adverse events	16 (4.5)	13 (3.6)	29 (4.1)
Patients temporarily discontinued bevacizumab only due to adverse events	16 (4.5)	11 (3.1)	27 (3.8)
Patients temporarily discontinued bevacizumab and chemotherapy due to adverse events	15 (4.2)	13 (3.6)	28 (3.9)
Patients temporarily discontinued paclitaxel due to adverse events	16 (4.5)	14 (3.9)	30 (4.2)
Patients temporarily discontinued carboplatin due to adverse events	14 (3.9)	13 (3.6)	27 (3.8)
Patients with dose reduction of bevacizumab only due to adverse events	0	0	0
Patients with dose reduction of bevacizumab and chemotherapy due to adverse events	0	0	0
Patients with dose reduction of paclitaxel due to adverse events	4 (1.1)	7 (2.0)	11 (1.5)
Patients with dose reduction of carboplatin due to adverse events	6 (1.7)	7 (2.0)	13 (1.8)

Included data up to 28 days after the last dose of study drug or to start of subsequent anti-cancer therapy (whichever came first).
Except for the "number of adverse events", patients were counted only once per treatment in each row.
Serious adverse events - according to the investigator's assessment.
Severity counts were based on the maximum severity or grade of events.
MedDRA version 20.1 coding dictionary applied.
Abbreviations: AE=adverse event; EU=European Union, IRR=infusion related reaction; MedDRA=Medical Dictionary for Regulatory Activities, N=number of patients evaluable for adverse events.
a. AEs related to bevacizumab with or without causal relationship to chemotherapy.
b. Bevacizumab discontinuations may have occurred concurrently with chemotherapy discontinuations.
c. Unifying diagnosis of 'infusion related reaction' included instead of the individual signs and symptoms of IRRs.

The most frequently reported Grade 3 and 4 bevacizumab-related TEAEs were hypertension, with 23 (6.5%) patients (Grade 3: 23) in the PF-06439535 group, and 14 (3.9%) patients (Grade 3: 14) in the bevacizumab-EU group followed by neutropenia with 6 (1.7%) patients (Grade 3: 4 [1.1%]; Grade 4: 2 [0.6%]) in the PF-06439535 group and 8 (2.2%) patients (Grade 3: 2 [0.6%]; Grade 4: 6 [1.7%]) in the bevacizumab-EU group) and anaemia, with 5 (1.4%) patients (Grade 3: 5) in the PF-06439535 group and 4 (1.1%) patients (Grade 3: 4) in the bevacizumab-EU group.

Bevacizumab related TEAEs were similar both in the combination and/or monotherapy setting.

Other significant adverse events

- **Infusion related reactions (IRR)**

Study B7391003

Table 31: Summary of infusion related reaction (all causalities) – safety population, study B7391003

Number (%) of Patients	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Number of adverse events	22	36	58
Patients with adverse events	19 (5.3)	22 (6.1)	41 (5.7)
Patients with serious adverse events	0	1 (0.3)	1 (0.1)
Patients with Grade 3 or 4 adverse events	6 (1.7)[a]	5 (1.4)[a]	11 (1.5)[a]
Patients with Grade 5 adverse events	0	0	0
Patients discontinued any treatment due to adverse events	0	4 (1.1)	4 (0.6)

Included data up to 28 days after the last dose of study drug or to start of subsequent anti-cancer therapy (whichever came first).
Except for the "number of adverse events", patients were counted only once per treatment in each row.
Serious adverse events - according to the investigator's assessment.
Severity counts were based on the maximum severity or grade of events.
MedDRA version 20.1 coding dictionary applied.
Abbreviations: EU=European Union, MedDRA=Medical Dictionary for Regulatory Activities, N=number of patients evaluable for adverse events.
a. No patients had Grade 4 adverse events.

Hypertension is the most frequently reported IRR (10 [2.8%] patients in the PF-06439535 group and 11 [3.1%] in the bevacizumab EU group) - each treatment group for all causality IRRs. Ten (2.8%) patients in the PF-06439535 group and 8 (2.2%) patients in the bevacizumab EU group experienced bevacizumab-related hypertension.

There were no IRR related SAEs reported and no temporary or permanent study treatment discontinuations due to bevacizumab-related IRRs.

- **Potential hypersensitivity/Anaphylaxis**

Study B7391003

Table 32: Summary of Treatment-Emergent Adverse Events (All Causalities - Anaphylactic Reaction and Hypersensitivity) - Safety Population, study B7391003

Number (%) of Patients	PF-06439535 N=356	Bevacizumab-EU N=358
Number of TEAEs	178	207
Number (%) of patients with		
Any TEAEs	114 (32.0)	132 (36.9)
Grade 3 or higher TEAEs	16 (4.5)	21 (5.9)
Treatment-related TEAEs	72 (20.2)	71 (19.8)
Bevacizumab-related TEAEs	44 (12.4)	38 (10.6)
Treatment-related TEAEs resulting in discontinuation	2 (0.6)	5 (1.4)
Bevacizumab related TEAEs resulting in discontinuation	2 (0.6)	1 (0.3)
Serious TEAEs	6 (1.7)	9 (2.5)
Serious TEAEs resulting in bevacizumab discontinuation	4 (1.1)	3 (0.8)

Bevacizumab Related: Related to Bevacizumab with or without background chemotherapy.
Treatment Related: Related to Bevacizumab, Paclitaxel and/or Carboplatin.

Treatment-emergent adverse event of special interest

In Study B7391003, TEAEs of special interest were selected based on the established safety profile of Bevacizumab (as reported in the Avastin USPI and SmPC).

- **Arterial Thromboembolic Events (ATE)**

Study B7391003

Table 33: Risk Difference of Treatment-Emergent Arterial Thromboembolic Events (All Causalities) - Safety Population

Number (%) of Patients With AEs by SOC and MedDRA[a] Preferred Term	PF-06439535 (N=356)	Bevacizumab-EU (N=358)		95% Confidence Interval	
	n (%)		Risk Difference	Lower Limit	Upper Limit
Total	8 (2.2)	7 (2.0)	0.292	-2.009	2.640
Cardiac disorders					
Acute myocardial infarction	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Myocardial infarction	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Silent myocardial infarction	0	1 (0.3)	-0.279	-1.563	0.763
Nervous system disorders					
Cerebral ischaemia	2 (0.6)	0	0.562	-0.475	2.015
Cerebrovascular insufficiency	1 (0.3)	0	0.281	-0.772	1.558
Ischemic stroke	0	3 (0.8)	-0.838	-2.429	0.249
Vascular disorders					
Embolism arterial	2 (0.6)	1 (0.3)	0.282	-1.048	1.746
Peripheral artery thrombosis	1 (0.3)	0	0.281	-0.772	1.558
Arterial occlusive disease	0	1 (0.3)	-0.279	-1.563	0.763

Included data up to 28 days after the last dose of study drug or start of subsequent anti-cancer therapy (whichever was earlier).
95% CIs were provided to help gauge the precision of the estimates for risk difference.
CIs were not adjusted for multiplicity and were to be used for screening purposes only.
Risk difference was computed as PF-06439535 versus bevacizumab-EU.
Risk difference and its lower and upper limits were represented as percent in the report.
95% CIs were obtained using the exact method by Chan and Zhang (1999).

A total of 4 patients in the PF-06439535 group and 1 patient in the bevacizumab-EU group had a bevacizumab-related ATE, including acute myocardial infarction (Grade 5), cerebral ischemia (Grade 1), embolism arterial (Grade 3), and peripheral artery thrombosis (Grade 3), reported in 1 patient each in the PF-06439535 group and embolism arterial (Grade 3) and arterial occlusive disease (Grade 3) reported by 1 patient in the bevacizumab-EU group.

- **Bleeding/Haemorrhage**

Study B7391003

Table 34: Risk Difference of Treatment-Emergent Adverse Events of Special Interest (All Causalities) - Bleeding/Haemorrhage (Including Pulmonary Haemorrhage) - Safety Population

Number (%) of Patients With AEs by SOC and MedDRA[a] Preferred Term	PF-06439535 (N=356)	Bevacizumab-EU (N=358)		95% Confidence Interval	
	n (%)		Risk Difference	Lower Limit	Upper Limit
Total	83 (23.3)	69 (19.3)	4.041	-1.985	10.082
Gastrointestinal disorders					
Haematochezia	3 (0.8)	1 (0.3)	0.563	-0.810	2.186
Haemorrhoidal haemorrhage	2 (0.6)	0	0.562	-0.475	2.015
Gingival bleeding	17 (4.8)	16 (4.5)	0.306	-2.896	3.534
Anal haemorrhage	1 (0.3)	0	0.281	-0.772	1.558
Lip haemorrhage	1 (0.3)	0	0.281	-0.772	1.558
Lower gastrointestinal haemorrhage	1 (0.3)	0	0.281	-0.772	1.558
Melaena	1 (0.3)	0	0.281	-0.772	1.558
Mouth haemorrhage	1 (0.3)	0	0.281	-0.772	1.558
Rectal haemorrhage	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Haematemesis	0	1 (0.3)	-0.279	-1.563	0.763
Injury, poisoning and procedural complications					
Procedural haemorrhage	1 (0.3)	0	0.281	-0.772	1.558
Subarachnoid haemorrhage	0	1 (0.3)	-0.279	-1.563	0.763
Nervous system disorders					
Cerebral haemorrhage	1 (0.3)	0	0.281	-0.772	1.558
Haemorrhagic stroke	1 (0.3)	0	0.281	-0.772	1.558
Renal and urinary disorders					
Haematuria	8 (2.2)	9 (2.5)	-0.267	-2.734	2.159
Respiratory, thoracic and mediastinal disorders					
Epistaxis	41 (11.5)	33 (9.2)	2.299	-2.219	6.868
Haemoptysis	15 (4.2)	13 (3.6)	0.582	-2.387	3.612
Laryngeal haemorrhage	1 (0.3)	0	0.281	-0.772	1.558
Pulmonary haemorrhage	3 (0.8)	3 (0.8)	0.005	-1.669	1.694
Skin and subcutaneous tissue disorders					
Petechiae	0	1 (0.3)	-0.279	-1.563	0.763
Vascular disorders					
Haemorrhage	1 (0.3)	0	0.281	-0.772	1.558
Subgaleal haematoma	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Shock haemorrhagic	0	1 (0.3)	-0.279	-1.563	0.763

Source: Module 5.3.5.1 B7391003 (Week 55) Table 14.3.1.2.5.3.1
Included data up to 28 days after the last dose of study drug or start of subsequent anti-cancer therapy (whichever was earlier).
95% CIs were provided to help gauge the precision of the estimates for risk difference.
CIs were not adjusted for multiplicity and were to be used for screening purposes only.
Risk difference was computed as PF-06439535 versus bevacizumab-EU.
Risk difference and its lower and upper limits were represented as percent in the table.
95% CIs were obtained using the exact method by Chan and Zhang (1999).
Abbreviations: AE=adverse event; CI=confidence interval; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients evaluable for AEs; n=number of patients with the event; SOC=system organ class.
a. MedDRA version 20.1 coding dictionary applied.

The majority of the events of epistaxis and gingival bleeding were of Grade 1 or Grade 2 in both the treatment groups. There was one Grade 3 event of epistaxis in the PF-06439535 group which was reported as resolved at the time of this report. The majority of the bevacizumab-related haemoptysis events in both the treatment groups were of Grade 1 and Grade 2, and all of them resolved at the time of this report. One event of Grade 5 haemoptysis related to PF-06439535 was reported in the PF-06439535 group.

- **Cardiac disorder**

Study B7391003

Table 35: Risk Difference of Treatment-Emergent Cardiac Disorders (All Causalities) - Safety Population

Number (%) of Patients With AEs by SOC and MedDRA[a] Preferred Term	PF-06439535 (N=356)	Bevacizumab-EU (N=358)		95% Confidence Interval	
	n (%)		Risk Difference	Lower Limit	Upper Limit
Total	29 (8.1)	29 (8.1)	0.046	-4.053	4.152
Cardiac disorders					
Bundle branch block right	2 (0.6)	0	0.562	-0.475	2.015
Extrasystoles	2 (0.6)	0	0.562	-0.475	2.015
Mitral valve incompetence	2 (0.6)	0	0.562	-0.475	2.015
Tricuspid valve incompetence	2 (0.6)	0	0.562	-0.475	2.015
Tachycardia	4 (1.1)	3 (0.8)	0.286	-1.422	2.107
Left ventricular dysfunction	3 (0.8)	2 (0.6)	0.284	-1.253	1.943
Cardiac arrest	2 (0.6)	1 (0.3)	0.282	-1.048	1.746
Ventricular extrasystoles	2 (0.6)	1 (0.3)	0.282	-1.048	1.746
Angina unstable	1 (0.3)	0	0.281	-0.772	1.558
Degenerative aortic valve disease	1 (0.3)	0	0.281	-0.772	1.558
Diastolic dysfunction	1 (0.3)	0	0.281	-0.772	1.558
Left atrial dilatation	1 (0.3)	0	0.281	-0.772	1.558
Mitral valve sclerosis	1 (0.3)	0	0.281	-0.772	1.558
Sinus tachycardia	1 (0.3)	0	0.281	-0.772	1.558
Ventricular flutter	1 (0.3)	0	0.281	-0.772	1.558
Cardiac failure	2 (0.6)	2 (0.6)	0.003	-1.498	1.507
Acute coronary syndrome	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Acute myocardial infarction	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Cardiac septal hypertrophy	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Cardiovascular insufficiency	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Left ventricular hypertrophy	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Myocardial infarction	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Pericardial effusion	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Supraventricular extrasystoles	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Arrhythmia	1 (0.3)	2 (0.6)	-0.278	-1.752	1.059
Arteriosclerosis coronary artery	0	1 (0.3)	-0.279	-1.563	0.763
Bradycardia	0	1 (0.3)	-0.279	-1.563	0.763
Cardiomyopathy	0	1 (0.3)	-0.279	-1.563	0.763
Metabolic cardiomyopathy	0	1 (0.3)	-0.279	-1.563	0.763
Mitral valve disease	0	1 (0.3)	-0.279	-1.563	0.763
Myocardial ischaemia	0	1 (0.3)	-0.279	-1.563	0.763
Palpitations	0	1 (0.3)	-0.279	-1.563	0.763
Pericarditis	0	1 (0.3)	-0.279	-1.563	0.763
Right ventricular failure	0	1 (0.3)	-0.279	-1.563	0.763
Silent myocardial infarction	0	1 (0.3)	-0.279	-1.563	0.763
Sinus bradycardia	0	1 (0.3)	-0.279	-1.563	0.763
Supraventricular tachycardia	0	1 (0.3)	-0.279	-1.563	0.763
Cardio-respiratory arrest	0	2 (0.6)	-0.559	-2.003	0.495
Atrial fibrillation	0	3 (0.8)	-0.838	-2.429	0.249

Included data up to 28 days after the last dose of study drug or start of subsequent anti-cancer therapy (whichever was earlier).

95% CIs were provided to help gauge the precision of the estimates for risk difference.
CIs were not adjusted for multiplicity and were to be used for screening purposes only.
Risk difference was computed as PF-06439535 versus bevacizumab-EU.
Risk difference and its lower and upper limits were represented as percent in the table.
95% CIs were obtained using the exact method by Chan and Zhang (1999).
Abbreviations: AE=adverse event; CI=confidence interval; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients evaluable for AEs; n=number of patients with the event; SOC=system organ class.
a. MedDRA version 20.1 coding dictionary applied.

In total, the number of patients with cardiac disorders (all causality) were identical with 29 patients in each group. Bevacizumab-related cardiac disorder events were reported in eight (2.2%) patients in the PF 06439535 group and 7 (2.0%) in the bevacizumab-EU group.

The events of bevacizumab-related congestive heart failure were reported in one (0.3%) patient in the PF-06439535 group and two (0.6%) patients in the bevacizumab-EU group.

One (0.3%) patient each in PF-06439535 group and bevacizumab-EU group had Grade 3 or higher ejection fraction decreased. In the bevacizumab-EU group one (0.3%) patient each had Grade 3 or higher right ventricular failure and pulmonary oedema (all-causality).

- **Hypertension (Grade 3 or higher)**

Study B7391003

Table 36: Risk Difference of Treatment-Emergent Hypertension (Grade 3 or Higher)-Safety Population

Number (%) of Patients With AEs by SOC and MedDRA[a] Preferred Term	PF-06439535 (N=356)	Bevacizumab-EU (N=358)		95% Confidence Interval	
	n (%)		Risk Difference	Lower Limit	Upper Limit
Total	34 (9.6)	32 (8.9)	0.612	-3.711	4.949
Investigations					
Blood pressure increased	1 (0.3)	0	0.281	-0.772	1.558
Blood pressure systolic increased	0	1 (0.3)	-0.279	-1.563	0.763
Vascular disorders					
Hypertension	33 (9.3)	31 (8.7)	0.610	-3.645	4.883
Hypertensive crisis	0	1 (0.3)	-0.279	-1.563	0.763

Included data up to 28 days after the last dose of study drug or start of subsequent anti-cancer therapy (whichever was earlier).
95% CIs were provided to help gauge the precision of the estimates for risk difference.
CIs were not adjusted for multiplicity and were to be used for screening purposes only.
Risk difference was computed as PF-06439535 versus bevacizumab-EU.
Risk difference and its lower and upper limits were represented as percent in the table.
95% CIs were obtained using the exact method by Chan and Zhang (1999).
Abbreviations: AE=adverse event; CI=confidence interval; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients evaluable for AEs; n=number of patients with the event; SOC=system organ class.
a) MedDRA version 20.1 coding dictionary applied.

A total of 23 (6.5%) patients in the PF 06439535 group and 14 (3.9%) patients in the bevacizumab EU group had bevacizumab-related Grade 3 or higher hypertension.

- **Proteinuria/Nephrotic Syndrome**

Study B7391003

A total of 28 (7.9%) patients in the PF-06439535 group and 34 (9.5%) patients in the bevacizumab-EU group had an all-causality TEAE of proteinuria/nephrotic syndrome. Four (1.1%) patients in PF-06439535 group and

five (1.4%) patients in the bevacizumab-EU group had Grade 3 or higher TEAE of proteinuria. A total of 21 (5.9%) patients in the PF-06439535 group and 27 (7.5%) patients in the bevacizumab-EU group had bevacizumab related proteinuria nephrotic syndrome.

- **Venous Thromboembolic Events (VTEs)**

Study B7391003

Table 37: Risk Difference of Treatment-Emergent Venous Thromboembolic Events (All Causalities)-Safety Population

Number (%) of Patients With AEs by SOC and MedDRA[a] Preferred Term	PF-06439535 (N=356)	Bevacizumab-EU (N=358)		95% Confidence Interval	
	n (%)		Risk Difference	Lower Limit	Upper Limit
Total	13 (3.7)	11 (3.1)	0.579	-2.195	3.424
Respiratory, thoracic and mediastinal disorders					
Pulmonary embolism	10 (2.8)	6 (1.7)	1.133	-1.168	3.609
Pulmonary infarction	0	1 (0.3)	-0.279	-1.563	0.763
Vascular disorders					
Brachiocephalic vein occlusion	1 (0.3)	0	0.281	-0.772	1.558
Brachiocephalic vein thrombosis	1 (0.3)	0	0.281	-0.772	1.558
Deep vein thrombosis	1 (0.3)	1 (0.3)	0.002	-1.301	1.320
Paget-Schroetter syndrome	0	1 (0.3)	-0.279	-1.563	0.763
Subclavian vein thrombosis	0	1 (0.3)	-0.279	-1.563	0.763
Thrombophlebitis superficial	0	1 (0.3)	-0.279	-1.563	0.763
Venous thrombosis	0	1 (0.3)	-0.279	-1.563	0.763

Included data up to 28 days after the last dose of study drug or start of subsequent anti-cancer therapy (whichever was earlier).
95% CIs were provided to help gauge the precision of the estimates for risk difference.
CIs were not adjusted for multiplicity and were to be used for screening purposes only.
Risk difference was computed as PF-06439535 versus bevacizumab-EU.
Risk difference and its lower and upper limits were represented as percent in the table.
95% CIs were obtained using the exact method by Chan and Zhang (1999).
Abbreviations: AE=adverse event; CI=confidence interval; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients evaluable for AEs; n=number of patients with the event; SOC=system organ class.
a. MedDRA version 20.1 coding dictionary applied.

Grade 3 and 4 events of pulmonary embolism were reported in 8 (2.2%) patients in the PF-06439535 group and in four (1.1%) patients in the bevacizumab-EU group. From the eight patients with pulmonary embolism of Grade 3 or 4 in the PF-06439535 group, the causality was assessed as disease under study for three (0.8%) patients, PF-06439535 for four (1.1%) patients, of which one event was also attributed to paclitaxel and carboplatin in one (0.3%) patient, and disease under study in one (0.3%) patient also possibly attributable to PF-06439535. In the bevacizumab-EU group, Grade 3 and 4 events of pulmonary embolism were due to bevacizumab alone for three (0.8%) patients and disease under study for one (0.3%) patients.

- **Gastrointestinal (GI) Perforations**

Study B7391003

In the PF-06439535 group there were no GI perforation related events reported. In the bevacizumab-EU group there was one (0.3%) patient each with small intestinal perforation, appendicitis perforated and peritonitis. The event of peritonitis was Grade 1, and the event of small intestinal perforation and appendicitis perforated were

Grade 4 in one patient each. The grade 4 small intestinal perforation and appendicitis perforated were reported as resolved at the time of this report.

- **Wound Healing Complications**

Study B7391003

In the PF-06439535 group, one (0.3%) patient reported a TEAE wound abscess event. There were no events reported in the bevacizumab EU group.

- **Non-Gastrointestinal Fistula**

One grade 1 event of non-gastrointestinal fistula was reported for one (0.3%) patient in each treatment group.

- **Posterior Reversible Encephalopathy Syndrome (PRES)**

No TEAE of Posterior Reversible Encephalopathy Syndrome (PRES) was reported in either treatment group.

Serious adverse event/deaths/other significant events

Study B7391001

Two serious adverse events (SAE) were reported in this study:

- One SAE of Grade 4 concussion was reported for a subject who was involved in a motor vehicle accident as a passenger.
- One SAE of appendicitis occurred prior to study medication administration in one subject.

Both SAEs were assessed as not related to treatment by the investigator.

Study B7391003

Table 38: Treatment-Emergent Serious Adverse Events Occurring in ≥1% of Patients in Either Treatment Group (All Causalities, All Cycles) – Safety Population

Number (%) of Patients with AEs by MedDRA[a] Preferred Term	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Any AEs	**81 (22.8)**	**80 (22.3)**	**161 (22.5)**
Pneumonia	8 (2.2)	6 (1.7)	14 (2.0)
Febrile neutropenia	5 (1.4)	7 (2.0)	12 (1.7)
Neutropenia	4 (1.1)	6 (1.7)	10 (1.4)
Disease progression	4 (1.1)	5 (1.4)	9 (1.3)
Pulmonary embolism	7 (2.0)	2 (0.6)	9 (1.3)
Anaemia	2 (0.6)	5 (1.4)	7 (1.0)
Asthenia	4 (1.1)	1 (0.3)	5 (0.7)
Gastroenteritis	4 (1.1)	0	4 (0.6)
Hyponatraemia	4 (1.1)	0	4 (0.6)

Included data up to 28 days after the last dose of study drug or start of subsequent anti-cancer therapy (whichever was earlier).
Abbreviations: AE=adverse event; EU=European Union, MedDRA=Medical Dictionary for Regulatory Activities, N=number of patients evaluable for adverse events.
a. MedDRA version 20.1 coding dictionary applied.

In the PF-06439535 group, there were 34 (9.6%) patients, 15 (4.2%) patients, and 21 (5.9%) patients with maximum CTCAE Grade 3, Grade 4, and Grade 5 SAEs, respectively, and in the bevacizumab-EU group, the corresponding number of patients were 30 (8.4%), 20 (5.6%), and 24 (6.7%), respectively.

Bevacizumab related SAEs

A total of 23 (6.5%) patients in the PF-06439535 group, and 17 (4.7%) patients in the bevacizumab-EU group had at least 1 bevacizumab-related SAE. The most frequently reported bevacizumab-related SAEs were neutropenia, which was reported by 1 (0.3%) patient in the PF-06439535 group and 3 (0.8%) patients in the bevacizumab-EU group, and pulmonary embolism, which was reported by 2 (0.6%) patients in the PF-06439535 group and 2 (0.6%) patients in the bevacizumab-EU group. In the PF-06439535 group, there were 11 (3.1%) patients, 3 (0.8%) patients, and 6 (1.7%) patients with maximum CTCAE Grade 3, Grade 4, and Grade 5 bevacizumab-related SAEs, respectively, and in the bevacizumab-EU group, the corresponding number of patients were 5 (1.4%), 9 (2.5%), and 1 (0.3%), respectively.

Deaths

Study B7391003

Grade 5 TEAEs

In the PF 06439535 group, out of 356 patients that received study treatment, 21 (5.9%) patients had Grade 5, and in the bevacizumab-EU group, out of 358 patients, 24 (6.7%) patients had Grade 5 TEAEs within the safety reporting period TEAEs (all-causality). There was 1 bevacizumab-related Grade 5 event (pulmonary haemorrhage) in the bevacizumab-EU group and six bevacizumab-related Grade 5 events (acute myocardial infarction, pneumonia, haemoptysis, pulmonary haemorrhage, haemorrhage and death) in the PF-06439535 group.

Deaths for Overall Survival

Table 39: Summary of Deaths Reported During the Study – ITT Population

	PF-06439535	Bevacizumab-EU	Total
Number of Subjects	358	361	719
Death	144 (40.2)	149 (41.3)	293 (40.8)
Disease under Study	129 (36.0)	127 (35.2)	256 (35.6)
Study Treatment Toxicity	3 (0.8)	1 (0.3)	4 (0.6)
Unknown	3 (0.8)	10 (2.8)	13 (1.8)
Other	10 (2.8)	11 (3.0)	21 (2.9)

Patients may have more than one reported reason for the cause of death.

Laboratory findings

Study B7391003 (NSCLC Patients)

Hematology

The majority of patients in both treatment groups had hematology baseline values of Grade 0 or Grade 1. A few patients shifted from lower grades to Grade 4 as follows:

Platelet count: Ten (10, 3.2%) patients in the PF-06439535 group and 7 (2.1%) patients in the bevacizumab-EU group had post-baseline shifts to Grade 3 platelet count from baseline. Two (2, 0.6%) patients

in the PF-06439535 group and 7 (2.1%) patients in the bevacizumab-EU group had post-baseline shifts to Grade 4 platelet counts from baseline.

White blood cell counts: Six (6, 1.9%) patients in the PF-06439535 group and 15 (4.5%) patients in the bevacizumab-EU group had post-baseline shifts to Grade 3 white blood cell count from baseline. One (1, 0.3%) patient in the PF-06439535 group and 3 (0.9%) patients in the bevacizumab-EU group had post-baseline shifts to Grade 4 white blood cell count from baseline.

Hemoglobin: Sixteen (16, 4.7%) patients in the PF-06439535 group and 19 (5.5%) patients in the bevacizumab-EU group had post-baseline shifts to Grade 3 hemoglobin decreased/ anaemia from baseline. No patients had post-baseline shifts to Grade 4 hemoglobin decreased/anaemia in either treatment group.

Chemistry

The majority of patients in both treatment groups had chemistry baseline values of Grade 0 or Grade 1. Shifts from lower grades to higher Grades are as follows:

ALT: Nine (9, 2.6%) patients in the PF-06439535 group and 3 (0.9%) patients in the bevacizumab-EU group had post-baseline shifts to Grade 3 ALT from baseline. No patients had post-baseline shifts to Grade 4 ALT in either treatment group.

AST: Six (6, 1.8%) patients in the PF-06439535 group and 5 (1.4%) patients in the bevacizumab-EU group had post-baseline shifts to Grade 3 AST from baseline. No patients had post-baseline shifts to Grade 4 AST in either treatment group.

Alkaline phosphatase: One (1, 0.3%) patient in the PF-06439535 group and 2 (0.6%) patients in the bevacizumab-EU group had post-baseline Grade 3 alkaline phosphatase. No patients had post-baseline Grade 4 alkaline phosphatase in either treatment group.

Total bilirubin: Five (5, 1.5%) patients in the PF-06439535 group and 2 (0.6%) patients in the bevacizumab-EU group had post-baseline shifts to Grade 3 total bilirubin from baseline. No patients had post-baseline shifts to Grade 4 total bilirubin in either treatment group.

Serum or Plasma Creatinine: One (1, 0.3%) patient in the PF-06439535 group and 1 (0.3%) patient in the bevacizumab-EU group had post-baseline shifts to Grade 3 creatinine increase from baseline. No patients had post-baseline shifts to Grade 4 creatinine increase in either treatment group.

Albumin: Two (2, 0.6%) patients in the PF-06439535 group and no patients in the bevacizumab-EU group had post-baseline shifts to Grade 3 hypoalbuminemia from baseline. No patients had post-baseline shifts to Grade 4 hypoalbuminemia in either treatment group.

Sodium: Ninety-three (93) patients in the PF-06439535 group and 96 patients in the bevacizumab-EU group had low sodium results post-baseline. Of these patients, 26 (28%) patients in the PF-06439535 group and 22 (22.9%) patients in the bevacizumab-EU group had post-baseline Grade 3 hyponatremia. No patients in the PF-06439535 group and 2 (2.1%) patients in the bevacizumab-EU group had post-baseline Grade 4 hyponatremia.

Urine Protein

Based on the initial dipstick urinalysis results, no patients shifted to Grade 3 or Grade 4 proteinuria from lesser baseline Grades in either treatment group.

Individual Clinically Significant Laboratory Abnormalities

Of the safety population, 3 patients had elevated ALT or AST defined as ≥3 × ULN and elevated total bilirubin of ≥2 × ULN.

One patient in the PF-06439535 group experienced elevated ALT of 683 IU/L (16 × ULN, reference range: 8 - 42 IU/L), elevated total bilirubin 46.1 µmol/L (2.45 × ULN, reference range: 2 - 18.8 µmol/L) with AST and alkaline phosphatase within normal range on Study Day 106 after 6 cycles of combinational therapy and met the laboratory abnormalities component of the Hy's law criteria. The patient continued on maintenance blinded bevacizumab monotherapy for an additional 16 cycles without recurrence of LFTs and/or total bilirubin elevations. Considering the ALT, AST and bilirubin values normalized despite continuing the bevacizumab-blinded therapy and background paclitaxel and carboplatin; the study Sponsor did not attribute the increased ALT and increased total bilirubin to bevacizumab-blinded therapy, to background chemotherapy or to any study procedure.

The remaining 2 patients did not meet the Hy's law criteria. Two (2) patients had elevated alkaline phosphatase (cholestasis) concurrently with elevated AST or ALT and total bilirubin. The investigators reported the alternative cause of the elevations as disease under study for both cases.

Electrocardiograms

A review of the data concluded that no clinically meaningful differences were observed for ECGs between the 2 treatment groups.

Left Ventricular Ejection Fraction

The mean LVEF values were generally comparable across the 2 treatment groups. A total of 30 patients had a maximum decrease of 10% to 19% from Baseline in LVEF at the End of Treatment visit, among whom 13 patients were in the PF-06439535 group and 17 patients were in the bevacizumab-EU group. A total of 2 patients had a maximum decrease of ≥20% from Baseline in LVEF at the End of Treatment visit (1 patient each in the PF-06439535 group and the bevacizumab-EU group).

Immunological events

Results from analyses based on Week 55 data

Results of monitoring of immunogenicity, including long-term data until week 55, also showed comparable results between PF-06439535 and bevacizumab-EU, which supports biosimilarity.

Table 40: **Summary of ADA incidence by treatment group - safety population**

Visit	Criteria	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Cycle 1 (prior to treatment)	n	352	353	705
	Positive	1 (0.3)	3 (0.8)	4 (0.6)
	Negative	350 (99.4)	350 (99.2)	700 (99.3)
	Not tested	1 (0.3)	0	1 (0.1)
Overall (post-treatment)	n	339	350	689
	Positive	5 (1.5)	5 (1.4)	10 (1.5)
	Negative	334 (98.5)	345 (98.6)	679 (98.5)

Abbreviations: ADA=anti-drug antibody, EU=European Union, N=the number of patients who received study drug, n=the number of patients evaluated at each visit.

According to the applicant, percentages were based on the number of patients at each visit. All samples were taken prior to dosing. For calculation of the overall incidence of post-treatment ADA, n=number of patients with at least 1 post Cycle 1 ADA sample were tested. Patients with a positive ADA sample at any time post Cycle 1 were defined as having an overall positive ADA status. ADA positive samples was defined as ADA titer ≥2.29, ADA negative samples was defined as ADA titer <2.29.

Table 41: Summary of neutralising Ab incidence by treatment group - safety population

Visit	Criteria	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Cycle 1 (prior to treatment)	n	352	353	705
	Positive	1 (0.3)	0	1 (0.1)
	Negative	0	3 (0.8)	3 (0.4)
	Not tested	351 (99.7)	350 (99.2)	701 (99.4)
Overall (post-treatment)	n	339	350	689
	Positive	0	3 (0.9)	3 (0.4)
	Negative	339 (100.0)	347 (99.1)	686 (99.6)

Mean serum concentrations of PF-06439535 and bevacizumab-EU seemed to be comparable between the two treatment groups at selected time points from Baseline (Cycle 1 Day 1) through Cycle 18 Day 1 in both chemotherapy and monotherapy periods. The observed rate of both ADAs and NAbs was low, with comparable percentages of patients with ADAs and NAbs observed for both treatment groups.

Due to the low number of patients with ADAs, the association between immunogenicity and safety was difficult to evaluate. The presence of ADAs was apparently not associated with serious infusion related reactions or anaphylactic reactions.

No apparent impact of the observed ADAs on PK was seen, since the PK concentrations in the ones with ADA positive samples were in general close to the group average of the observed concentrations in the corresponding treatment group.

All five patients with treatment-emergent ADA in the PF-06439535 group had low titers and the observed treatment-emergent ADAs appeared to be transient. The same conclusion could be drawn for the bevacizumab-EU group, where the four patients with detected treatment-emergent ADAs had low titers and the treatment-emergent ADAs also appeared to be transient.

Discontinuation due to adverse events

Permanent Discontinuation From Study Due to Adverse Events

Study B7391003

Table 42: Reasons for Discontinuations from Treatment – Safety Population

Number (%) of patients	PF-06439535 (N=356)	Bevacizumab-EU (N=358)	Total (N=714)
Primary reason for discontinuation from bevacizumab treatment[a]			
Adverse event	52 (14.6)	39 (10.9)	91 (12.7)
Completed	2 (0.6)	0	2 (0.3)
Global deterioration of health status	14 (3.9)	10 (2.8)	24 (3.4)
Lost to follow-up	2 (0.6)	4 (1.1)	6 (0.8)
Objective progression or relapse	153 (43.0)	170 (47.5)	323 (45.2)
Other	5 (1.4)	5 (1.4)	10 (1.4)
Protocol violation	1 (0.3)	3 (0.8)	4 (0.6)
Patient died[b]	17 (4.8)	19 (5.3)	36 (5.0)
Patient refused continued treatment for reason other than adverse event	15 (4.2)	12 (3.4)	27 (3.8)
Total	**261 (73.3)**	**262 (73.2)**	**523 (73.2)**
Primary reason for discontinuation from paclitaxel treatment			
Adverse event	41 (11.5)	48 (13.4)	89 (12.5)
Completed	246 (69.1)	240 (67.0)	486 (68.1)
Global deterioration of health status	10 (2.8)	8 (2.2)	18 (2.5)
Lost to follow-up	1 (0.3)	3 (0.8)	4 (0.6)
Objective progression or relapse	27 (7.6)	26 (7.3)	53 (7.4)
Other	5 (1.4)	3 (0.8)	8 (1.1)
Protocol violation	0	3 (0.8)	3 (0.4)
Patient died[b]	13 (3.7)	14 (3.9)	27 (3.8)
Patient refused continued treatment for reason other than adverse event	6 (1.7)	6 (1.7)	12 (1.7)
Total	**349 (98.0)**	**351 (98.0)**	**700 (98.0)**
Primary reason for discontinuation from carboplatin treatment			
Adverse event	38 (10.7)	42 (11.7)	80 (11.2)
Completed	249 (69.9)	245 (68.4)	494 (69.2)
Global deterioration of health status	11 (3.1)	8 (2.2)	19 (2.7)
Lost to follow-up	1 (0.3)	3 (0.8)	4 (0.6)
Objective progression or relapse	26 (7.3)	26 (7.3)	52 (7.3)
Other	5 (1.4)	3 (0.8)	8 (1.1)
Protocol violation	0	3 (0.8)	3 (0.4)
Patient died[b]	13 (3.7)	15 (4.2)	28 (3.9)
Patient refused continued treatment for reason other than adverse event	6 (1.7)	6 (1.7)	12 (1.7)
Total	**349 (98.0)**	**351 (98.0)**	**700 (98.0)**

Completed: Patients had completed 4-6 cycles of carboplatin and paclitaxel.
Abbreviation: EU=European Union, N=number of patients who received study treatments.
[a]Bevacizumab discontinuations may have occurred concurrently with chemotherapy discontinuations.
[b]Death is the primary reason for treatment discontinuation. Other reasons for treatment discontinuation (e.g., adverse event, global deterioration of health status or disease progression) are reported for the remaining deaths which occurred during the safety reporting period.

The number of patients that temporarily discontinued from bevacizumab only due to AEs was similar in the two groups (11.8 % in PF-06439535 vs. 10.9% in the bevacizumab-EU group).

Blinded bevacizumab therapy continued until objective progression, intolerable toxicity or withdrawn consent.

2.5.1. Discussion on clinical safety

The safety population consisted of all subjects who received at least one dose of either PF06439535 from the single-dose, comparative PK study (study B7391001, N= 101) in healthy males and the phase 3, multi-dose study (study B7391003, N = 714) designed to compare the safety and efficacy in patients with advanced NSCLCs. The number of subjects exposed to PF-06439535 was 33 healthy males and 355 patients with advanced NSCLCs.

The safety population is considered sufficient to study relevant safety signals of this comparability exercise.

In study B7391001 the subjects were randomised to one of three arms (PF-06439535, bevacizumab-EU, bevacizumab-US) to receive a single IV dose of 5 mg/kg whereas in study B7391003 patients were randomized in a 1:1 ratio to receive a IV dose of 15 mg/kg of PF-06439535 plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin for at least four and no more than six cycles, followed by the assigned blinded bevacizumab monotherapy. Overall, in the B7391003 study, the extent of exposure was the same across both treatment groups with a mean duration of bevacizumab treatment being 12 cycles (week 55 data cutoff). Paclitaxel and carboplatin treatment also had a similar median duration of treatment across both arms. In addition, the number of patients in each treatment cycle in the monotherapy setting was also similar between the two groups. Similar numbers of subjects that experienced TEAEs were reported in the three arms of the single-dose study 7391001 in healthy volunteers with no clinically meaningful differences. Also, the number of subjects with AEs as per SOC and PT are small and similar, and do not indicate a clinically relevant difference in safety signals between PF-06439535, bevacizumab-EU and bevacizumab-US given as single dose of 5 mg/kg in the study B7391001 of healthy subjects. No infusion related reactions (IRRs) were reported in this study.

For study B7391003 the majority of patients (97 % in both arms) had at least one all causality TEAE, with similar number of patients that experienced SAE, grade 3 or 4 AE and grade 5 AE. Moreover, reported discontinuations were similar between the two groups and the primary reason for discontinuation of bevacizumab in both treatment groups was disease progression or relapse. The most frequently reported all causality TEAEs (>15%) were alopecia, anaemia, fatigue, nausea, neutropenia, thrombocytopenia, hypertension and peripheral neuropathy. The majority of the events reported were Grade 1 or Grade 2 in both treatment groups with the exception of hypertension, where 9% had Grade 3 events in both groups. All causality SAEs were reported for 22.8% in the PF-06439535 group and 22.3% in the bevacizumab-EU group, with the most frequent events including pneumonia, febrile neutropenia and pulmonary embolism with comparable numbers in both arms. Moreover, reported discontinuations were similar between the two groups and the primary reason for discontinuation of bevacizumab in both treatment groups was disease progression or relapse. The number of patients that temporarily discontinued from bevacizumab only due to AEs was similar in the two groups (11.8 % in PF-06439535 vs. 10.9% in the bevacizumab-EU group.

Approximately half of all patients experienced at least one bevacizumab-related TEAE, with an even distribution between the two groups for the totality of events. However, a numerical imbalance between the two groups is generally reported with a higher incidence of patients that experienced bevacizumab-related SAEs (6.5 % vs 4.7% in the PF-06439535 and bevacizumab-EU, respectively), grade 3 or 4 TEAEs (16.9 % vs 13.7%, respectively) and grade 5 TEAEs (1.7 % vs 0.3%, respectively) in the PF-06439535 arm. No clustering to a single SOC or PT was observed and the numerical imbalance is generally spread over the different PTs with few patients in each term (except for hypertension, neutropenia and anaemia that were reported most frequently). Based on the distribution of events over the different preferred terms, this difference is noteworthy, but is considered not to constitute a safety issue.

There were no bevacizumab-related IRR SAEs reported and no temporary or permanent study treatment discontinuations due to bevacizumab-related IRRs. For AESIs, similar frequencies were reported in both arms overall and considered to have no clinically meaningful differences.

Importantly, the reported TEAEs are generally in line with the safety profile of the reference product Avastin, with no new safety findings reported in this study. No deaths were reported in study B7391001.

In the PF-06439535 group 5.9% patients had Grade 5 events compared to 6.7% of patients in the bevacizumab-EU group, within the safety reporting period of TEAEs (all-causality). A notable difference in bevacizumab-related grade 5 events between the two arms was reported, with one bevacizumab-related Grade 5 event (pulmonary haemorrhage) in the bevacizumab-EU group and six bevacizumab-related Grade 5 events (acute myocardial infarction, pneumonia, haemoptysis, pulmonary haemorrhage, haemorrhage and death) in the PF-06439535 group. This may relate to the general tendency of numerically more TEAEs in the PF-06439535 group as compared to the bevacizumab group. Immunogenicity was demonstrated to be comparable between PF-06439535 and bevacizumab-EU also after updating with long-term results from week 55.

Laboratory values for both haematology and chemistry were generally comparable between the two treatment groups. Few and comparable shifts in haematology to Grade 4 were reported in the two arms. Two patients in the bevacizumab-EU group and 1 patient in the PF-06439535 group had a post-baseline shift to Grade 4 hyponatremia.

One patient in the PF-06439535 group experienced elevated ALT of 683 U/L (16 × ULN, reference range: 8 - 42 U/L), elevated total bilirubin 46.1 µmol/L (2.45 × ULN, reference range: 2 - 18.8 µmol/L) with AST and alkaline phosphatase within normal range on Study Day 106 after 6 cycles of combinational therapy and met the laboratory abnormalities component of the Hy's law criteria. The patient continued on maintenance blinded bevacizumab monotherapy for an additional 16 cycles without recurrence of LFTs and/or total bilirubin elevations. Considering the ALT, AST and bilirubin values normalized despite continuing the bevacizumab-blinded therapy and background paclitaxel and carboplatin, it is not considered that the increased ALT and increased total bilirubin is attributed to bevacizumab-blinded therapy, to background chemotherapy, or to any study procedure.

2.5.2. Conclusions on the clinical safety

Based on the safety documentation of comparative study B7391003 where PF-06439535 was compared to bevacizumab-EU (Avastin), no new safety signals different from the Avastin SmPC were detected. The submitted safety data are considered satisfactory to support a biosimilar claim for PF-06439535.

2.6. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Bleeding/haemorrhage Pulmonary haemorrhage Proteinuria

Summary of safety concerns	
	Arterial thromboembolic events (ATE) Hypertension Congestive heart failure Wound-healing complications Gastrointestinal perforations Posterior reversible encephalopathy syndrome (PRES) Neutropenia Venous thromboembolic events (VTE) Fistula (other than gastrointestinal) Thrombotic microangiopathy Pulmonary hypertension Ovarian failure Hypersensitivity reactions/infusion reactions Gallbladder perforation Peripheral sensory neuropathy Cardiac disorders (excluding CHF and ATE) Osteonecrosis of the jaw Necrotizing fasciitis Adverse events following off-label intravitreal use Embryo-foetal development disturbance Osteonecrosis in children
Important potential risks	None
Missing information	Safety profile of the different treatment combinations in patients with non-squamous NSCLC Long-term effects of bevacizumab when used in the paediatric population Safety and efficacy in patients with renal impairment

Summary of safety concerns	
	Safety and efficacy in patients with hepatic impairment Use in lactating women

Pharmacovigilance plan

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product. Specific adverse reaction follow-up questionnaires are in place in accordance with the reference product: Arterial Thromboembolic Events (ATE), Interstitial Lung Disease, Osteonecrosis of the Jaw and Congestive Heart Failure.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Bleeding/haemorrhage	SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.	None
Pulmonary haemorrhage	SmPC Sections 4.4 and 4.8; PL Sections 2 and 4.	None
Proteinuria	SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.	None
Arterial thromboembolic events	SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4. Data Capture Aids (DCA)	None
Hypertension	SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.	None
Congestive heart failure	SmPC Sections 4.4 and 4.8; PL Sections 2 and 4. Data Capture Aids (DCA)	None
Wound healing complications	SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.	None
Gastrointestinal perforation	SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.	None
Posterior Reversible Encephalopathy Syndrome (PRES)	SmPC Sections 4.4 and 4.8; PL Sections 2 and 4.	None
Neutropenia	SmPC Sections 4.4 and 4.8; PL Sections 2 and 4.	None
Venous thromboembolic events	SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.	None
Fistula (other than gastrointestinal)	SmPC Sections 4.4 and 4.8; PL	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Sections 2, 3, and 4.	
Thrombotic microangiopathy	SmPC Section 4.8; PL Section 4.	None
Pulmonary hypertension	SmPC Section 4.8; PL Section 4.	None
Ovarian failure	SmPC Sections 4.4, 4.6, and 4.8; PL Section 4.	None
Hypersensitivity reactions and infusion reactions	SmPC Sections 4.3, 4.4 and 4.8; PL Sections 2 and 4.	None
Gallbladder perforation	SmPC Sections 4.4 and 4.8; PL Section 4.	None
Peripheral sensory neuropathy	SmPC Section 4.8; PL Section 4.	None
Cardiac Disorders (excl. CHF and ATE)	SmPC Section 4.8; PL Section 4.	None
Osteonecrosis of the jaw	SmPC Sections 4.4 and 4.8; PL Sections 2 and 4. Data Capture Aids (DCA)	None
Necrotizing fasciitis	SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.	None
AEs following Off-Label lntravitreal Use	SmPC Section 4.4; PL Section 4.	None
Embryo-foetal development disturbance	SmPC Sections 4.3, 4.6, 4.8, and 5.3; PL Section 2.	None
Osteonecrosis in Children	SmPC Section 4.8; PL Section 2.	None
Missing information		
Safety profile of the different treatment combinations in patients with nonsquamous NSCLC	None.	None
Long-term use in paediatric patients	SmPC Section 4.2, 4.8, and 5.1; PL Section 2.	None
Patients with renal impairment	SmPC Section 4.2 and 5.2	None
Patients with Hepatic Impairment	SmPC Section 4.2 and 5.2	None
Use in Lactating Women	SmPC Section 4.3 and 4.6; PL Section 2.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable as the package leaflet will have the same content and layout as the reference medicinal product Avastin.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zirabev (bevacizumab) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

The applicant seeks a marketing authorisation in the same therapeutic indication as approved for bevacizumab-EU (Avastin) which are not currently under patent protection: Adult patients with metastatic carcinoma of the colon or rectum, metastatic breast cancer, unresectable advanced, metastatic or recurrent non-small cell lung cancer, advanced and/or metastatic renal cell cancer and persistent, recurrent, or metastatic carcinoma of the cervix.

Quality

To establish biosimilarity of PF-06439535 to Avastin bevacizumab-EU and bevacizumab-US on the quality level, an analytical similarity study was performed comparing PF-06439535 to reference bevacizumab-EU and bevacizumab-US. A total of 10 drug substance batches and 16 drug product batches of PF-06439535, 50 batches of the reference product bevacizumab-EU and 46 batches of bevacizumab-US drug product (400 mg/16 mL and 100 mg/4 mL presentations), were included in the analytical similarity study.

Non-clinical

Formal scientific advice from CHMP in 2015 included an opinion related to non-clinical development. In general the CHMP agreed that the proposed preclinical and pharmacological approach was sufficient for biosimilarity purposes. A GLP-compliant, 1-month, repeat-dose intravenous (IV) bolus comparative toxicity study in *Cynomolgus* monkeys of PF-06439535 with bevacizumab-EU has been conducted (Study 13GR179). In

addition, a non-comparative 2 week repeat-dose toxicity with only PF-06439535 was performed in rats, on the request of a regulatory authority outside Europe (Study 8305590).

Clinical

Pharmacokinetics

With the present application (EMEA/H/C/4697) the applicant provided study results from three clinical trials regarding pharmacokinetics.

In the phase I clinical study B7391002 in healthy subjects, the primary objective was to assess inter-subject variability in single dose pharmacokinetics (PK) of bevacizumab in healthy subjects and for the planning of the pivotal PK study.

The pivotal phase I clinical study B7391001 was conducted to compare the pharmacokinetics and pharmacodynamics following injection of 5 mg/kg body weight of PF-06439535 or bevacizumab (Avastin). Comparability could be concluded for both primary endpoints C_{max} and AUC_{inf}, and none of the other PK parameters revealed any statistically significant difference between PF-06439535 and Avastin.

In the phase III clinical study B7391003, no difference in C_{trough} was observed between the PF-06439535 and the bevacizumab groups at any time-point.

Efficacy and safety

Study B7391003: A completed, multinational, double-blind, randomised (1:1), parallel-group, multiple dose study evaluating the efficacy, safety, PK, and immunogenicity of PF-06439535 plus paclitaxel and carboplatin versus bevacizumab-EU plus paclitaxel and carboplatin in first-line treatment for patients with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC in the first-line treatment setting. The primary objective of the study was to compare the efficacy, immunogenicity and safety of PF-06439535 versus bevacizumab-EU. The primary endpoint was overall response rate (ORR)- the percent of patients within each treatment group that achieved complete response (CR) or partial response (PR) by Week 19 of the study and subsequently confirmed on a follow-up tumour assessment by Week 25, based on the pre-specified equivalence margins required by EMA. Data from week 55 support the secondary endpoints.

3.2. Results supporting biosimilarity

Quality

A comprehensive analytical similarity assessment which included comparative evaluations of biological activities, primary structure, higher order structure, N-linked glycan profile, charge heterogeneity, product purity (monomer, HMMS, HC+LC, fragments), disulfide bonds and forced degradation profiles. The biological activities were evaluated by a comprehensive set of functional assays and binding studies addressing both Fab and Fc-functions of the molecule. The inhibition of growth assay using HUVEC cells, used to measure potency, showed comparable responses for PF-06439535 and reference products. Comparable binding to VEGF target antigen by ELISA, was observed for isoforms $VEGF_{165}$, $VEGF_{121}$, $VEGF_{189}$ and $VEGF_{206}$. No differences are observed in FcRn, Fcγ and C1q binding. Additionally, no ADCC or CDC activity was observed.

Non-clinical

Overall, the results from the comparative toxicity study in *Cynomolgus* monkeys (Study 13GR179) add to the totality of evidence to support the demonstration of PF-06439535 as a biosimilar product to bevacizumab (EU). Repeated dose toxicity studies in non-human primates are usually not recommended for similar biological

products (EMA/CHMP/BMWP/403543/2010). From a 3R perspective and with reference to the European guidance document EMA/CHMP/BMWP/403543/2010, neither the study in monkey, nor the study in rat were warranted.

Clinical

Pharmacokinetics

Comparability between PF-06439535 and bevacizumab-EU at the PK level has been shown in an adequately performed phase I PK study and a phase III efficacy/safety study.

Efficacy

Trial B7391003 met its primary objective.

The results of the analysis of the primary endpoint, ORR, met the pre-specified equivalence criterion (-13% to 13%) for the ITT population, the ORR was similar between both treatment groups (45.3% in the PF-06439535 group and 44.6% in the bevacizumab-EU group). The analysis of ORR provided an un-stratified risk difference of 0.6531% (PF-06439535 versus bevacizumab-EU), with a 95% CI of (-6.6080%, 7.9082%), which fell within the pre-defined equivalence margins. Results obtained with the ITT population were supported by sensitivity analyses of the PP population and analysis of un-stratified risk ratio. Sensitivity analysis of data from Week 55 further supports the conclusion made above.

Safety

Based on the safety documentation of the phase III study B7391003 where PF-06439535 was compared to bevacizumab-EU (Avastin), no new safety signals different from the Avastin SmPC were detected. The safety data are comparable in the two treatment groups and considered satisfactory to support a biosimilar claim for PF-06439535.

Results of monitoring of immunogenicity, including long-term data until week 55, showed comparable results between PF-06439535 and bevacizumab-EU, also supporting biosimilarity.

3.3. Uncertainties and limitations about biosimilarity

Quality

For PF-06439535 batches, the relative potency (measured by inhibition of cell growth assay) was observed to be in the lower region compared to that of bevacizumab-EU. However, the statistical quality range for relative potency of bevacizumab-EU covers the range for PF-06439535. In addition, binding studies to isoforms of VEGF by ELISA demonstrated comparable results between PF-06439535 and bevacizumab-EU.

Clinical

N/A

3.4. Discussion on biosimilarity

Quality

Analytical similarity of PF-06439535 drug product to reference product Avastin (bevacizumab-EU and bevacizumab-US) has been acceptably demonstrated, excepted for the potency measured by inhibition of cell growth assay (HUVEC assay).

Clinical

Pharmacokinetics

Comparability between PF-06439535 and Avastin at the PK level has been shown in a phase I PK similarity study and a phase III efficacy/safety study.

Efficacy

Similarity between PF-06439535 and EU-licensed bevacizumab reference product was demonstrated in the ITT population. Equivalence between PF-06439535 and reference bevacizumab was also supported by sensitivity analysis of the PP population.

Safety

No signals of new adverse reaction were detected in the comparative study and within the limitation of a single study with a limited number of patients, the safety profile of PF-06439535 versus bevacizumab-EU is considered similar.

3.5. Extrapolation of safety and efficacy

The mechanism of action of bevacizumab is the same, independent of indication. Therefore, extrapolation to all other indications labelled for the reference product bevacizumab is considered acceptable, provided that similarity of PF-06439535 to the bevacizumab reference product is convincingly demonstrated both at the quality, non-clinical and clinical level. Currently patented indications are excluded.

3.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Zirabev is considered biosimilar to the reference product Avastin. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zirabev is favourable in the following indication:

Zirabev in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.

Zirabev in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status, please refer to section 5.1.

Zirabev, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.

Zirabev in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer.

Zirabev, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.