EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/427966/2020
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Equidacent

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/005181/0000

Administrative information

Name of the medicinal product:	Equidacent
Applicant:	Centus Biotherapeutics Europe Limited 6th Floor South Bank House Barrow Street Dublin 4 IRELAND
Active substance:	BEVACIZUMAB
International Non-proprietary Name/Common Name:	bevacizumab
Pharmaco-therapeutic group (ATC Code):	other antineoplastic agents, monoclonal antibodies (L01XC07)
Therapeutic indication(s):	Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum. Bevacizumab 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. Bevacizumab in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline- containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Equidacent in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1. Bevacizumab, 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. Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1). Bevacizumab in combination with interferon alfa-2a is indicated for first-line treatment of adult patients with advanced and/or metastatic renal cell cancer. Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer (see section 5.1). Bevacizumab, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents. Bevacizumab, 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).
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	25 mg/mL
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)

Package size(s):	4 mL solution in a vial, pack of 1 vial 16 mL solution in a vial, pack of 1 vial

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List of abbreviations

%AUCext	The percentage of AUC0-∞ that is due to extrapolation from Ct to infinity
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell cytotoxicity
ALK	Anaplastic lymphoma kinase
AUC	Area under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve extrapolated to infinity
AUC_{0-T}	Area under the concentration-time curve to last quantifiable sampling time
BICR	Blinded independent central review
BOR	Best overall response
CD	Circular dichroism
CDC	Complement dependent cytotoxicity
CEX-HPLC	Cation Exchange High Performance Liquid Chromatography
CHO	Chinese Hamster Ovary
CI	Confidence interval
cIEF	Capillary isoelectric focusing
CL	Clearance
C_{max}	Maximum concentration
CQA	Critical quality attribute
CR	Complete response
CSR	Clinical study report
Ct	Last quantifiable sampling time
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
DCO	Data cut-off
DNA	Deoxyribonucleic Acid
DP	Drug product
DS	Drug Substance
DSC	Differential scanning calorimetry
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
EU-Avastin	European Union-approved Avastin
FDS	Forced degradation studies
GCP	Good Clinical Practice
HCP	Host Cell Protein
HER2	Human Epidermal Growth Factor Receptor 2
HMWS	High molecular weight species detection
HPLC	High Performance Liquid Chromatography
ICH	International Council for Harmonisation
IgG1	Immunoglobulin G1
IP	Investigational product
IPC	In-process Controls
IRR	Infusion-related reactions
ITT	Intent-to-treat

iv	Intravenous
LC	Liquid Chromatography
LC-MS	Liquid chromatography mass spectrometry
LMWS	Low molecular weight species
LS	Least squares
LVEF	Left ventricular ejection fraction
MAA	Marketing Authorisation Application
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MoA	Mechanism of action
MS	Mass Spectroscopy
MSD	Meso Scale Discovery
NAb	Neutralising antibody
NS-NSCLC	Non-squamous, non-small cell lung cancer
OD	Optimal density
ORR	Overall response rate
OS	Overall survival
PA	Process attributes
PD	Progressive disease
PFS	Progression-free survival
PI	Isoelectric point
PP	process parameter
PPS	Per Protocol Set
PR	Partial response
PT	Preferred term
PVDF	Polyvinylidene difluoride
QA	Quality assurance
RMP	Reference medicinal product
RT	Retention time
SAE	Serious adverse event
SD	Standard deviation
SE	Size Exclusion
SE-HPLC	Size exclusion high precision liquid chromatography
SOC	System organ class
SPR	Surface plasma resonance
SUB	Single use bioreactor
$t_{1/2}$	Half-life
TEADR	Treatment-emergent adverse drug reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIC	Total ion chromatogram
t_{max}	Time to maximum concentration
TSE	Transmitting Animal Spongiform Encephalopathy
US	United States
US-Avastin	United States-licensed Avastin
USP	United States pharmacopeia
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WCB	Working Cell Bank
WoC	Withdrawal of consent

λ_z	Elimination rate constant

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Centus Biotherapeutics Europe Limited submitted on 13 September 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Equidacent, 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 indications:

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

Bevacizumab 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.

Bevacizumab in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline- containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with bevacizumab in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1.

Bevacizumab, 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.

Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1).

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

Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer (see section 5.1).

Bevacizumab, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

Bevacizumab, 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.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Avastin 25 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 01/12/2005
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/04/300/001-002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Avastin 25 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 01/12/2005
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/04/300/001-002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Avastin 25 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 01/12/2005
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation numbers: EU/1/04/300/001-002

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 submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant received Scientific Advice on 26 March 2015 (EMEA/H/SA/3041/1/2015/III) and 17 December 2015 (EMEA/H/SA/3041/1/FU/1/2015/III) for the development programme supporting the

indication granted by CHMP.

The Scientific Advice pertained to the following quality, preclinical and clinical aspects of the dossier:

Quality:

- The strategy to support a demonstration of biosimilarity in terms of physicochemical and biological analyses.
- The strategy to demonstrate the suitability of the biosimilar candidate formulation.
- The comparability exercise to support the DP manufacturing facility change.
- The suitability of HUVEC potency assay versus a cell-based reporter gene bioassay.

Preclinical:

- The appropriateness and adequacy of the non-clinical comparability studies to demonstrate similarity to the reference medicinal product.

The main clinical aspects under consideration were:

- The design of the PK study in healthy volunteer to demonstrate similarity in PK profiles of the biosimilar candidate, EU Avastin, and US Avastin.
- The design of the efficacy/safety trial in patients with advanced/recurrent non-squamous non-small cell lung cancer and supportive PK assessment to demonstrate biosimilarity of the biosimilar candidate to the reference medicinal product. Aspects pertained the population selected, the primary endpoint, the selected dose/regime of the study drugs and the combination chemotherapy, the proposed equivalence margin, the statistical assumptions, the duration of the trial and the safety and immunogenicity evaluation.
- Extrapolation of the clinical results in non-small cell lung cancer to support registration in the other indications approved for the reference medicinal product.

Date	**Reference**	**SAWP Co-ordinators**
26/03/2015	EMEA/H/SA/3041/1/2015/III	*Dr Juha Kolehmainen, Mr Christian Gartner*
17/12/2015	EMEA/H/SA/3041/1/FU/1/2015/III	*Dr Walter Janssens, Dr Ira Palminger Hallen*

1.2. Steps taken for the assessment of the product

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

Rapporteur: Ingrid Wang Co-Rapporteur: Outi Mäki-Ikola

The application was received by the EMA on	13 September 2019
The procedure started on	3 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	19 December 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	19 December 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	20 December 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 January 2020
The applicant submitted the responses to the CHMP consolidated List of	27 March 2020

Questions on	
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at an investigator site in Russia, at an investigator site in Bosnia and Herzegovina and at the sponsor site between 13 January and 14 February 2020. The outcome of the inspection carried out was issued on 1 April 2020	14 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	4 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 May 2020
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	28 May 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	08 July 2020
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 Equidacent on	23 July 2020
The CHMP adopted a report on similarity of Equidacent with Zejula on (Appendix 1)	23 July 2020

2. Scientific discussion

2.1. Problem statement

About the product

Equidacent (FKB238) has been developed as a biosimilar to the reference product Avastin (bevacizumab).

Equidacent belongs to the pharmacotherapeutic group "monoclonal antibodies" (ATC code: L01XC07).

Bevacizumab selectively binds to human VEGF and inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralizing the biologic activity of VEGF reduces the vascularization of tumours, thereby inhibiting tumour growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was also inhibited, and microvascular permeability was reduced.

The applicant is seeking all the indications for which Avastin is licensed in the EU, except for the treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. The recommended posology and method of administration correspond to those of Avastin.

Equidacent must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

2.2. Quality aspects

2.2.1. Introduction

Equidacent is a biosimilar medicinal product (reference product Avastin). It is presented as a sterile concentrate for solution for infusion containing 100 mg of bevacizumab in a 4 mL vial or 400 mg bevacizumab in a 16 mL vial. Each mL of concentrate contains 25 mg of bevacizumab (25 mg/mL). The active substance bevacizumab (also referred to as FKB238) is formulated with commonly used excipients: sodium L-glutamate, sorbitol (E420), polysorbate 80, hydrochloric acid (for pH-adjustment) and water for injections (WFI).

Equidacent is provided in a single use Type I glass vial with a butyl rubber stopper and an aluminium sealing cap. Equidacent is supplied in packs of 1 vial of 4 mL or 16 mL.

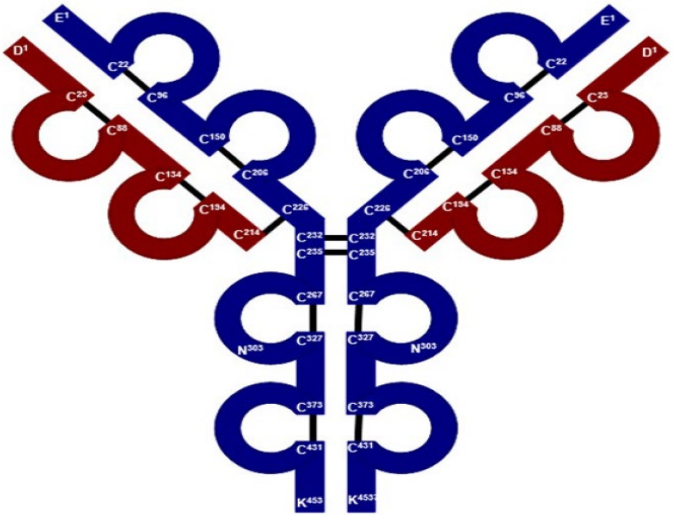
2.2.2. Active Substance

General information

Bevacizumab (also referred to as FKB238) is a recombinant humanised IgG1 monoclonal antibody produced by DNA technology in Chinese Hamster Ovary (CHO) cells. It selectively binds to human vascular endothelial growth factor (VEGF).

Bevacizumab is composed of two heavy chains (HC) (453 amino acid residues) and two light chains (LC) (214 amino acid residues) with a total molecular weight of 149 kDa. One N-linked glycosylation site is located at Asn303.

Figure 1 Primary structure of bevacizumab



HCs are shown in blue and LCs are shown in red.
Black lines show the location of disulfide bonds.
N303 of HC: glycosylation site

Manufacture, process controls and characterisation

Manufacture

The active substance is manufactured at Kyowa Kirin Co., Ltd., Takasaki Plant, 100-1 Hagiwara-machi, Takasaki, Gunma, 370-0013, Japan. The site is EU GMP compliant.

The manufacturing process follows a standard monoclonal antibody platform technology. The FKB238 active substance (AS) commercial manufacturing process starts from the Working Cell Bank (WCB) (derived from a CHO cell line) and is performed in two key stages: 1) Upstream cell culture process and 2) Downstream purification process.

FKB238 is produced in a CHO cell line by expansion in shake flasks and rocker bags, seed culture expansion in seed bioreactors, before fed-batch production and supernatant harvest. The subsequent downstream purification process consists of Protein A affinity chromatography, low-pH virus inactivation, cation exchange chromatography, multimodal chromatography, virus filtration ultrafiltration/diafiltration (UF/DF), formulation, filtration, bulk filling, and storage. The upstream and downstream processes have been adequately described.

Control of materials

Raw materials

Raw materials used in the active substance manufacturing process are controlled to ensure the quality and safety of the active substance and to maintain the consistency of the manufacturing process.

All manufacturing raw materials are accepted for use based on in-house testing to pre-determined specifications and/or the vendor Certificate of Analysis (CoA), according to written procedures, as required by current Good Manufacturing Practices (cGMP). Alternative suppliers or raw materials of the same quality grade may be used following a change control procedure upon completion of vendor qualification.

No raw materials of animal origin are used in the active substance manufacturing process or in the establishment of the master cell bank (MCB) and working cell bank (WCB).

Source, history and generation of the cell substrate

The source, the method of construction, and the structure of all expression vectors is included in the dossier, as well as the cDNA sequence and deduced amino acid sequence of heavy chain and light chain. The method of construction of the expression plasmid is adequately described.

A two-tiered cell banking system consisting of an MCB and WCB was utilised. The end-of-production cells (EOP) were collected from the end of fed-batch production culture of an active substance lot and were used to establish the cells at the limit of *in vitro* cell age used for production (LIVCA). Release tests, including safety and characterisation of the MCB and WCB and qualification of the LIVCA cells, were performed in accordance with the ICH guidelines Q5A, Q5B, and Q5D and are sufficiently described.

Control of critical steps and intermediates

Process parameters and in-process controls (IPCs) are defined and controlled by acceptable ranges and limits. The operating ranges are themselves the acceptable ranges or are set within the acceptable range of a process parameter, to allow for variance within the normal operating ranges.

In summary, the manufacturing process is sufficiently described and the overall control strategy adequately explained.

Process validation

The lifecycle approach to process validation follows 3 stages: process development and evaluation, process verification and ongoing process verification.

A list of the elements of the FKB238 active substance manufacturing process that have been validated and/or evaluated is included, as well as a list of the analytical procedures used for the process validation. The results from process verification activities are acceptable.

Cleaning and reuse validation for the chromatography columns used in the active substance purification process was performed at full scale within a maximum acceptable number of reuse cycles determined in the bench-scale process evaluation studies. A summary of the validated number of reuse cycles for each column is presented. Sufficient details have been provided for the cleaning and reuse validation studies.

Validation of the commercial manufacturing process for the active substance is considered satisfactory.

Manufacturing process development

Risk-based approaches, which included identification of the critical quality attributes (CQAs), assessment of the criticality of the performance attributes and the process parameters, were employed during the establishment of the control strategy.

The CQAs for the active substance were identified based on the assessment of CQAs for the final finished product to meet the quality target product profile (QTPP). The CQAs are presented, along with a summary of the control strategies for the different categorised CQAs. Each CQA is controlled by critical and key process parameters and material attributes, in addition to the testing plans during the FKB238 active substance manufacturing process. The rationale to set in-process and/or release testing for each CQA is also presented. Manufacturing data from clinical and commercial scale lots was evaluated in order to classify the criticality of the in-process quality attributes (IPQAs), based on the attribute's potential to impact the quality of the active substance.

Process evaluation studies were performed. The results of the process evaluation studies for the upstream cell culture process and the downstream purification process are included. The results were used for identification and classification of process parameters. From the effects observed in the process evaluation studies on performance attributes, the acceptance ranges were identified as ranges for process parameters that can deliver acceptable process performance and consequently, acceptable

product quality. Operating ranges were established equal to or within the acceptable ranges in order to control the process and product quality.

The only change in the manufacturing process during development has been discussed and justified.

A risk assessment of leachables from in-process product contact materials used in the FKB238 active substance manufacturing process is provided. Based on the vendor's product information or equivalent, it was confirmed that neither biological reactivities nor any safety concerning leachables are anticipated for the components listed as the high-risk components.

Characterisation

Elucidation of structure and other characteristics

The active substance was characterised in accordance with ICH Q6B using state-of-the-art analytical procedures for confirming the structural, physicochemical and immunochemical properties and the biological activity of the active substance. All characterisation studies were performed using the FKB238 active substance lot, which is the primary reference standard. Additional FKB238 active substance lots were included to demonstrate manufacturing consistency. The results from the characterisation studies are adequately presented.

All characterisation and elucidation studies were conducted on FKB238 manufactured by the commercial manufacturing process. The analytical techniques and methodologies applied to the characterisation of FKB238 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 FKB238 has the expected structure and functional properties. Assays used for characterisation of product-related variants and physicochemical properties are adequately described.

Impurities

The characterisation and risk assessment of impurities as presented are in line with ICH Q6B. All characterisations in this section were performed using five active substance lots manufactured by the same commercial process.

Product-related impurities are molecular variants of the product arising during manufacture and/or storage, which do not have properties comparable to those of the desired product with respect to activity, efficacy and safety.

Characterisation data and the results of the criticality assessment of each of the API/product-related impurities, including its impact on efficacy, PK, safety and immunogenicity is included.

The process-related impurities identified in FKB238 active substance are considered part of the AS critical quality attributes (CQA) and are controlled during the manufacturing process, by analytical testing at release and on stability testing.

A summary of the process-related impurities is presented, which includes the limit of quantitation, the source of impurity, residual impurity in active substance, and the maximum patient exposure calculated as the maximum adult dose per kg.

Specification

Specification

The active substance release and shelf-life specifications list the attributes, references to the compendial test methods and the acceptance criteria. The proposed specification tests are adequate and in line with

relevant guidelines and include appropriate tests for physicochemical characteristics, identity, purity and potency.

Analytical procedures

Detailed descriptions of all analytical procedures used in routine control of FKB238 active substance, as well as summaries of method validations have been provided.

Limit of quantitation and range are analysed as described in the ICH Q2R1 guideline. The strategies and the data provided to demonstrate specificity, accuracy, limit of quantitation and range are considered appropriate.

The validation characteristics of the methods are sufficient. The Applicant has clarified the approach to calculate intermediate precision and repeatability, and repeatability was adequately demonstrated. The robustness of the methods was evaluated.

Batch analyses

Batch analysis data for active substance lots produced is included in the dossier. These are the batches used in the non-clinical studies, clinical studies and stability studies. The data was used to assess manufacturing consistency and to establish commercial specification limits. All lots were tested to and complied with the specification in place at the time of product release.

Reference standards

The reference standard is routinely used in identity and potency tests for both active substance and finished product. The history of the reference standards is provided.

Future reference standards will be prepared to ensure sufficient inventory for release and stability testing and will be filled from representative material, qualified for use and monitored on stability.

Container closure system

FKB238 active substance is stored in single use bags that have been selected and assessed according to the EMA *"Guideline on plastic immediate packaging materials (CPMP/QWP/4359/03)".* The bag meets the criteria stated/indicated in Ph. Eur. 3.2.2.1.

Stability

A suitable shelf life is proposed for active substance stored at the intended storage conditions.

Active substance lots manufactured by the commercial process were used for the stability study. The test methods were selected based on their ability to assess potential changes that may affect product quality, safety, and/or efficacy.

Adequate information regarding the containers used for active substance stability studies is provided. The proposed shelf-life for FKB238 active substance is justified by the available data from the long-term stability studies. The long-term stability studies were performed per ICH guidelines. In addition, stability studies were conducted under elevated and stress storage conditions - and photostability storage conditions to evaluate the effect of these conditions on the active substance quality.

All results are within specifications.

The Applicant will continue the ongoing stability studies through completion. A minimum of one lot of FKB238 active substance manufactured at the commercial site per year will be put on long-term stability studies. Commercial lots will be assessed using the post-approval stability protocol.

Based on the stability results, the proposed shelf-life for the active substance is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description and composition of the drug product

FKB238 finished product is supplied as a 100 mg or 400 mg sterile, single-use, preservative-free, clear to opalescent, colourless to pale brownish-yellow solution in a glass vial for intravenous administration.

Each vial (10 and 20 mL respectively) contains 4 mL or 16 mL deliverable volume of FKB238 at a concentration of 25 mg/mL. The method of administration is described in the SmPC. Bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/mL (0.9%) solution. The concentration of the final solution should be kept within the range of 1.4 mg/mL to 16.5 mg/mL and administered as an intravenous infusion. The components and function of the formulation are summarised in Table 1. Sorbitol is an excipient with known effect and each vial of 4 mL of concentrate contains 191 mg sorbitol (E420) and each vial of 16 mL of concentrate contains 764 mg sorbitol (E420).

Table 1 – Composition of FKB238 finished product

Component	Function
FKB238	API
Monosodium glutamate	Buffering agent
Sorbitol	Tonicity agent
Polysorbate 80	Stabiliser
Hydrochloric acid, dilute	pH modifier
Water for injection	Solvent

Each vial of FKB238 finished product is filled with an overfill. The excess fill volume is provided to ensure that the labelled volume of the finished product solution can be withdrawn from the vial. There are no overages in the FKB238 finished product formulation.

Pharmaceutical development

A control strategy was adequately developed. A QTTP with associated CQAs has been defined and justified.

Formulation development

The formulation of FKB238 is not identical to the EU-reference product formulation. Detailed formulation studies were executed to justify the use the new formulation. The description is satisfactory. The formulation is designed to provide the appropriate osmolality and pH and to prevent antibody aggregation, degradation, loss of biological activity and to ensure that the desired product quality is maintained during storage and shipping. Formulation development studies were performed to identify the final formulation. The control strategy for critical formulation parameters is acceptable A control strategy of critical formulation parameters is defined. To minimise formation of aggregates and visible particles during storage and shipping it was instrumental to control protein concentration and polysorbate 80 concentration together with the pH. In order to minimise formations of fragments, oxidised species and the change in charge variants, pH is controlled.

Manufacturing development

The finished product manufacturing process is described in the dossier. The process was characterised and CQAs that are instrumental for achieving the QTTP and to consistently deliver the required product

quality were identified. Process attributes needed for evaluation of product quality and process performance were identified and assessed with regards to criticality. Further process parameters of each step were identified and their impact on each process attribute was evaluated with a risk assessment. Appropriate range for process attributes and process parameters were set. There are no reprocessing steps in the finished product manufacturing process.

Comparability

Comparability between the 100 mg and 400 mg presentations were discussed and it was demonstrated that the FKB238 finished product 100 mg/4 mL and 400 mg/16 mL are comparable.

Container closure

The container closure system consists of type I, clear borosilicate tubing glass vial (10 mL and 20 mL), f butyl rubber stopper and an aluminium sealing cap with polypropylene top. The container closure has been evaluated for safety, compatibility, functionality and ability to prevent microbiological contamination. Extractables and leachables were also assessed. The level of leachables detected in the study does not compromise the purity, efficacy, and safety of the finished product.

FKB238 is a sterile, preservative-free solution for intravenous infusion.

Compatibility

In-use compatibility studies are performed, investigating the compatibility with the infusion bag and line. The results support the proposed use

Impurities

Impurities were described in detail. Adequate controls are in place for all impurities.

Purity and stability profiles have been compared between active substance and finished product. It is concluded that no further API-related impurities are arising from formulation and manufacture of the finished product. Process/material-related impurities from excipients are considered well-controlled and the contamination risk is low. An assessment and characterisation of visible and sub-visible particles are examined. Stress studies did not lead to generation of new particle species in term of morphology. Lot-to-lot consistency of particle size distribution was shown in the finished product at release. Sub-visible particles are considered adequately controlled.

A risk assessment of potential source of elemental impurities found no high-risk sources. From the safety assessment, no elemental impurities of toxicological concern have been identified in the FKB238 finished product.

Manufacture of the product and process controls

Manufacture

The lot release site in Europe/EEA is Geryon Pharma Ireland Ltd., Dublin K67 P6K2, Ireland. The manufacturing sites for the finished product are EU GMP compliant.

The manufacturing process is described in an appropriate level of detail. The finished product presentations of 100 mg/4 mL and 400 mg/16 mL (both 25 mg/mL) are manufactured using the same process steps and controls. The only differences between the presentations are the fill volume and size of vial. All other manufacturing steps and process parameters are the same. A batch formula is defined for maximum and minimum batch size.

Critical steps were identified and controlled adequately.

Process validation

The process validation approach was designed to demonstrate that the commercial manufacturing process is controlled and reproducible, consistently yielding finished product with the defined product quality.

Process validation acceptance criteria were established. Process validation was performed using three finished product lots of each presentation (100 mg/4 mL and 400 mg/16 mL) manufactured at the commercial facility and at a minimum and maximum scale. This is considered acceptable.

All validation results met the predetermined acceptance criteria.

Aseptic process validation studies including filter validation and media fills together with equipment performance qualification are presented in sufficient detail and demonstrate that the process is capable of producing a sterile product. Process validation lot data are all within specification.

The Applicant will conduct ongoing process verification where monitored data will be collected and evaluated on a lot-by-lot basis. In addition, the results accumulated by continued monitoring will be reviewed annually and the knowledge gained will be used for the manufacturing process and monitoring program improvements, as appropriate.

Shipping

Shipping and shipping container validation concluded that the finished product quality was not affected by the shipping conditions. The study was designed to mimic actual shipment and temperature was within the range of 2°C to 8°C. To maintain 2°C to 8°C during transport, temperature is controlled via qualified shipping containers. Shipping information and shipping container validation were provided in sufficient detail.

Product specification

The product specification includes appropriate physicochemical tests and tests for identity, purity and potency. To ensure that the selected panel of methods has stability indicating capabilities, forced degradation studies (FDS) were conducted. A rationale was provided for the QAs not included in the specification.

Multiple finished product lots are included to justify the specification. There have been no major process changes for the lots used for this purpose. Different statistical approaches were employed. Justifications for the statistical strategy were provided.

The finished product release and shelf-life specifications are acceptable.

Analytical procedures

The panel of analytical procedures is considered adequate to monitor and control the quality of FKB238 at release and during shelf-life. Several of the analytical procedures are common to the active substance and finished product and only those specific for finished product are described in this section.

The description of all analytical methods is satisfactory. All methods are validated or verified for intended use.

Batch analysis

Analytical data for multiple FKB238 finished product lots are included. All lots met the acceptance criteria in place at the time of release and end of shelf life at long term storage condition. Overall, the results demonstrate consistency of the manufacturing process capabilities.

Reference standards

The reference standard used in the analysis of the FKB238 finished product is the same as that used for the FKB238 active substance.

Stability of the product

The proposed shelf-life of 100 mg/4 mL and 400 mg/16 mL finished product is 3 years when stored at the recommended temperature of 2-8°C and protected from light.

Stability studies are performed according to ICH guidelines and at the recommended storage temperature to support the expiry period. The lots are of the same formulation and packed in the same container closure system as proposed for marketing. Additionally, photostability (in accordance with ICH Q1B) study is performed and concludes that the finished product is sensitive to light. Stability-indicating parameters/methods are identified by forced degradation studies and justified at an appropriate level.

Chemical and physical in-use stability of diluted finished product in sodium chloride 9 mg/mL (0.9%) solution for injection stored for 48 hours at 2°C to 30°C has been demonstrated. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Short term temperature excursions above and below the recommended storage conditions are supported by the forced degradation studies described in the dossier. "Do not freeze" is stated in the product information under "Special precautions for storage", which is acceptable.

Overall, results of these studies, together with results from the accelerated and stressed stability studies, demonstrate that the finished product is stable in the primary container, protected from light, under conditions that may be encountered during transport, storage, handling, and use.

The Applicant will continue the ongoing primary long-term and accelerated stability studies described in the dossier through to completion. In addition, a minimum of one lot per year of each FKB238 finished product, 100 mg/4 mL finished product or 400 mg/16 mL finished product, manufactured at the commercial site, will be added to the post-approval long-term stability studies. A shelf-life for the finished product of 3 years when stored at 2°C - 8°C is supported based on the available stability data**.**

Adventitious agents

The microbial control strategy includes control of materials, monitoring of bioburden and bacterial endotoxins levels at critical manufacturing steps, control of active substance and finished product and an adequate container closure system.

The MCB, WCB and unprocessed bulk have been tested for viral contamination in accordance with ICH Q5A and the results are acceptable. No substance of animal or human origin are used in manufacture of FKB238. A risk assessment with regards to TSE exposure during early cell line development is provided together with certificates of suitability and is acceptable.

Viral clearance studies were performed with a suitable panel of model viruses on qualified small-scale models. The results showed that the current FKB238 purification process has the capability to reduce retrovirus particles. The approach to ensure viral safety is considered sufficient and supports acceptable viral clearance for the downstream process.

Biosimilarity

The applicant has conducted a comprehensive biosimilarity exercise, which is in line with the relevant EMA guidelines. The results are summarised in Table 2.

Table 2 – Results of analytical biosimilarity exercise

Category	Quality attribute	Test method	Similarity Assessment
Primary structure	N-terminal amino acid	Edman sequencing	Pass
	Amino acid sequence, C-terminal amino acid	Peptide mapping (LC/MS)	Pass
	Disulfide bond	Reduced/Non-reduced peptide mapping (LC/MS)	Pass
	N-glycosylation site	N-glycosydase F-digested/Nondigested peptide mapping	Pass
	Molecular weight	Intact MS	Pass
	pI	cIEF	Pass
	Extinction coefficient	AAA and UV spectroscopy	Pass
Glycosylation	Sialic acid, Other Minor Peaks (OMP), High mannose species (M5), Afucosylated species (F0), Fucosylated species (F1) and Gal/N	N-linked glycan profiling	Minor differences in glycosylation are considered not significant. Sialic acid, Gal/N: Pass OMP: contents for 3 lots of FKB238 DS were at the higher end than the reference product and other FKB238 DS lots. M5: contents for 3 lots of FKB238 DS were at the higher end than the reference product and other FKB238 DS lots. F0: contents for 3 lots of FKB238 DS were at the higher end than the reference product and other FKB238 DS lots. F1: contents for 3 lots of FKB238 DS were at the lower end than the reference product and other FKB238 DS lots.
	Galactose, Mannose, Fucose (Neutral sugar), GlcNAc (Amino sugar), Neu5Ac, Neu5Gc (Sialic acid)	Monosaccharide composition	Pass
	Glycosylation site occupancy	CE-SDS (R)	Pass
Higher order structure	Secondary structure	Far-UV CD	Pass
	Secondary structure	FT-IR	Pass
	Tertiary structure	Near-UV CD	Pass
	Tertiary structure	FL	Pass
	Thermo transition properties	DSC	Pass

Size heterogeneity	Main species (HC+LC), MMWS and LMWS (Fragments)	CE-SDS (R)	Pass
	Monomer, LMWS (Fragments)	CE-SDS (NR)	Minor differences in size heterogeneity are considered not significant. Contents for 2 lots of FKB238 DS were at the higher end than the reference product and other FKB238 DS lots.
	HMWS (Aggregates), Monomer	SE-HPLC	Pass
	HMWS (Aggregates), Monomer, LMWS (Fragments)	FFF	Pass
Charge heterogeneity	Acidic variants, Main species, Basic variants	CEX-HPLC	Minor differences in charge heterogeneity are considered not significant. Basic variants: Pass Acidic variants: contents for 2 lots of FKB238 DS were at the higher end than the reference product and other FKB238 DS lots. Main species: main peak contents for 2 lots of FKB238 DS were at the lower end than the reference product and other FKB238 DS lots.
	Acidic variants, Main species, Basic variants	cIEF	Pass
Amino acid modifications	C-terminal variants (Lys variants, Amidated proline), N-terminal variants and Deamidation/Isomerisation	Reduced peptide mapping (LC/MS)	Pass
	Glycation	BAC	Pass
	Oxidation	Reduced peptide mapping (LC/MS)	Pass
	Glycation	HI-HPLC	Pass
	Free thiol	Colorimetric method	Pass
	Trisulfide and Tioether	Non-reduced peptide mapping (LC/MS)	Pass
	Cysteinylation	Non-reduced peptide mapping (LC/MS)	-
Strength	Protein concentration	UV spectroscopy	Pass
Binding to target antigen(s)	Binding to VEGF A_{165} and VEGF A_{121}	ELISA	Pass
	Binding to VEGF A121, VEGF A_{165}, VEGF A_{189} and VEGF B, C, D	SPR	Pass
Binding to Fc	Binding to FcγRI, FcγRIIa and	SPR	Pass

receptors	FcγRIIb		
	Binding to FcγRIIIa(V) and FcγRIIIa(F)	SPR	Binding Affinity to FcγRIIIa(V) and FcγRIIIa(F) for 3 lots of FKB238 DS were at the higher end than the reference product and other FKB238 DS lots. Minor differences in binding are considered not significant
	Binding to FcγRIIIb-NA1, FcγRIIIb-NA2 and FcRn	SPR	Minor differences in binding are considered not significant
Fab-associated functions	Neutralisation of VEGF induced biological activity	Cell-based assays: HUVEC and Reporter Gene Assay	Pass
Fc-associated functions	ADCC and CDC	Cell-based assay	Pass
Binding to complement	Binding to C1q	ELISA	Pass

The Applicant has conducted an extensive, robust, comprehensive physicochemical and functional exercise to develop a similarity program using state-of-the-art techniques capable to assess the analytical similarity of FKB238 with EU-approved Avastin and to demonstrate that the proposed biosimilar and reference product are highly similar. The similarity exercise was conducted to provide a comprehensive understanding of the physicochemical and functional characteristics of the reference product. The similarity study is consistent with the provisions of the EMA Guideline on "Similar Biological Medicinal Products containing biotechnology-derived proteins as active substance: quality issues"3.

In general, the biosimilarity assessment performed by the Applicant is considered adequate to confirm the analytical similarity between FKB238 and EU-approved Avastin The similarity ranges were established for quantitative key quality parameters using data from EU-licensed Avastin batches. The statistical approach involved tolerance intervals using mean ± 3SD based on the criticality of the quality attribute to demonstrating biosimilarity and the variability of the analytical methods. Similarity for the attributes were accepted when an individual value of 90% of the test product falls within the quality range of the reference product. The biosimilarity criteria for the quality range testing used by the applicant, where a positive conclusion on comparability will be made if more than 90 % of individual batches of FKB238 fall within the calculated range of mean ± 3 SD for reference product, was not considered to be acceptable. However, as data from the analysis of individual batches were provided, assessment could be performed independent of the statistical model used by the applicant. Attributes considered to have the lowest risk to clinical outcomes were assessed by graphical methods or raw data comparisons to confirm similarity and no statistical approach was used. In addition to comparisons between FKB238 to EU-licensed Avastin, comparisons for FKB238 vs US-licensed Avastin and EU-licensed Avastin vs US-licensed Avastin are also presented.

The Applicant presented a justification why the differences observed in glycan profiles do not impact clinical efficacy for bevacizumab, which is accepted.

Both Avastin and FKB238 finished product contain the active substance bevacizumab, the same dosage form, administration route and indication for use. The FKB238 finished product is supplied as a sterile and preservative-free solution. The formulation is designed to provide appropriate osmolality and pH and to prevent degradation.

A comparability study was performed between active substance batches and finished product batches, in order to support the use of active substance in establishing biosimilarity between FKB238 and Avastin. The tests and analysis used for establishment of the comparability between active substance and finished product are considered sufficient.

An accelerated stability study is presented. Overall the tests included are acceptable including assessment of FKB238 potency, CEX-HPLC degradation rates, SE-HPLC degradation rates, CE-SDS-LIF degradation. However, the results indicate increased thermal stability of FKB238 in comparison to the reference medicinal product at both 25°C and 40°C, when compared to the reference medicinal product. A long-term stability protocol is presented. This is acceptable.

The similarity assessment indicates similar biological activity of both the Fab and Fc-based functionality of FKB238, EU-licensed Avastin and US-licensed Avastin. Overall, FKB238 is considered to be highly similar to EU-licensed Avastin with respect to the presented physicochemical and biological characteristics. Differences are identified with respect to glycosylation, charge/size heterogeneity and FcγR binding, for which the Applicant claims no clinical relevance or clinical impact, which can be accepted. It is noted that the data presented for process verification batches tends to represent the extreme values in several of the FKB238 data sets, trending towards or beyond the acceptance limits. However, taking in to account the mode of action and potential impact of the relevant datasets, the justification of highly unlikely meaningful clinical impact is accepted.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The fermentation and purification of the active substance are adequately described, controlled and validated. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

The chemical, pharmaceutical and biological documentation comply with existing guidelines.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

From a quality point of view, biosimilarity with the reference product Avastin is considered demonstrated.

The overall quality of Equidacent is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

From a quality point view, the marketing authorisation application for Equidacent is considered approvable.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

The FKB238 non-clinical programme consists of a number of *in vitro* assays, an *in vivo* study in SCID mice, a single dose toxicity study in rats and a 2-week repeat-dose toxicity study in Cynomolgus monkeys. All studies were done in comparison with EU and US-Avastin, except the mouse study, which only included US-Avastin. In addition, a 2-week repeat dose toxicity study with only FKB238 were performed in rats.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A number of *in vitro* functional assays were conducted to substantiate similarity between FKB238 and the European reference product Avastin. The assays included binding to VEGF isoforms, Fcγ receptors, FcRn and C1q, neutralisation of VEGF signal transduction (reporter gene assay) and neutralisation of VEGF induced cell proliferation of HUVEC. In addition, ADCC and CDC activities were investigated. Generally, the data presented by the applicant indicate similarity between FKB238 and Avastin.

Table 1: Summary of in vitro pharmacology studies for FK238 and Avastin

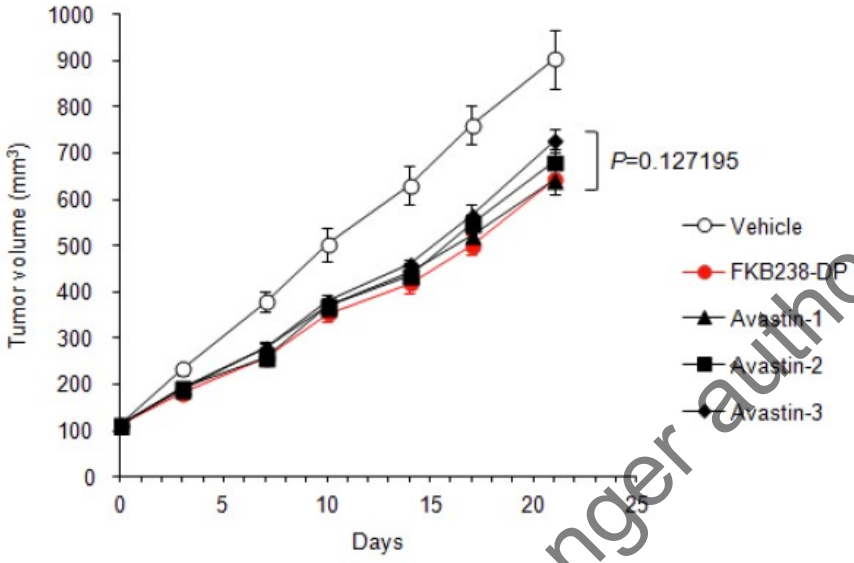
Product	FKB238DS	Avastin (US)	Avastin (EU)
VEGF-A165 binding by ELISA (%) a	96.6 ± 2.8 (97.8 ±2.8)b	99.8 ± 4.6	98.6 ± 3.5
VEGF-A121 binding by ELISA (%) a	106.0 ± 5.5	97.6 ± 2.5	102.1 ± 1.0
VEGF-A165 binding by SPR (× 10-10 M)	4.2 ± 1.4	3.9 ± 1.1	4.3 ± 1.4
VEGF-A121 binding by SPR (× 10-10 M)	6.6 ± 3.4	6.7 ± 2.5	7.4 ± 2.7
VEGF-A189 binding by SPR (× 10-10 M)	4.9 ± 2.3	5.1 ± 2.1	5.6 ± 2.5
VEGF-B/C/D binding by SPR	No binding	No binding	No binding
FcγRI binding by SPR (× 10-10 M)	8.3 ± 5.5	5.4 ± 3.1	5.7 ± 3.8
FcγRIIa binding by SPR (× 10-6 M)	9.4 ± 0.7	9.4 ± 0.5	9.4 ± 0.6
FcγRIIb binding by SPR (× 10-6 M)	13.0 ± 1.5	13.9 ± 1.3	14.0 ± 1.1
FcγRIIIa(F) binding by SPR (× 10-6 M)	9.8 ± 0.8	11.3 ± 0.5	11.4 ± 0.5
FcγRIIIa(V) binding by SPR (× 10-6 M)	5.9 ± 0.3	6.8 ± 0.3	6.8 ± 0.3
FcγRIIIbNA1 binding by SPR (× 10-6 M)	9.6 ± 0.8	13.3 ± 0.8	13.5 ± 1.1
FcγRIIIbNA2 binding by SPR (× 10-6 M)	9.3 ± 0.6	11.8 ± 0.6	11.9 ± 0.5
FcRn binding by SPR (× 10-8 M)	13.1 ± 1.3	12.6 ± 0.9	13.4 ± 1.1
Neutralization of VEGF induced HUVEC cell proliferation (%) a	106.3 ± 7.6 (108.0 ± 7.1) b	106.6 ± 6.4	104.0 ± 5.1
Neutralization of VEGF induced signal transduction (Reporter gene assay) (%) a	97.5 ± 5.9	97.8 ± 5.0	101.5 ± 3.7
Binding to cell-associated VEGF in SKOV-3 cells (%) a	98.1 to 103.7	78.5 to 105.4	93.7 to 108.0
ADCC	No activity	No activity	No activity
CDC	No activity	No activity	No activity
C1q binding by ELISA (%) a	99.4 ± 2.1	99.9 ± 4.8	98.1 ± 3.1

Each value represents mean ± standard deviation. a, relative activity to reference standard.
b, mean ± standard deviation from DS and DP

<u>Anti-tumour activity of FKB238 and Avastin (US) against human colorectal adenocarcinoma DLD-1 cells, (study no. c-14-0133, non-GLP)</u>

Anti-tumour activity of FKB238-DP and Avastin (US) was examined in severe combined immunodeficient (SCID) mice xenografted with human colorectal adenocarcinoma DLD-1 cells expressing VEGF. Seven

days after cell inoculation, animals were administered intraperitoneally with FKB238 DP or 3 lots of US-Avastin at 1 mg/kg once weekly for 3 weeks (Days 0, 7 and 14). Remaining mice with cell inoculation were used for pharmacokinetic analysis. The tumour diameters were measured twice a week and the tumour volume (V) was estimated. Statistical analysis (Anova) indicated that there was comparable (p=0.127195) anti-tumour activity after once weekly dosing between FKB238 DP and US-Avastin in this mouse xenograft model (Figure 2).



Each point represents mean ± standard error from 10 animals in tumour volume.

Figure 2: Anti-tumor activity of FKB238 and US-Avastin against DLD-1 tumour xenografts in SCID mice

<u>Determination of biomarker concentrations in a 4-week repeat dose toxicity study in cynomolgus monkeys, (study no. SBL330-020, GLP)</u>

FKB238 DP, US-Avastin or EU-Avastin was intravenously administered to cynomolgus monkeys twice a week for 4 weeks at a dose level of 10 mg/kg (6 males and 6 females in each group). Concentrations of sVEGFR1 in serum and concentrations of VEGF in plasma were measured at Day 1 (before dosing), Day 2 (24 hours after the end of the first dose), Day 25 (before dosing) and Day 26 (24 hours after the end of the last dose) using validated analytical methods.

sVEGFR1 concentrations in serum were below the lower limit of quantification (LLOQ; 2441.5 pg/mL) in all animals at all sampling time points.

VEGF concentrations in plasma increased after dosing of FKB238, US-Avastin and EU-Avastin on Day 2 and Day 25, and decreased on Day 26 of dosing, see Table 2.

Table 2: VEGF concentration in plasma in male and female cynomolgus monkeys (study no SBL330-020).

VEGF (pg/mL)					
Sex	**Group**	**Day 1**	**Day 2**	**Day 25**	**Day 26**
Male	P.Saline	20.45 ± 1.80	22.34 ± 3.50	18.56 ± 2.29	19.64 ± 4.28
	FKB238	20.19 ± 4.76	31.72 ± 7.97	59.60 ± 15.29	46.85 ± 15.87
	US-Avastin	20.31 ± 3.47	32.38 ± 5.97	47.13 ± 19.69	38.95 ± 14.86
	EU-Avastin	21.20 ± 2.86	31.42 ± 2.20	55.47 ± 9.27	45.16 ± 8.37

Female	P. Saline	18.80 ± 3.20	19.31 ± 3.55	17.19 ± 2.06	18.42 ± 1.18
	FKB238	18.18 ± 2.14	31.24 ± 4.13	55.09 ± 10.37	43.92 ± 9.59
	US-Avastin	19.58 ± 3.11	30.47 ± 2.83	42.16 ± 21.59	34.92 ± 15.82
	EU-Avastin	20.96 ± 3.77	33.25 ± 4.30	57.11 ± 13.38	46.72 ± 11.09

Each value shows mean ± standard deviation from 6 animals.
P.Saline; physiological saline

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were submitted (see discussion on non-clinical aspects).

Safety pharmacology programme

No safety pharmacodynamics studies were submitted (see discussion on non-clinical aspects).

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

Pharmacokinetic properties of FKB238 and bevacizumab (EU and US) were characterised in rats (single dose), SCID mice (US Avastin only) and in a GLP 4-week repeat dose toxicity study. A 2-week repeat dose toxicity study were also performed in rats, which only evaluated TK parameters of FKB238.

Repeat-dose PK of FKB238 and Avastin (US) in SCID mice (study no. d-14-0207, non-GLP).

FKB238 DP or US-Avastin (3 lots) was intraperitoneally administered to male SCID mice bearing human colorectal adenocarcinoma DLD-1 tumours at 1 mg/kg (8 males in each group) once weekly for three weeks.

Serum samples were obtained prior to dosing, at 0.5, 4, and 24 hours and at 2, 4, and 7 days after the 1st and 3rd doses.

Pharmacokinetic profiles of FKB238 and Avastin showed no clear differences between FKB238 and Avastin (US). The serum concentration of FKB238 and Avastin (US) increased with tmax of 4 to 48 h after intraperitoneally administration and no clear differences were observed in Cmax between FKB238 and Avastin (US).

Single-dose PK of FKB238 and Avastin (US or EU) and anti-drug antibody evaluation in rats (study no. SBL330-009, non-GLP).

A single-dose PK study was conducted in male and female Crl:CD(SD) rats. FKB238 DP, US-Avastin or EU-Avastin was intravenously administered to rats at 10 mg/kg (6 males and 6 females in each group).

Serum samples were obtained prior to dosing, at 0.5, 2, 8 and 24 hours and at 2, 4, 7, 14, and 28 days after dosing. Serum concentrations of FKB238 and Avastin were analysed using a validated method with a lower limit of quantification of 0.1 µg/mL in serum. ADA production was assessed prior to dosing and on Day 14 and Day 28 after administration and samples were analysed using a bridging ECL format.

The serum drug concentration-time curves and PK parameters were similar for FKB238, US-Avastin and EU-Avastin (Table 3: Single dose toxicokinetics of FKB238 in a 2-week rat study (study no. SBL330-009, non-GLP).). ADA was detected in pre-dose samples and post-dose sample at Day 28 after dosing. One female in the FKB238 group, 2 females in the US-Avastin group, and one male in the EU-Avastin group were ADA positive in pre-dose. One male in the EU-approved Avastin dosing group showed positive at 672 hours after dosing.

Table 3: Single dose toxicokinetics of FKB238 in a 2-week rat study (study no. SBL330-009, non-GLP).

Dosing Article	Sex	Cmax (µg/mL)	AUC0-28d µg.day/mL	AUC0-∞	T1/2 (day)	CL (mL/kg/day)	Vss mL/Kg	MRT (day)
FKB238	Male	241	1530	2010	14.0	5.05	96.5	19.1
	Female	207	1560	2090	14.5	4.83	96.7	20.0
US-Avastin	Male	284	1620	2160	14.3	4.72	90.4	19.4
	Female	241	1420	1800	13.1	5.56	97.8	17.6
EU-Avastin	Male*	305	1770	2330	14.0	4.35	81.5	18.9
	Female	305	1700	2240	14.1	4.50	85.1	19.1

* In 1 male in the EU-Avastin group, serum anti-FKB238 antibody was positive at 672 hours after dosing. Therefore, the group mean and S.D. was calculated except this animal.

<u>Repeat-dose PK of FKB238 in rats (study no. SBL330-008, non-GLP).</u>

The objective of the repeat-dose toxicity study in rats was to evaluate the toxicity of FKB238 when administered intravenously at 15 and 75 mg/kg, twice a week for 2 weeks. In addition, systemic exposure to FKB238 and ADA production was assessed in the satellite group (5 animals per group) with blood samples collected on Day 1 of dosing and after the final dose for TK (prior to dosing, at 0.5, 4, and 24 hours and at 2, and 3 days after dosing) and on Day -6 and at 72 hours after the final dose for ADA assessment.

FKB238 concentrations and AUC levels increased with increasing dose levels and repeated dosing, without sex-related differences. The t1/2 was not affected by the dose level or repeated dosing. ADAs were not detected in any animals at 72 hours after FKB238 dosing.

<u>Repeat dose TK of FKB238 and Avastin in a 4-week monkey study (study no. SBL330-013, GLP).</u>

Systemic exposure to FKB238, US-Avastin and EU-Avastin and ADA production were assessed in a repeat-dose toxicity study in cynomolgus monkeys (8 males per group). The animals were administered intravenously at 10 mg/kg twice weekly for 4 weeks (8 doses), followed by a 4-week recovery period. Blood samples were collected at pre-dose, 0.5, 1, 2, 4, 8, 24, 48, 72 hours after Day 1 (1st dose) and Day 25 (8th dose) for TK measurements and on Day -7 and Days 1 and 28 during the recovery period for ADA assessment. There were no clear differences in TK parameters between the FKB238, US-Avastin, and EU-Avastin groups, and there were no clear sex differences in any parameters (Table 4).

ADAs were detected in one female in the US-Avastin group on Day 28 of recovery. This animal showed lower serum drug concentrations than the other animals in the same group from Day 25 of dosing, and this observation was considered to be related to ADA production.

Table 4: Toxicokinetic parameters after the first and final dose of 10 mg/kg in the Cynomolgus Monkey toxicity study following twice-weekly administration for four weeks.

Group		FKB238	US-Avastin	EU-Avastin	FKB238	US-Avastin	EU-Avastin
Sex		Male			Female		
Dose		10 mg/kg, twice a week, 4 weeks			10 mg/kg, twice a week, 4 weeks		
Toxicokinetics (mean ± standard deviation from 6 animals)							
Cmax (µg/mL)	1st dose	275 ± 38	250 ± 25	302 ± 29	249 ± 17	245 ± 21	302 ± 32
	8th dose	712 ± 135	650 ± 292	768 ± 98	764 ± 70	751 ± 45 b	760 ± 79
AUC0-3d (µg·day/mL)	1st dose	477 ± 53	435 ± 54	548 ± 45	491 ± 64	489 ± 35	553 ± 74
	8th dose	1650 ± 360	1390 ± 660	1730 ± 220	1900 ± 120	1880 ± 180 b	1910 ± 150
AUC0-∞ (µg·day/mL)	1st dose	1140 ± 260	1070 ± 220	1490 ± 270	1200 ± 220	1290 ± 140	1460 ± 170
	8th dose	6970 ± 3430	6370 ± 4190	6730 ± 1160	9530 ± 2520	9610 ± 3010 b	10200 ± 3900
t1/2 (day) a	1st dose	3.92 ± 0.72	4.12 ± 0.54	4.74 ± 1.02	4.07 ± 1.04	4.51 ± 0.82	4.58 ± 0.50
	8th dose	7.47 ± 2.35	7.67 ± 4.07	7.21 ± 1.64	9.58 ± 3.16	9.55 ± 2.26 b	9.92 ± 3.84

a. t1/2 was calculated using 3 time points (from 24 to 72 hours after dosing).
b. The values in an animal judged anti-drug antibody positive (no. 20) was excluded from the calculation for mean ± standard deviation.

2.3.4. Toxicology

To support development of FKB238 for global registration, *in vivo* GLP repeat-dose toxicity studies in rats (FKB238) and cynomolgus monkeys (FKB238, US-Avastin, EU-Avastin) were conducted.

Single dose toxicity

No single-dose toxicity studies were submitted (see discussion on non-clinical aspects).

Repeat dose toxicity

FKB238: two-week repeat dose toxicity study in rats (study no. SBL330-008, GLP).

The objective of this study was to investigate the toxicity of FKB238 when repeatedly administered intravenously to Crl:CD(SD) rats at 15 and 75 mg/kg, twice weekly for 2 weeks.

Potential toxicity was evaluated by clinical signs, body weight, food consumption, water consumption, ophthalmology, urinalysis, haematology, blood chemistry, bone marrow examination, organ weights, necropsy, and histopathology. Systemic exposure to FKB238 and ADA production were also assessed, see section Pharmacokinetics.

There were no unscheduled deaths and no animal was euthanized. There were no treatment-related changes for clinical signs, body weight, food consumption, water consumption, ophthalmology, urinalysis, haematology, blood chemistry, bone marrow examination, organ weights, necropsy, and histopathology. Under the conditions of this study, no-observed-adverse-effect level (NOAEL) was considered to be 75 mg/kg.

FKB238 and bevacizumab (EU and US): 4-week intermittent intravenous repeat dose toxicity study in cynomolgus monkeys (study no. SBL-013, GLP)

This study was conducted to evaluate and compare the toxicity of FKB238 with that of US-Avastin and EU-Avastin when administered intravenously (10 mg/kg) to cynomolgus monkeys (6 males and 6 females per group, 3-4 years old) twice weekly for 4 weeks (8 doses in total), and to assess the reversibility of toxicity during a 4-week recovery period. Systemic exposure and ADA were also assessed, see section 3.2 Absorption. Clinical signs, body weight, food consumption, ophthalmology, physical examination (including oxygen saturation and respiratory rate), body temperature, blood pressure, electrocardiography, urinalysis, haematology, blood chemistry, necropsy, organ weights, bone marrow examination and histopathology were evaluated. Biomarker concentrations were evaluated under non-GLP conditions and reported separately

Increases in fibrinogen (treatment related) were noted in FKB238, US-Avastin and EU-Avastin groups, but were without corresponding inflammatory changes and no treatment-related changes were observed in prothrombin time or activated partial thromboplastin time.

In blood chemistry, an increase in globulin and a decrease in albumin/globulin ratio (A/G) were noted in 1 male in FKB238 group and statistically significant differences were noted in A/G in males on Day 28 between FKB238 and US-Avastin, but not between FKB238 and EU-Avastin. Further, the findings were not related to histopathological lesions.

Histopathology revealed hypertrophy of the chondrocytes in the epiphyseal plate of the femur in all males and in one to two females in the FKB238, US-Avastin, and EU-Avastin groups and thickening of the epiphyseal plate of the femur in one to three males in FKB238, US-Avastin, and EU-Avastin groups. The bevacizumab-related physeal changes were similar for all three groups. These treatment related changes recovered by the end of the 4-week recovery period.

Genotoxicity

No genotoxicity studies have been submitted (see discussion on non-clinical aspects).

Carcinogenicity

No genotoxicity studies have been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No reproductive or developmental toxicity studies have been submitted (see discussion on non-clinical aspects).

2.3.5. Ecotoxicity/environmental risk assessment

The applicant has provided a justification for not conducting an environmental risk assessment (ERA) for FKB238. FKB238 is a monoclonal antibody not expected to pose a risk to the environment. ERA studies are therefore not required, in accordance with EMEA/CHMP/SWP/4447/00.

2.3.6. Discussion on non-clinical aspects

A comprehensive number of in vitro functional assays has been conducted to substantiate similarity between FKB238 and the EU reference product Avastin.

Slightly higher binding affinities were observed for FKB238 on FcγRIIIa(F), IIIa(V), IIIbNA1 and IIIbNA2 as compared to Avastin that could be attributed to differences identified in the glycan profile. These differences can be considered acceptable from a non-clinical point of view, given that there were no ADCC activity of bevacizumab.

In line with EU guidance (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; EMEA/CHMP/BMWP/42832/2005 Rev1), *in vivo* studies are generally not considered necessary in terms of the non-clinical development. However, in order to support global development, the applicant conducted studies to compare anti-tumour effects in a mouse xenograft model (FKB238 and US-Avastin), and to evaluate effects on VEGF and sVEGFR in cynomolgus monkeys (FKB238, US-Avastin and EU-Avastin).

The results showed that FKB238 and US-Avastin are able to inhibit tumour growth in a similar way. Further, there were no clear differences in VEGF concentrations in plasma between FKB238, US-Avastin and EU-Avastin.

In the rat single dose PK study one male in the EU-Avastin group was ADA positive on Day 28 after administration. In the monkey study, one female cynomolgus monkey in the US-Avastin group was ADA positive on day 28 of recovery period. Both animals showed lower exposure to bevacizumab, suggesting that the ADA affected TK.

In the single-dose PK study in rats, a total of four animals were ADA positive pre-dosing (1 FKB238 female, 2 US-Avastin females, 1 EU-Avastin male). The reason for these findings is not known, but the results are considered as false positives. Similar findings were not reported in other PK or TK studies. Ig in animal is generally not predictive for immunogenicity in human (see section on immunological events).

A 2-week repeat dose toxicity study was conducted with FKB238 in rats. The formulation used was the same as intended formulation in the product to be marketed. As expected, due to lack of binding to rodent VEGF, no VEGF-related toxicity was observed. Further, no indication of systemic or local toxicity was observed, indicating that the formulation was well tolerated.

A 4-week repeat dose toxicity study was conducted with FKB238 and Avastin (US and EU) in cynomolgus monkeys. Increased fibrinogen was noted in FKB238, US-Avastin and EU-Avastin groups. Histopathology revealed hypertrophy of the chondrocytes and thickening of the epiphyseal plate in the femur in the FKB238, US-Avastin, and EU-Avastin groups with a similar incidence. These reversible changes were considered to be pharmacologically related and were similar for all three groups.

Non-human primate toxicity studies are considered of limited value for biosimilarity evaluation and such studies are not generally recommended. It is however, acknowledged that these studies were conducted as part of a global development and may be considered supportive for the claimed biosimilarity.

Local toxicity studies were not performed per se, but local toxicity was evaluated as a part of the repeat dose toxicity studies. The intended formulation for FKB238 is different from Avastin with respect to excipients used. The excipients are however well known and did not trigger adverse effects at the site of administration in rats or monkeys.

Studies on secondary pharmacodynamics, safety pharmacology, pharmacodynamics drug interactions, genotoxicity, carcinogenicity, and reproduction and developmental toxicity were not conducted, in line with EMA/CHMP/BMWP/403543/2010.

2.3.7. Conclusion on the non-clinical aspects

The data submitted are acceptable from a non-clinical point of view to support the approval of FKB238.

2.4. Clinical aspects

2.4.1. 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 5: Clinical studies of FKB238

Study	Design	Subject/patient population	Number of subjects/patients	Primary endpoint(s)
FKB238-001 PK Completed	Randomised, double-blind, single-dose, parallel study	Healthy male subjects	Enrolled and treated: 33 FKB238, 34 EU-Avastin, 32 US-Avastin	PK similarity between primary PK endpoints: $AUC_{0-\infty}$ and AUC_{0-t}
FKB238-002 Comparative clinical Completed (primary analysis)[a]	Randomised, double-blind, parallel study	Patients with advanced/recurrent NS-NSCLC in combination with paclitaxel and carboplatin	Enrolled: 731 Treated: 728 (362 FKB238, 366 EU-Avastin)	ORR (by RECIST v1.1) assessed as the rate of the best response (CR or PR) by BICR
Additional study				
FKB238-003 PK Completed	Randomised, double-blind, single-dose, parallel study	Japanese healthy male subjects	Enrolled and treated: 20 FKB238, 20 EU-Avastin	PK similarity between primary PK endpoints: AUC_{0-t} and $AUC_{0-\infty}$

AUC0-∞=area under the concentration-time curve extrapolated to infinite time; AUC0-t=area under the concentration-time curve up to the last detectable value; BICR=blinded independent central review; CR=complete response; DCO=data cut-off; EU-Avastin=European Union-approved Avastin; NS-NSCLC=non-squamous non-small cell lung cancer; ORR=overall response rate; PK=pharmacokinetic(s); PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; US-Avastin=United States-licensed Avastin.

[a]An Extended Treatment Period is ongoing (defined as the time after DCO to the end of study, in which patients could continue receiving IP if they were considered by the treating investigator to be gaining clinical benefit).

2.4.2. Pharmacokinetics

Three studies provided PK data:

- **<u>FKB238-001</u>: PK similarity in healthy male individuals from the United Kingdom**

Study FKB238-001 was a randomised, double-blind, parallel, single-dose study in healthy male subjects aged 18 to 55 years. The primary objective of the study was to compare the safety and PK of FKB238 with EU-Avastin and US-Avastin after single 5 mg/kg doses, by iv infusion, in healthy male subjects, with a secondary objective of the assessment of tolerability and immunogenicity. A total of 99 healthy volunteers were randomised to receive FKB238 (n=33), EU-Avastin (n=34) and US-Avastin (n=32). Two subjects received wrong doses, and were not included in the PK similarity exercise.

The concentrations of FKB238, US-Avastin and EU-Avastin in human serum were quantitatively determined using ECL-based ligand binding assays.

- **FKB238-003: PK similarity in healthy male individuals from Japan**

Study FKB238-003 was a randomised, double-blind, parallel, single-dose study in healthy male subjects aged 20 to 45 years. The PK objective of the study was to demonstrate the PK similarity of FKB238 with EU-Avastin after single 5 mg/kg doses, by iv infusion, in Japanese healthy male subjects, with a safety objective of the assessment of tolerability and immunogenicity. A total of 40 healthy volunteers were randomised to FKB238 (n=20) and EU-Avastin (n=20).

The concentrations of FKB238 and EU-Avastin in human serum were quantitatively determined using enzyme linked immunosorbent assay (ELISA).

- **FKB238-002: Multicentre, comparative clinical study in patients with non-squamous, non-small cell lung cancer (NS-NSCLC).**

Study FKB238-002 was a randomised, double-blind, parallel study to compare the efficacy and safety of 15 mg/kg doses of FKB238 to EU-Avastin when used in combination with paclitaxel and carboplatin in the first-line treatment of patients aged 18 years or older with advanced/recurrent NS-NSCLC. The primary objective of the study was to demonstrate the efficacy equivalence of FKB238 and EU-Avastin when used in combination with paclitaxel/carboplatin as measured by overall response rate (ORR). Secondary objectives included the comparison of safety, anti-drug antibodies (ADAs) produced by FKB238 and EU-Avastin, and the comparison of the serum trough concentration (C_{trough}) of FKB238 and EU-Avastin. A total of 728 patients with NS-NSCLC were randomised and received treatment with FKB238 (n=362) and EU-Avastin (n=366).

Serum concentrations of FKB238 and EU-Avastin were determined with the same assay as in study FKB238-003.

PK similarity

- **Phase I study FKB238-001**

The terminal phase elimination rate constant (λ_z) was estimated as the slope of a regression line fitted to the terminal phase logged concentration values over time. The goodness of fit statistic, r^2, was high and greater than 0.80 in all subjects. In addition, $\%AUC_{ext}$ was less than 20% of $AUC_{0-\infty}$ in all subjects.

The primary and secondary PK endpoints fell within the predefined similarity ranges (Table 6).

The serum concentration-time profiles of bevacizumab following a single iv infusion of FKB238, EU-Avastin, and US-Avastin are shown in Figure 3. No samples underwent intentional repeat analysis.

The non-compartmental PK parameters are presented in Table 7.

Table 6: Summary of PK similarity of FKB238, EU-Avastin and US-Avastin in study FKB238-001

	Pharmacokinetic parameter	Geometric LS mean			Ratio of geometric LS means (90% CI)		
		FKB238 (N=32)	EU Avastin (N=33)	US Avastin (N=32)	FKB238/ EU Avastin	FKB238/ US Avastin	EU Avastin/ US Avastin
Primary	AUC0-inf (h*ug/mL)	52500	50800	53500	1.03 (0.97, 1.10)	0.98 (0.92, 1.04)	0.95 (0.89, 1.01)
	AUC0-t (h*ug/mL)	50800	49300	51800	1.03 (0.97, 1.09)	0.98 (0.93, 1.04)	0.95 (0.90, 1.01)
Secondary	Cmax (ug/mL)	139	142	138	0.97 (0.91, 1.04)	1.01 (0.94, 1.07)	1.03 (0.97, 1.10)
	t1/2 (h)	456.13	438.06	462.56	1.04 (0.95, 1.14)	0.99 (0.90, 1.08)	0.95 (0.87, 1.04)

CI = Confidence interval; LS = Least squares.
PK parameters were logarithmically transformed prior to an analysis of variance (ANOVA) including a term for treatment group.
Bioequivalence is concluded if the 90% CI of the ratio Test:Reference is included within the range of 0.8 to 1.25 for both primary PK parameters (AUC0-inf and AUC0-t), and for all three treatment comparisons.

Table 7: Pharmacokinetic parameters from study FKB238-001

Pharmacokinetic parameter	Statistic	FKB238 (N=32)	EU Avastin (N=33)	US Avastin (N=32)
Cmax (ug/mL)	Arithmetic mean	140	145	139
	Arithmetic SD	22.0	26.6	21.2
	Arithmetic CV (%)	15.7	18.4	15.2
	Geometric mean	139	142	138
	Geometric CV (%)	15.1	17.3	15.3
	Median	134	145	139
	Min	116	103	107
	Max	186	240	186
tmax (h)	Arithmetic mean	2.19	1.49	4.45
	Arithmetic SD	3.980	0.015	16.709
	Arithmetic CV (%)			
	Geometric mean			
	Geometric CV (%)			
	Median	1.48	1.48	1.48
	Min	1.45	1.47	1.45
	Max	24.00	1.55	96.02

Pharmacokinetic parameter	Statistic	FKB238 (N=32)	EU Avastin (N=33)	US Avastin (N=32)
AUC0-t (h*ug/mL)	Arithmetic mean	51200	49900	52100
	Arithmetic SD	6800.0	7920.0	5520.0
	Arithmetic CV (%)	13.3	15.8	10.6
	Geometric mean	50800	49300	51800
	Geometric CV (%)	13.3	16.6	10.7
	Median	50400	49000	50700
	Min	39300	33600	40700
	Max	66100	66900	63500
AUC0-inf (h*ug/mL)	Arithmetic mean	53000	51800	53900
	Arithmetic SD	7500.0	8970.0	6370.0
	Arithmetic CV (%)	14.1	17.4	11.8
	Geometric mean	52500	50800	53500
	Geometric CV (%)	14.3	18.2	11.9
	Median	51900	50400	51600
	Min	39800	34100	41300
	Max	67500	70100	66800

Pharmacokinetic parameter	Statistic	FKB238 (N=32)	EU Avastin (N=33)	US Avastin (N=32)
Lam_z (1/h)	Arithmetic mean	0.0016	0.0016	0.0015
	Arithmetic SD	0.0003	0.0005	0.0002
	Arithmetic CV (%)	20.5	29.6	15.2
	Geometric mean	0.0015	0.0016	0.0015
	Geometric CV (%)	20.6	27.8	15.9
	Median	0.0015	0.0015	0.0015
	Min	0.0009	0.0010	0.0010
	Max	0.0025	0.0032	0.0019
t1/2 (h)	Arithmetic mean	465.46	453.38	468.28
	Arithmetic SD	97.329	116.421	76.606
	Arithmetic CV (%)	20.9	25.7	16.4
	Geometric mean	456.13	438.06	462.56
	Geometric CV (%)	20.6	27.8	15.9
	Median	461.95	452.30	463.50
	Min	281.48	214.60	371.26
	Max	768.00	681.36	676.36

Pharmacokinetic parameter	Statistic	FKB238 (N=32)	EU Avastin (N=33)	US Avastin (N=32)
MRT (h)	Arithmetic mean	565.47	552.02	583.97
	Arithmetic SD	52.720	82.417	67.206
	Arithmetic CV (%)	9.3	14.9	11.5
	Geometric mean	563.07	545.11	580.26
	Geometric CV (%)	9.4	16.9	11.5
	Median	562.40	572.01	576.22
	Min	454.37	302.79	480.64
	Max	681.17	665.06	719.73
Vss (mL/kg)	Arithmetic mean	61.17	60.81	61.49
	Arithmetic SD	7.323	8.752	6.842
	Arithmetic CV (%)	12.0	14.4	11.1
	Geometric mean	60.75	60.16	61.11
	Geometric CV (%)	12.1	15.2	11.5
	Median	61.05	61.50	60.35
	Min	45.50	40.34	44.08
	Max	79.33	73.92	74.62

Pharmacokinetic parameter	Statistic	FKB238 (N=32)	EU Avastin (N=33)	US Avastin (N=32)
Vz (mL/kg)	Arithmetic mean	63.70	63.19	62.87
	Arithmetic SD	11.683	11.075	8.329
	Arithmetic CV (%)	18.3	17.5	13.2
	Geometric mean	62.72	62.23	62.33
	Geometric CV (%)	17.9	18.0	13.4
	Median	63.38	63.27	61.07
	Min	43.73	40.91	46.38
	Max	96.53	94.54	79.63
CL (mL/h/kg)	Arithmetic mean	0.096	0.100	0.094
	Arithmetic SD	0.0137	0.0188	0.0111
	Arithmetic CV (%)	14.2	18.8	11.8
	Geometric mean	0.095	0.098	0.093
	Geometric CV (%)	14.3	18.2	11.9
	Median	0.096	0.099	0.097
	Min	0.074	0.071	0.075
	Max	0.126	0.146	0.121

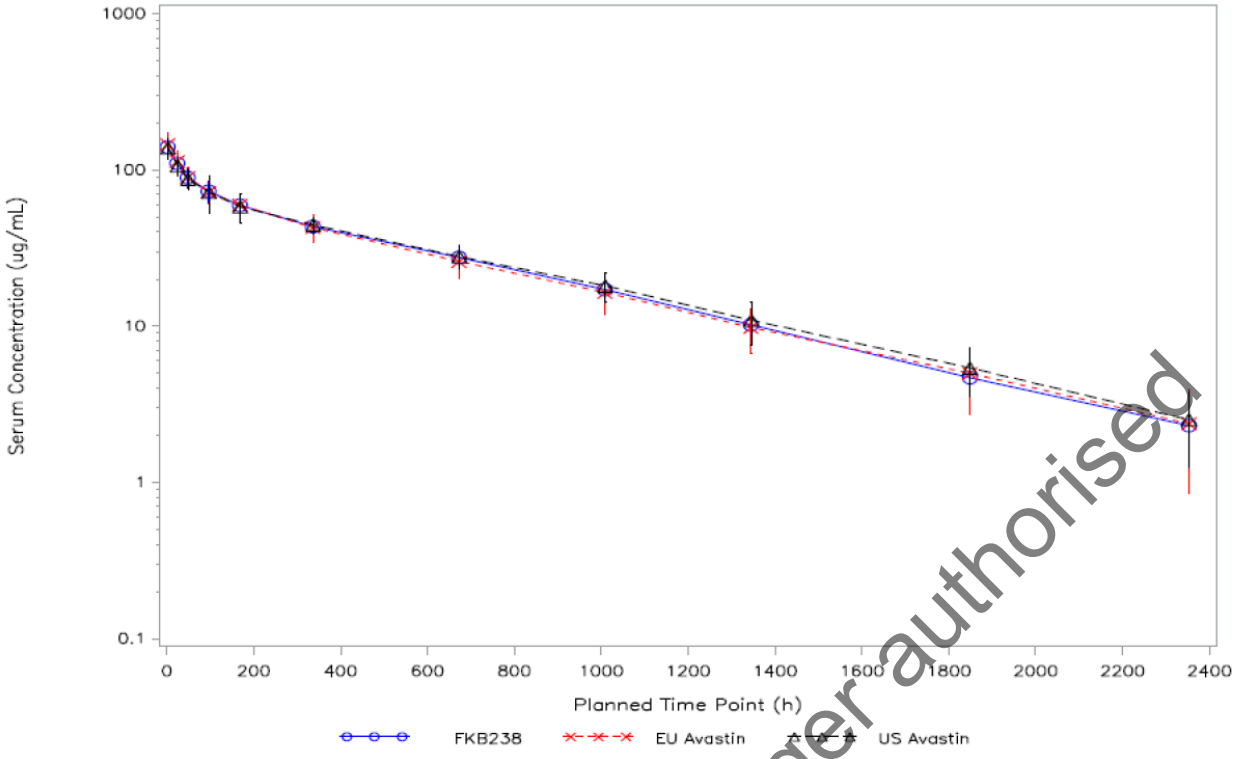


Figure 3. Mean (SD) serum concentration-time profiles of bevacizumab by treatment in FKB238-001

Phase I study FKB238-003

The terminal phase λz was estimated as the slope of a regression line fitted to the terminal phase logged concentration values over time. The goodness of fit statistic, r2, was high and greater than 0.80 in all subjects. In addition, $\%AUC_{ext}$ was less than 20% of $AUC_{0-\infty}$ in all subjects.

The primary and secondary PK endpoints fell within the predefined similarity ranges (Table 8).

The noncompartmental PK parameters are presented in Table 9 while the serum concentration-time profiles of bevacizumab following a single iv infusion of FKB238 and EU-Avastin are shown in Figure 4. No samples underwent intentional repeat analysis.

Table 8: Summary of PK similarity of FKB238 and EU-Avastin in study FKB238-003

	Pharmacokinetic parameter	Geometric LS mean		Ratio of geometric LS means (90% CI)
		FKB238 (N=20)	EU Avastin (N=20)	FKB238/ EU Avastin
Primary	AUC0-inf (h*ug/mL)	41400	43900	0.94 (0.88, 1.01)
	AUC0-t (h*ug/mL)	40800	43100	0.95 (0.89, 1.01)
Secondary	Cmax (ug/mL)	116	118	0.99 (0.90, 1.08)
	t1/2 (h)	388.77	418.65	0.93 (0.86, 1.00)

CI = Confidence interval; LS = Least squares.
PK parameters were logarithmically transformed prior to an analysis of variance (ANOVA) including a term for treatment group.
Bioequivalence is concluded if the 90% CI of the ratio Test:Reference is included within the range of 0.8 to 1.25 for both primary PK parameters (AUC0-inf and AUC0-t), and for all three treatment comparisons.

Table 9: Pharmacokinetic parameters from study FKB238-003

Pharmacokinetic parameter	Statistic	FKB238 (N=20)	EU Avastin (N=20)
Cmax (ug/mL)	Arithmetic mean	118	120
	Arithmetic SD	17.6	26.7
	Arithmetic CV (%)	14.9	22.2
	Geometric mean	116	118
	Geometric CV (%)	14.5	19.6
	Median	117	113
	Min	92.7	93.5
	Max	161	203
tmax (h)	Arithmetic mean	2.63	4.88
	Arithmetic SD	5.031	8.243
	Arithmetic CV (%)		
	Geometric mean		
	Geometric CV (%)		
	Median	1.50	1.50
	Min	1.50	1.50
	Max	24.00	24.00

Pharmacokinetic parameter	Statistic	FKB238 (N=20)	EU Avastin (N=20)
AUC0-t (h*ug/mL)	Arithmetic mean	41000	43100
	Arithmetic SD	4750.0	5370.0
	Arithmetic CV (%)	11.6	12.4
	Geometric mean	40800	43100
	Geometric CV (%)	11.5	12.7
	Median	40300	43100
	Min	32300	34000
	Max	52900	54600
AUC0-inf (h*ug/mL)	Arithmetic mean	41700	44300
	Arithmetic SD	5000.0	5790.0
	Arithmetic CV (%)	12.0	13.1
	Geometric mean	41400	43900
	Geometric CV (%)	11.9	13.4
	Median	40900	43700
	Min	32700	34200
	Max	54500	56500

Pharmacokinetic parameter	Statistic	FKB238 (N=20)	EU Avastin (N=20)
Lam_z (1/h)	Arithmetic mean	0.0018	0.0017
	Arithmetic SD	0.0002	0.0002
	Arithmetic CV (%)	13.2	13.2
	Geometric mean	0.0018	0.0017
	Geometric CV (%)	13.0	14.7
	Median	0.0017	0.0017
	Min	0.0015	0.0011
	Max	0.0023	0.0020
t1/2 (h)	Arithmetic mean	391.83	423.29
	Arithmetic SD	49.736	69.863
	Arithmetic CV (%)	12.7	16.5
	Geometric mean	388.77	418.65
	Geometric CV (%)	13.0	14.7
	Median	396.81	399.42
	Min	296.07	353.71
	Max	472.46	655.54

Pharmacokinetic parameter	Statistic	FKB238 (N=20)	EU Avastin (N=20)
MRT (h)	Arithmetic mean	549.73	581.78
	Arithmetic SD	70.485	87.742
	Arithmetic CV (%)	12.8	15.1
	Geometric mean	545.30	575.53
	Geometric CV (%)	13.2	15.2
	Median	563.41	564.91
	Min	410.06	430.15
	Max	677.09	735.71
Vss (mL/kg)	Arithmetic mean	66.38	65.88
	Arithmetic SD	8.638	7.496
	Arithmetic CV (%)	13.0	11.4
	Geometric mean	65.85	65.48
	Geometric CV (%)	13.0	11.4
	Median	63.75	64.66
	Min	53.03	52.51
	Max	83.34	81.00

Pharmacokinetic parameter	Statistic	FKB238 (N=20)	EU Avastin (N=20)
Vz (mL/kg)	Arithmetic mean	68.32	69.22
	Arithmetic SD	9.284	8.993
	Arithmetic CV (%)	13.6	13.0
	Geometric mean	67.73	68.71
	Geometric CV (%)	13.5	12.3
	Median	67.73	66.95
	Min	54.47	58.19
	Max	87.56	96.20
CL (mL/h/kg)	Arithmetic mean	0.122	0.115
	Arithmetic SD	0.0144	0.0158
	Arithmetic CV (%)	11.9	13.7
	Geometric mean	0.121	0.114
	Geometric CV (%)	11.9	13.4
	Median	0.122	0.114
	Min	0.092	0.089
	Max	0.153	0.146

Geometric mean, geometric CV and arithmetic CV not reported for tmax.
Values not presented could not be calculated.

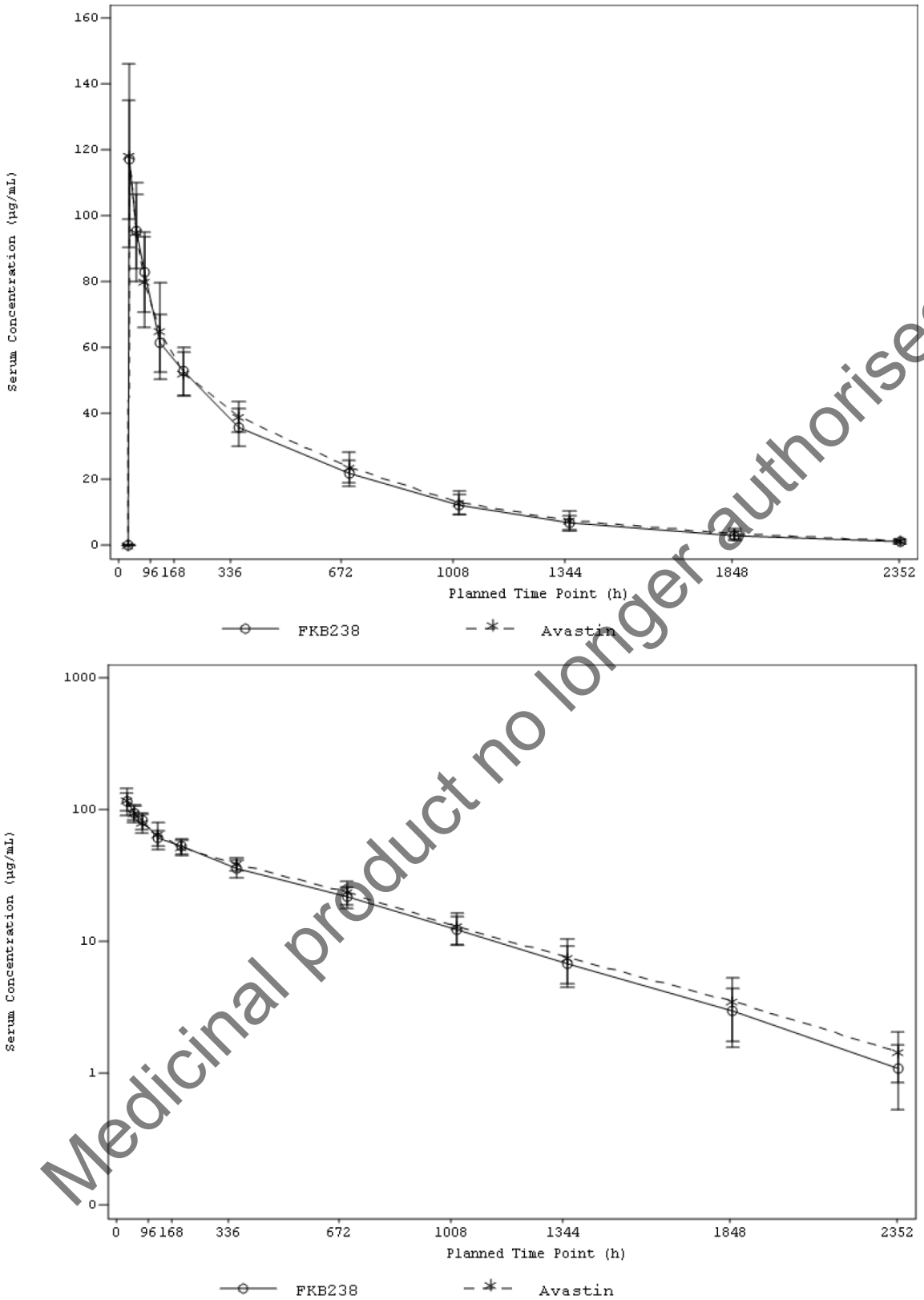


Figure 4. Mean (SD) serum drug concentration-time profiles in study FKB238-003

Phase III study FKB238-002

The mean serum concentrations from study FKB238-002 are presented in Table 10 and Figure 5. No samples underwent intentional repeat analysis.

Table 10: Serum concentrations of FKB238 and EU-Avastin in patients with NS-NSCLC from study FKB238-002

Visit	Serum concentration (µg/mL)	
	FKB238	Avastin
	(N=345)	(N=351)
Cycle 1, Day 1		
Pre-infusion		
n	342	351
Geometric mean (CV%)	NC (NC)	NC (NC)
End of infusion		
n	343	347
Geometric mean (CV%)	255.15 (45.1)	245.11 (37.8)
Cycle 2, Day 1		
Pre-infusion		
n	325	327
Geometric mean (CV%)	42.74 (44.9)	48.48 (56.3)
Cycle 4, Day 1		
Pre-infusion		
n	280	284
Geometric mean (CV%)	77.16 (37.6)	83.26 (49.3)
End of infusion		
n	278	283
Geometric mean (CV%)	339.91 (36.4)	373.92 (34.7)
Cycle 6, Day 1		
Pre-infusion		
n	247	253
Geometric mean (CV%)	87.25 (45.2)	108.22 (45.5)

BLQ=below the lower limit of quantification; CV=coefficient of variation; NC=not calculable; IP=investigational product (FKB238 or Avastin); PK=pharmacokinetics.

n is the number of not excluded non-missing values (including BLQ)

[a] Excluding pre-dose values after Cycle 1 without IP dose in the previous cycle and excluding post-dose values without IP dose in this cycle.

Source: Table 14.2.6.2.

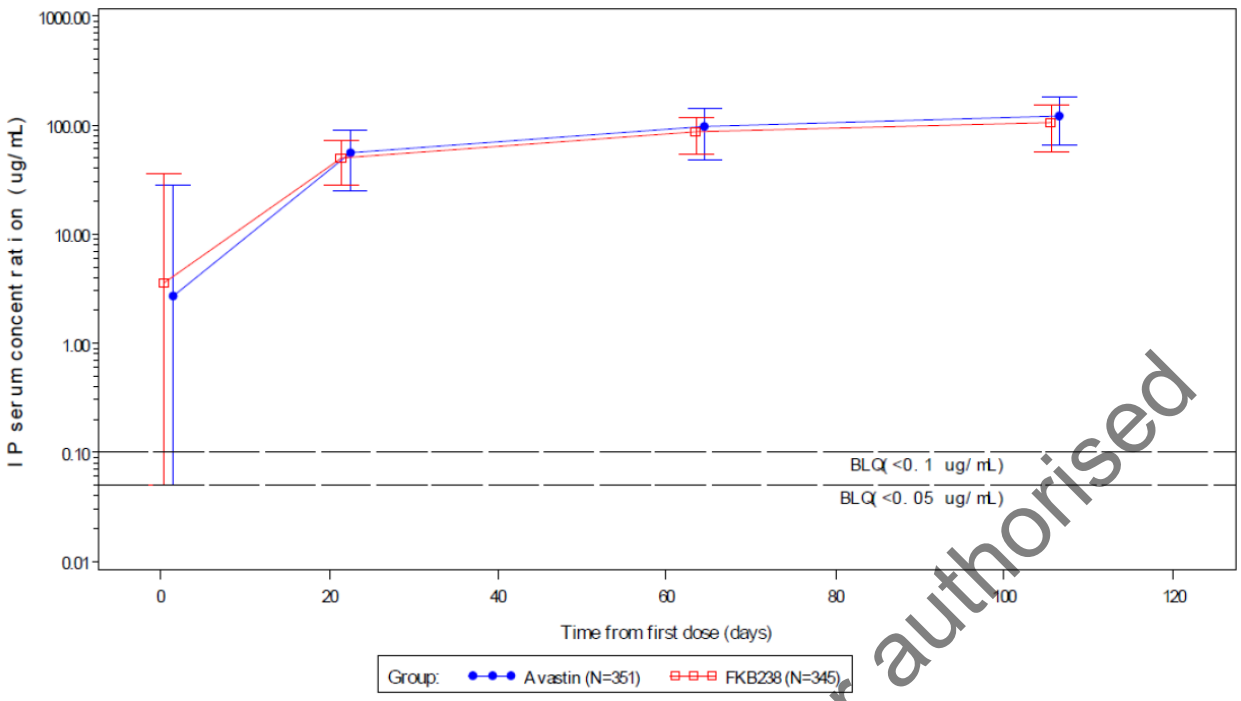


Figure 5. Mean (SD) concentration-time plots of C_{trough} in patients with NS-NSCLC from FKB238-002

2.4.3. Pharmacodynamics

No clinical pharmacodynamic studies have been performed with FKB238.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic properties of FKB238 were compared with both EU- and US-sourced bevacizumab (Avastin) in a pivotal phase I clinical trial in healthy male subjects (FKB238-001), following a 5 mg/kg body weight single iv injection. In addition, pharmacokinetics of FKB238 was compared with EU-Avastin in healthy Japanese males (FKB238-003).

In the initial submission, the applicant omitted several subjects from analyses of PK similarity in the FKB238-001 and -003 trials. Eight subjects (3 subjects in the FKB238- and 5 in the EU-Avastin arm) in FKB238-001 and one subject in the EU-Avastin arm in FKB238-003 were omitted from the PK similarity analyses of $AUC_{0-\infty}$ and $t_{1/2}$. Subjects were omitted due to what the applicant defined as "unreliable" PK-data. The applicant had a predefined rule which stated that subjects should be omitted if the time period over which λ_z was estimated was less than 2-fold the associated $t_{1/2}$. In essence, the subjects were excluded due to long $t_{1/2}$.

Per request, the applicant resubmitted PK similarity analyses from study FKB238-001 and -003, where all subjects were included. The results demonstrated PK similarity between FKB238 and EU-Avastin both in the pivotal FKB238-001 study (Table 6), and in the supportive FKB238-003 study (Table 8).

In the pivotal phase III trial (FKB238-002), FKB238 was compared with EU-Avastin by side by side analyses of C_{trough} and C_{max} serum concentrations of FKB238 or EU-Avastin following repeat 15 mg/kg dose administration in patients with NS-NSCLC. The geometric mean pre-dose concentrations of FKB238 were slightly lower than that of EU-Avastin at some timepoints (Table 10). The differences in the pre-dose concentrations; however, are so small that they can be considered as clinically insignificant.

Even though previous treatment with VEGF inhibitors was an exclusion criteria in study FKB238-002, the C_{trough} sampled before the first cycle ranged from BLQ to 528.6 µg/mL for FKB238 and from BLQ to 410.3 µg/mL for EU-Avastin (Figure 5). The applicant presented all PK data from the 34 subjects that had quantifiable concentrations before infusion at C1D1 (data not shown). Of the 34 subjects, 33 also had quantifiable concentrations post-dose, ruling out the possibility of switching pre- and post-dose samples for these individual subjects. The applicant also mentioned that samples could have been contaminated with drug without elaborating on how this could happen. There could be many possible scenarios, but one possible explanation may be that several samples were pipetted with the same pipette. This could explain the samples with concentrations close to the LLoQ. Another explanation, which was not discussed by the applicant, is that some pre-dose samples may have been collected during the infusion of the investigational drug. The applicant concluded that the samples with quantifiable concentrations were due sample mislabelling, sample switching and/or drug contamination. It is unknown for which samples the applicant suspects the different scenarios may have happened. The matter was not pursued since it was not expected that the validity of samples collected from C2D1 and onwards would be affected to a relevant degree. This was supported by a routine GCP-inspection of two centres in Russia and Bosnia-Herzegovina that did not report any minor- or major findings with regards to PK sampling (GCP Inspection Report INS/GCP/2019/036).

Validation reports of the bioanalysis/immunogenicity analyses for review were submitted and considered adequate.

No new pharmacodynamic data have been submitted as part of this application. Validated PD markers considered relevant to predicting efficacy of bevacizumab in patients do not exist. Therefore, no PD markers were included in the PK study, and clinical endpoints were utilized in the phase III study in NSCLC patients.

2.4.5. Conclusions on clinical pharmacology

PK similarity between FKB238 and EU-Avastin has been demonstrated in two Phase I "bioequivalence" trials.

2.5. Clinical efficacy

One phase 3 study in non-squamous non-small cell lung cancer (NS-NSCLC) patients for the efficacy and safety comparison of FKB238 with the reference product EU-Avastin, including monitoring of immunogenicity, was submitted by the applicant.

Table 11: Description of the comparative clinical phase 3 efficacy and safety study

Study ID	Number of centres Location(s)	First patient consent Last patient consent Randomised/ Treated	Design	Study & ctrl drugs Dose, route & regimen	Study objective	Patients by treatment Randomised/ Ongoing at DCO	Duration	Gender M/F Mean age (range)	Diagnosis Inclusion criteria	Primary endpoint
FKB238-002	146/136[a] BA, BG, BY, DE, ES, GE, GR, HR, HU, IT, JP, KR, PE, PH, PO, RO, RS, RU, TH, TR, TW, UA, US, VN	21 Jun 2016 03 Jan 2018 731/728	R, P, DB, MC	FKB238: 15 mg/kg IV every 3 weeks Avastin: 15 mg/kg IV every 3 weeks Both in combination with paclitaxel and carboplatin for 4 to 6 cycles	Efficacy equivalence of FKB238 and Avastin	FKB238: 364/37 Avastin: 367/38	Until disease progression or other criteria for treatment discontinuation	483/248 61.0 years (26 to 84)	Patients aged 18 years or older with advanced or recurrent NS-NSCLC who had not received systemic anti-cancer therapy for metastatic disease.	ORR (by RECIST v1.1), assessed as the rate of the best response (CR or PR)

BA=Bosnia and Herzegovina; BG=Bulgaria; BY=Belarus; CR=complete response; Ctrl=control; DB=double blind; DCO=data cut-off; DE=Germany; ES=Spain; GE=Georgia; GR=Greece; HR=Croatia; HU=Hungary; IT=Italy; JP=Japan; KR=Republic of Korea; M=Male; MC=multicentre; ORR=overall response rate; P=parallel; PE=Peru; PH=Philippines; PO=Poland; PR=partial response; R=randomised; RECIST=Response Evaluation Criteria in Solid Tumours; RO=Romania; RS=Serbia; RU=Russia; TH=Thailand; TR=Turkey; TW=Taiwan; UA=Ukraine; US=United States; VN=Vietnam.
aNumber of centres that screened/randomised patients.

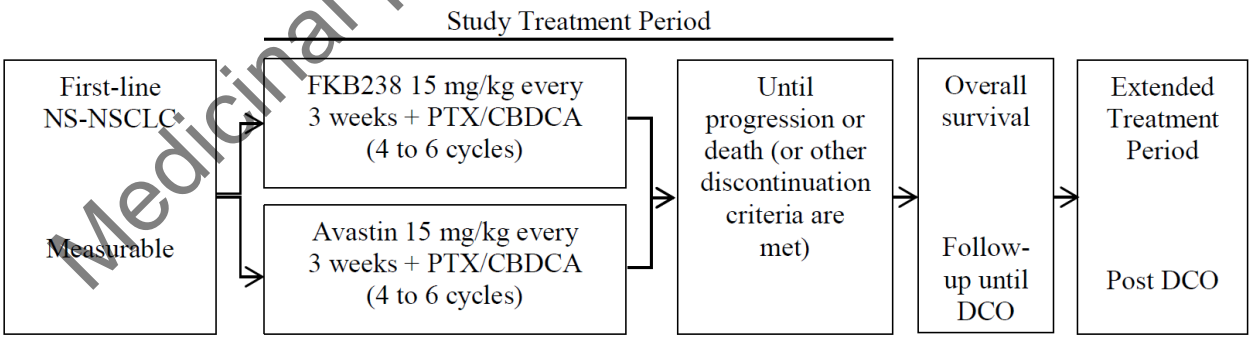
2.5.1. Dose response study

No dose response studies were performed and are not deemed necessary for a biosimilar medicinal product.

2.5.2. Main study

FKB238-002

Study FKB238-002 is a global, multicentre, double-blind, parallel, randomised, comparative clinical study designed to compare the efficacy and safety of FKB238 and bevacizumab EU-reference product (EU-Avastin) when used in combination with paclitaxel and carboplatin in the first-line treatment of advanced or recurrent NS-NSCLC.



CBDCA=carboplatin; DCO=data cut-off; IP=investigational product (FKB238 or Avastin); NS-NSCLC=non squamous non-small cell lung cancer; PD=progression of disease; PS=performance status; PTX=paclitaxel.

Figure 6. Flow chart of study design

Screening Period

Patients aged ≥18 years with advanced or recurrent NS-NSCLC were screened for participation in the study up to 28 days before randomisation.

Study Treatment Period

Upon randomisation, patients entered the Study Treatment Period. Following start of study treatment, patients were to return for study visits every 3 weeks as long as they were receiving study treatment. The combination drugs (paclitaxel + carboplatin) was administered on Day 1 of each 21-day cycle for at least four, and no more than six cycles. The number of cycles is determined by patients' need and the investigator's assessment. FKB238 or EU Avastin investigational product (IP) were also administrated on Day 1 of each 21-day cycle until objective PD or other criteria for treatment discontinuation are met.

Data cut-off (DCO)

Data cut-off was defined as 12 months from randomisation of the last patient enrolled in the study. Up to the time of DCO, all data on systemic anti-cancer treatment, radiotherapy or cancer surgery conducted after discontinuation of study treatment were to be collected until death, loss to follow-up, withdrawal of consent or until end of study. Assessments for survival should be made every eight weeks (± 1 week) following objective PD. At data cut-off all patients previously discontinued from study treatment and continuing in follow-up will complete the study and no further study assessments will be performed.

Extended treatment period (ETP)

The Extended Treatment Period is the time after data cut-off to end of study in which patients may continue receiving IP if they are considered by the treating investigator to be gaining clinical benefit. Complete assessments for safety, efficacy, PK, and immunology will not be collected by the applicant during this period.

End of study

End of study is defined as the last patient's last visit.

Methods

Study Participants

Key inclusion criteria

1. Patients aged 18 years or older
2. Newly diagnosed advanced (stage IV) /recurrent NS-NSCLC for which they had not received any systemic anti-cancer therapy for metastatic disease, including chemotherapy, biologic therapy, immunotherapy, or any investigational drug
3. Histologically or cytologically confirmed diagnosis of predominantly NS-NSCLC
4. Existence of at least one measurable lesion by response evaluation criteria (RECIST v1.1) defined as; at least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements
5. ECOG PS 0 or 1
6. Adequate haematological function: absolute neutrophil count (ANC) ≥ 1.5 × 109/L; platelets ≥ 100 × 109/L; haemoglobin ≥ 9 g/dL
7. International normalised ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) ≤ 1.5 × the upper limit of normal (ULN) within 7 days prior to starting study treatment

8. Adequate liver function: Serum bilirubin ≤ 1.5 × ULN (and in case of documented Gilbert's Syndrome [unconjugated hyperbilirubinaemia] ≤ 3 x ULN); transaminases ≤ 2.5 × ULN (and in case of liver metastases < 5 × ULN)
9. Adequate renal function:
    - Creatinine clearance, measured and/or calculated according to the formula of Cockroft and Gault ≥ 60 mL/min AND
    - Urine dipstick or urinalysis for proteinuria < 2+. If the urine dipstick or urinalysis is ≥ 2+, 24-hour urine must demonstrate ≤ 1 g of protein in 24 hours.

Key exclusion criteria

1. Small cell lung cancer (SCLC) or combination SCLC and NSCLC. Squamous-cell tumours and mixed adenosquamous carcinomas of predominantly squamous nature
2. Recurrence occurred within 12 months from the last dose of neoadjuvant/adjuvant therapy
3. Any unresolved toxicities from prior systemic therapy (e.g., adjuvant chemotherapy) greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 at the time of starting study drug with the exception of alopecia
4. Evidence of a tumour that compresses or invades major blood vessels or tumour cavitation that in the opinion of the investigator is likely to bleed
5. Known sensitising EGFR mutations (e.g., deletion 19 or L858R) or EML4-ALK translocation positive mutations
6. Previous dosing with VEGF inhibitor
7. Brain metastasis or spinal cord compression (computed tomography [CT] or magnetic resonance imaging [MRI] of the head is required within 4 weeks prior to randomisation)
8. Non-healing wound, ulcer, or bone fracture
9. Patients with unstable angina, myocardial infarction, coronary artery bypass graft, angioplasty, vascular stenting, or cardiovascular event within 6 months before the first dose of IP; coagulopathy, any bleeding disorders, poorly controlled diabetes, or active gastrointestinal inflammation such as gastric or duodenal ulcer, diverticulitis, inflammatory bowel disease, or cholecystitis
10. History of fistulas or abdominal perforations
11. History of arterial or venous thromboembolic or ischemic events, or congestive heart failure (New York Heart Association class ≥ 2) within 6 months before the first dose of IP
12. History of haemoptysis of ≥ ½ teaspoon of red blood within 28 days before the first dose of IP
13. Treatment with any other investigational agent for any reason within 28 days before the first dose of IP

Treatments

Doses and schedules of IPs and chemotherapy in the two treatment arms

FKB238 group:

- FKB238 15 mg/kg on Day 1 of each 21-day cycle (IV infusion, 90-30 min, depending on tolerability) until objective PD or other criteria for treatment discontinuation are met

- Paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for at least four, and no more than six cycles (IV infusion over three hours)
- Carboplatin area under the curve (AUC) 6.0 on Day 1 of each 21-day cycle for at least four, and no more than six cycles (IV infusion over 15-60 min)

EU-Avastin group:

- EU-Avastin 15 mg/kg on Day 1 of each 21-day cycle (IV infusion, 90-30 min, depending on tolerability) until objective PD or other criteria for treatment discontinuation are met
- Paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for at least four, and no more than six cycles (IV infusion over three hours)
- Carboplatin AUC 6.0 on Day 1 of each 21-day cycle for at least four, and no more than six cycles (IV infusion over 15-60 min)

Objectives

Primary objective

- To demonstrate equivalent efficacy of FKB238 and EU-Avastin.

Secondary objectives

- Continuous measure of clinical efficacy, to compare safety, ADAs produced and serum trough concentrations (Ctrough) of FKB238 and EU-Avastin

Outcomes/endpoints

Primary efficacy endpoint

- The primary efficacy endpoint of the study is overall response rate (ORR) defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) by RECIST v1.1, as assessed by blinded independent central review (BICR).

Secondary endpoints

Efficacy

- ORR (by RECIST v1.1) at week 19, defined as the rate of the best response of CR or PR assessed at week 19
- Progression-free survival (PFS), defined as the time from randomisation to the first documented disease progression (progressive disease [PD]) or death, whichever occurs first
- Overall survival (OS), defined as the time from randomisation to death from any cause
- Duration of response (DOR), defined as the time from the first documented PR or CR (by RECIST v1.1) to the first documented objective PD or death, whichever occurs first
- Disease control rate (DCR), defined as the rate of CR, PR, stable disease (SD) (≥ 6 weeks)

Safety endpoints

- Safety as evaluated through AEs, vital signs, haematology, clinical chemistry, urinalysis, electrocardiogram (ECG), Eastern Collaborative Oncology Group Performance Status (ECOG PS), and physical examination

Sample size

Assuming a dropout rate of 10%, it was anticipated that approximately 730 patients would be randomised into the study in a 1:1 ratio (365 patients in the FKB238 group and 365 patients in the Avastin group), in order to have a total of 656 patients who complete study treatment.

To fulfil the EMA requirements, a meta-analysis of available randomised clinical studies of Avastin demonstrated that the risk-difference for the ORR for the control arm compared to the Avastin treatment arms was calculated to be 0.1938 (80% CI: [0.1564, 0.2312]). Based on the result of the meta-analysis, an equivalence margin for the risk difference was determined to be 0.1221, which preserves 22% of the treatment effect characterised by the lower 80% CI for the risk-difference of ORR.

With the equivalence margin for the risk-difference of 0.1221, an expected response rate of 35% in both treatment arms, the study design employing a two one-sided test (TOST) procedure, and an overall Type I error rate of 2.5%, a sample size of 656 patients (328 per group) was calculated to provide 80% power to demonstrate that the 95% CI about the risk-difference comparing FKB238 and EU-Avastin falls completely within ± 0.1221.

Randomisation

Randomisation was stratified according to epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma receptor tyrosine kinase (ALK) gene arrangement status (both are tested and known negative versus status unknown for either), geographical region (North America, Western Europe, East Asia, All Other Regions), prior weight loss over the previous 6 months (< 5% yes versus no) and disease stage (advanced or recurrent).

Blinding (masking)

Investigators, site staff including pharmacy staff, patients, CRO personnel, and Sponsor personnel (except for a specified investigational product (IP) distribution manager and unblinded site pharmacists located only at sites conducting the study under an amended protocol that specifies an unblinded pharmacist role.) were blinded to individual patient treatment assignment during the course of the study.

The IP was packaged and labelled in such a way that visual inspection of the IP or packaging would not reveal the treatment assignment; however, each individual kit of IP was numbered so that, if necessary, the number could be used to break the treatment blind if this became necessary to protect the safety of the patient.

Statistical methods

This study was designed to test for equivalence. The Null hypothesis for the treatment comparison was that there is non-equivalence between EU-Avastin and FKB238 in ORR. The alternative hypothesis was that there is equivalence.

The following analysis populations were included for this study:

- ITT Population: all patients randomised to treatment. Patients included in the treatment group according to the randomisation assigned, regardless of the treatment actually given. All efficacy analyses to be performed on the ITT population. These analyses were to be treated as sensitivity analysis.

- Per Protocol Set: all patients randomised to treatment who received at least 1 dose of IP with no important protocol deviations. Patients were included in the treatment group according to the treatment

actually given. All efficacy analyses were to be performed on the PPS. These analyses were to be treated as the primary analysis. The subjects to be included in the PPS were to be identified in a Data Review Meeting to be held prior to database lock for final analysis.

- Safety Population: all patients randomised to treatment who received at least 1 dose of IP.

Patients will be included in the treatment group according to the treatment actually given.

All safety analyses will be performed on the Safety Population. Treatment groups will be analysed according to the first IP actually received.

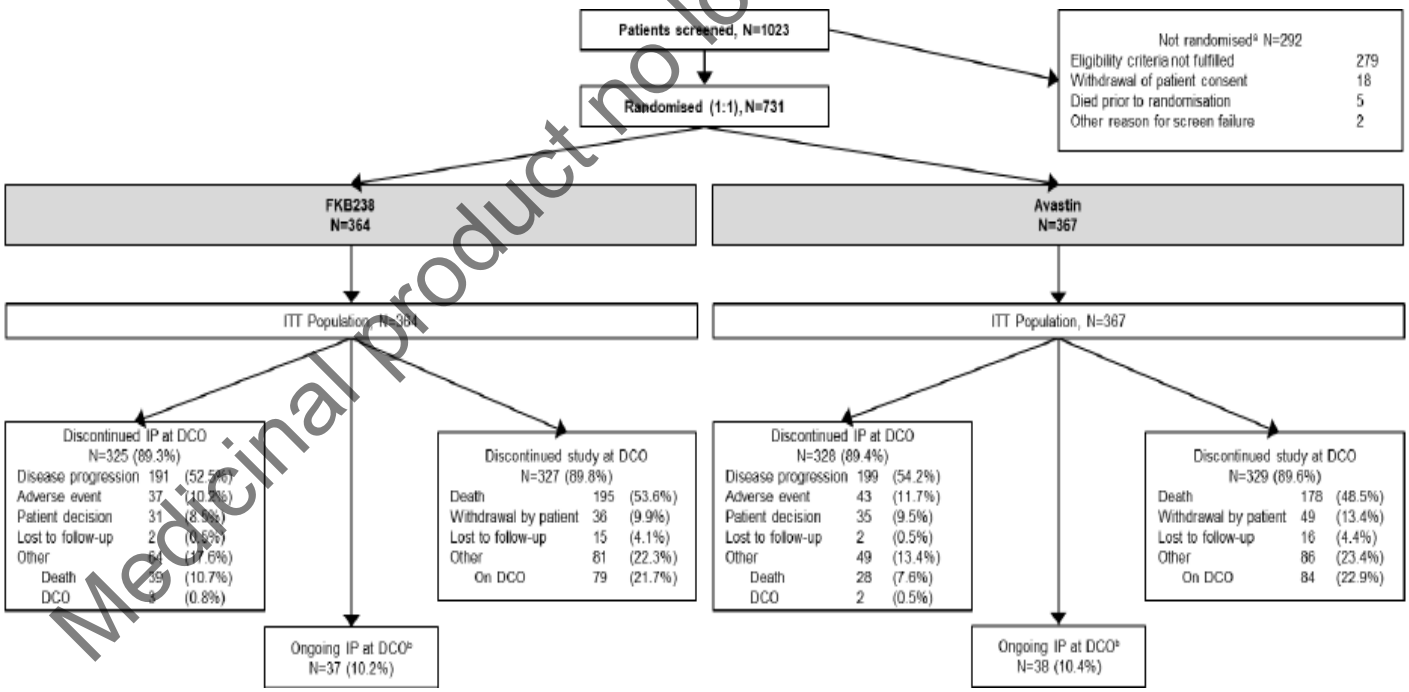
- PK Population: all PPS patients who have at least one serum drug concentration data,

which is defined in the study protocol, after IP administration. Patients will be included in the treatment group according to the treatment actually given.

A two one-sided test procedure was used to test this hypothesis. The analysis was performed using the per protocol set (PPS). A 95% CI for the ORR difference between FKB238 and EU-Avastin was estimated and compared to the margin [± 0.1221]. If the true CI was within the interval [± 0.1221], an equivalence between FKB238 and EU-Avastin, with respect to the ORR, was confirmed.

Results

Participant flow



CSR=clinical study report; DCO=data cut-off; IP=investigational product (FKB238 or Avastin); ITT=Intent-to-Treat.
aIndividual patients could have more than 1 reason for screen failure recorded.
bAll patients still receiving IP at DCO who entered the Extended Treatment Period. The Extended Treatment Period is ongoing as of the DCO for this CSR and data from the Extended Treatment Period are not presented herein.

Figure 7: Study participant flow

Recruitment

The first patient signed informed consent on 21 June 2016 and the last patient signed informed consent on 03 January 2018. The data cut-off, defined as 12 months from randomisation of the last patient enrolled in the study, was 24 January 2019 and all data up to and including this date were included in the study analyses.

Patients were screened at 146 centres in 24 countries, and of these 136 centres in 24 countries (patient numbers) randomised patients; Belarus (50), Bosnia and Herzegovina (23), Bulgaria (5), Croatia (8), Georgia (27), Germany (2), Greece (15), Hungary (52), Italy (5), Japan (5), South Korea (11), Peru (13), Philippines (13), Poland (31), Romania (13), Russia (184), Serbia (59), Spain (19), Taiwan (4), Thailand (36), Turkey (11), Ukraine (120), US (16) and Vietnam (9).

Conduct of the study

Amendments to the protocol

The original clinical study protocol (CSP) was dated 04 February 2016. There were four amendments to the original protocol, for details see table below. In addition, several country specific amendments have been implemented locally.

Table 12: Changes to planned analyses

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Person(s)/ group(s) responsible for amendment[a]
Amendments made before the start of patient recruitment			
Amendment 1 (07 April 2016)	Details added to the study procedure for EGFR mutation and ALK gene arrangement status, brain CT/MRI at Screening, blood pressure measurement, dose modifications for non-haematologic toxicity, other concomitant medications, primary efficacy assessment, and the type of palliative radiotherapy allowed (Sections 2, 9.1, 9.4.3, 9.4.5.3, 9.7.1.1, 10.1, and 10.4.2).	To provide more detailed clarification on the study procedure.	Medical and Safety
	Urine pregnancy test added as an alternative to serum pregnancy test (Section 9.3.1).	To provide more detailed clarification on the study procedure.	Medical and Safety
	Clarification of visit allowance for radiological tumour assessments and assessments for survival (Sections 2, 9.1, and 9.7.1.1).	To provide more detailed clarification on the study procedure.	Medical and Safety
Amendment 2 (20 April 2016)	Details added to the study procedure for prior weight loss definition and brain CT/MRI at Screening (Sections 2, 9.1, 9.4.3, and 9.7.1.1).	To provide more detailed clarification on the study procedure.	Medical and Safety
Amendments made after the start of patient recruitment			
Amendment 3 (12 April 2017)	Details added to the study procedure for urinalysis and urine dipstick, secondary objectives and secondary endpoints, treatments administered, re-start of study treatment, stop and re-initiation of IP prior to/after surgery, haematologic toxicities of the IP, study populations, screening procedures and screening failures, recording of AEs, and safety laboratory determinations (Sections 2, 8.2, 9.1, 9.3.1, 9.4.2, 9.4.5.4, 9.5.1, 9.7, 9.7.2.1, 9.7.2.2, 9.8.1.2.3, 9.8.2, 10.3, and 11.1.2.1).	To provide more detailed clarification on the study procedure.	Medical and Safety
	Exclusion criterion of hypersensitivity updated to include active ingredients of the IP or combination drugs (Section 9.3.2).	Updated to meet the Japan PMDA requirement	Medical and Safety
	Clarification added that patients who discontinue breastfeeding may be included in the study (Section 9.3.2).	Updated to meet the Japan PMDA requirement	Medical and Safety

	Exclusion criterion of treatment with any other investigational agent for any reason within 28 days before the first dose of IP updated to clarify that this treatment may be for any reason (Section 9.3.2).	Updated to meet the Japan PMDA requirement	Medical and Safety
	Introduction of the Coordinating Investigator (Section 6.1).	To introduce the Coordinating Investigator and his role as a signatory to the clinical study report.	Medical and Safety
Amendment 4 (22 May 2018)	Clarification of procedures to be completed prior to data cut-off and after data cut-off (ie, during the Extended Treatment Period) (Sections 9.1, 9.4.5.5, and 9.7.2).	To clarify procedures to be completed during the Extended Treatment Period.	Medical and Safety
	Sponsor details updated.	To update the Sponsor's signature page.	Medical and Safety

Changes to the statistical analysis plan

The original SAP (version 1.0) was dated 08 June 2016. During the development of the SAP and prior to unblinding of the study data, changes were made to the planned analyses in SAP version 2.0 (dated 07 March 2019). The changes to the planned analyses made after unblinding of the data on 07 May 2019 concerned listing of data and removal of duplicated presented data and split of listing due to large size.

Protocol deviations

Important protocol deviations that led to exclusion from the per-protocol set (PPS) are listed below.

Table 13: Important protocol deviations (ITT Population)

Important protocol deviation[a]	Number (%) of patients		
	FKB238 (N=364)	Avastin (N=367)	Total (N=731)
Number of patients with no important deviation	352 (96.7)	354 (96.5)	706 (96.6)
Number of patients with at least 1 important deviation	12 (3.3)	13 (3.5)	25 (3.4)
Failed inclusion criteria	0	0	0
Met exclusion criteria	1 (0.3)	0	1 (0.1)
Recurrence occurred within 12 months from the last dose of neoadjuvant/adjuvant therapy	1 (0.3)	0	1 (0.1)
Specific important protocol deviations	11 (3.0)	13 (3.5)	24 (3.3)
Baseline imaging >28 days prior to randomisation	4 (1.1)	2 (0.5)	6 (0.8)
Randomised but did not receive any IP	2 (0.5)	1 (0.3)	3 (0.4)
Delayed study treatment for more than 21 days due to any reason	4 (1.1)	9 (2.5)	13 (1.8)
Received the incorrect randomised therapy	2 (0.5)	1 (0.3)	3 (0.4)

IP=investigational product (FKB238 or Avastin); ITT=Intent-to-Treat.
Study treatment=IP and/or any combination drugs (paclitaxel and carboplatin).
Note that the same patient may have had more than 1 important protocol deviation.
[a]Important deviations before the start of treatment and during treatment.

Baseline data

Table 14: Demographics and other baseline characteristics (ITT Population)

Demographic characteristic	FKB238	Avastin	Total
	(N=364)	(N=367)	(N=731)
Age (years)			
n	364	367	731
Mean (STD)	60.8 (8.79)	61.1 (9.42)	61.0 (9.10)
Range	(26 to 84)	(26 to 82)	(26 to 84)
Age group (years), n (%)			
<65	238 (65.4)	224 (61.0)	462 (63.2)
18-39	5 (1.4)	8 (2.2)	13 (1.8)
40-64	233 (64.0)	216 (58.9)	449 (61.4)
≥65	126 (34.6)	143 (39.0)	269 (36.8)
65-74	107 (29.4)	116 (31.6)	223 (30.5)
75-84	19 (5.2)	27 (7.4)	46 (6.3)
≥85	0	0	0
Race, n (%)			
White	316 (86.8)	320 (87.2)	636 (87.0)
Black and African American	1 (0.3)	0	1 (0.1)
Asian, other than Japanese	37 (10.2)	37 (10.1)	74 (10.1)
Japanese	2 (0.5)	3 (0.8)	5 (0.7)
American Indian or Alaska Native	1 (0.3)	4 (1.1)	5 (0.7)
Other	7 (1.9)	3 (0.8)	10 (1.4)
Gender, n (%)			
Male	245 (67.3)	238 (64.9)	483 (66.1)
Female	119 (32.7)	129 (35.1)	248 (33.9)

Demographic characteristic	FKB238	Avastin	Total
	(N=364)	(N=367)	(N=731)
Geographical region[a]			
North America	8 (2.2)	8 (2.2)	16 (2.2)
Western Europe	13 (3.6)	13 (3.5)	26 (3.6)
East Asia	38 (10.4)	40 (10.9)	78 (10.7)
All other regions	304 (83.5)	306 (83.4)	610 (83.4)
Further stratum[b]	1 (0.3)	0	1 (0.1)
Ethnic group, n (%)			
Not Hispanic or Latino	349 (95.9)	356 (97.0)	705 (96.4)
Hispanic or Latino	15 (4.1)	11 (3.0)	26 (3.6)
BMI at baseline (kg/m^2)			
n	363	367	730
Mean (STD)	25.86 (5.173)	25.18 (4.884)	25.52 (5.038)
Range	(14.7 to 43.6)	(14.6 to 46.9)	(14.6 to 46.9)
Weight at baseline (kg)			
n	363	367	730
Mean (STD)	73.30 (16.372)	71.02 (15.007)	72.15 (15.731)
Range	(36.0 to 126.0)	(39.0 to 120.0)	(36.0 to 126.0)
Smoking status, n (%)			
Never	127 (34.9)	136 (37.1)	263 (36.0)
Current	112 (30.8)	103 (28.1)	215 (29.4)
Former	125 (34.3)	128 (34.9)	253 (34.6)
Number of pack years			
n	236	228	464
Mean (STD)	38.5 (27.23)	34.9 (21.39)	36.7 (24.57)
Range	(1 to 240)	(1 to 150)	(1 to 240)

BMI=body mass index; IWRS=interactive web response system; ITT=Intent-to-Treat; STD=standard deviation.
aAs recorded at randomisation by IWRS.
bOne patient was randomised in a further stratum, since at the time of randomisation it was not clear to which geographical region the patient should be assigned.

Table 15: Summary of disease characteristics at baseline (ITT Population)

Disease characteristic	FKB238 (N=364)	Avastin (N=367)	Total (N=731)
ECOG PS, n (%)			
0	136 (37.4)	138 (37.6)	274 (37.5)
1	228 (62.6)	229 (62.4)	457 (62.5)
2	0	0	0
3	0	0	0
4	0	0	0
Time from original diagnosis of lung cancer to randomisation (months)			
n	364	367	731
Mean (STD)	4.14 (10.552)	4.73 (14.668)	4.43 (12.780)
Median (range)	1.10 (0.1 to 105.7)	1.20 (0.0 to 166.3)	1.10 (0.0 to 166.3)
Histology type at original diagnosis, n (%)			
Adenocarcinoma (NOS)	350 (96.2)	351 (95.6)	701 (95.9)
Mixed with predominantly adenocarcinoma component	14 (3.8)	16 (4.4)	30 (4.1)
Overall disease classification at original diagnosis, n (%)[a]			
Metastatic	314 (86.3)	323 (88.0)	637 (87.1)
Locally advanced	31 (8.5)	29 (7.9)	60 (8.2)
Other	19 (5.2)	15 (4.1)	34 (4.7)
Disease stage, n (%)[b]			
Advanced	316 (86.8)	322 (87.7)	638 (87.3)
Recurrent	48 (13.2)	45 (12.3)	93 (12.7)
Initial AJCC staging, n (%)			
Stage IA	5 (1.4)	6 (1.6)	11 (1.5)
Stage IB	14 (3.8)	9 (2.5)	23 (3.1)
Stage IIA	6 (1.6)	6 (1.6)	12 (1.6)
Stage IIB	4 (1.1)	7 (1.9)	11 (1.5)
Stage IIIA	16 (4.4)	9 (2.5)	25 (3.4)
Stage IIIB	5 (1.4)	7 (1.9)	12 (1.6)
Stage IV	314 (86.3)	323 (88.0)	637 (87.1)
EGFR mutation status[c]			
Unknown	270 (74.2)	264 (71.9)	534 (73.1)
Known negative	94 (25.8)	103 (28.1)	197 (26.9)
ALK gene arrangement[c]			
Unknown	317 (87.1)	318 (86.6)	635 (86.9)
Known negative	47 (12.9)	49 (13.4)	96 (13.1)

AJCC=American Joint Committee on Cancer; ALK=anaplastic lymphoma kinase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF=electronic case report form; EGFR=epidermal growth factor receptor; ITT=Intent-to-Treat; IWRS=interactive web response system; NOS=not otherwise specified; STD=standard deviation.
a Locally advanced=Stage II (A & B) and III (A & B). Metastatic=Stage IV.
b Disease stage recorded in eCRF.
c As recorded at randomisation by IWRS.

Fifteen (4.1%) patients in the FKB238 arm and seven (1.9%) patients in the Avastin arm received prior anti-cancer therapy, predominantly cytotoxic chemotherapy. 193 (53.0%) patients in the FKB238 arm versus 187 (51.0%) patients in the Avastin arm had undergone any previous surgery. The majority of

patients (353 [97.0%] in the FKB238 arm and 355 [96.7%] in the Avastin arm) received concomitant medications during the study.

Numbers analysed

Table 16: Analysis set

	Number of patients		
	FKB238	Avastin	Total
Patients included in ITT Population[a, b]	364	367	731
Patients included in the PPS[c, d]	352	354	706

CSR=clinical study report; IP=investigational product (FKB238 or Avastin); ITT=Intent-to-Treat; PPS=Per Protocol Set.
a Includes all patients randomised.
b Patients included in treatment arm as randomised.
c Includes all patients randomised to treatment who received at least one dose of IP with no important protocol deviations.
dPatients included in treatment arm as actually given.

Outcomes and estimation

Primary outcome

Table 17: BOR and analysis of ORR – BICR assessment (PPS)

	Number (%) of patients	
	FKB238 (N=352)	Avastin (N=354)
Response status		
Best overall response		
Response	182 (51.7)	189 (53.4)
Complete response[a]	4 (1.1)	1 (0.3)
Partial response[a]	178 (50.6)	188 (53.1)
Non-response	170 (48.3)	165 (46.6)
Stable disease ≥6 weeks[b]	127 (36.1)	120 (33.9)
No evidence of disease ≥6 weeks[b]	1 (0.3)	0
Progression	33 (9.4)	29 (8.2)
RECIST progression	19 (5.4)	13 (3.7)
Death[c]	14 (4.0)	16 (4.5)
Analysis of ORR[d]		
Patients with a response	182 (51.7)	189 (53.4)
95% CI[e]	46.35 to 57.03	48.04 to 58.68
Comparison between arms		
Difference in ORR	-0.02	
95% CI[f, g]	-0.0905 to 0.0568	

BICR=blinded independent central review; BOR=best overall response; CI=confidence interval; ORR=overall response rate; PPS=Per Protocol Set; RECIST=Response Evaluation Criteria in Solid Tumours. RECIST Version 1.1.
A Response does not require confirmation.
B Stable disease or no evidence of disease ≥6 weeks includes RECIST visit window (±7 days).
C Death due to any reason in the absence of RECIST progression.
D Defined as the proportion of patients with a BOR of complete response or partial response.
e95% Pearson-Clopper CI.

F Wald asymptotic 95% CI.
G A 95% CI within ±0.1221 confirms equivalence between FKB238 and Avastin.

Table 18: Best Overall Response over Time - BICR Assessment (Per Protocol Set)

		Number (%) of patients	
Timepoint [a]	Responder status [b]	Avastin (N=354)	FKB238 (N=352)
6 Weeks	Responder	81 (22.9)	93 (26.4)
	Non-Responder	273 (77.1)	259 (73.6)
12 Weeks	Responder	150 (42.4)	153 (43.5)
	Non-Responder	204 (57.6)	199 (56.5)
18 Weeks	Responder	180 (50.8)	168 (47.7)
	Non-Responder	174 (49.2)	184 (52.3)
24 Weeks	Responder	187 (52.8)	176 (50.0)
	Non-Responder	167 (47.2)	176 (50.0)
33 Weeks	Responder	188 (53.1)	180 (51.1)
	Non-Responder	166 (46.9)	172 (48.9)
42 Weeks	Responder	189 (53.4)	181 (51.4)
	Non-Responder	165 (46.6)	171 (48.6)
51 Weeks	Responder	189 (53.4)	182 (51.7)
	Non-Responder	165 (46.6)	170 (48.3)

BICR = Blinded Independent Central Review. RECIST version 1.1.
[a] Only tumour assessment performed up until the timepoint (+/- 1 week) from randomisation are considered in the respective timepoint analysis.
[b] Response (complete response or partial response) does not require confirmation.

The median time to onset of objective response from randomisation was shorter in the FKB238 arm than in the Avastin arm (6.93 weeks versus 11.29 weeks, respectively).

Secondary endpoints

- ORR (by RECIST v1.1) at week 19

Table 19: Overall Response Rate at Week 19 - BICR Assessment (PPS)

Group	N	Number (%) of patients with response at week 19 [a]	Comparison between groups Difference in ORR at week 19	95% CI [b]
Avastin	354	180 (50.8) [45.51, 56.17]	-0.03	-0.1049, 0.0425
FKB238	352	168 (47.7) [42.41, 53.09]		

BICR = Blinded Independent Central Review. ORR = Overall Response Rate. RECIST version 1.1.
Only tumour assessment performed up until 18 weeks (+/- 1 week) from randomisation are considered in this analysis.
a95% Pearson-Clopper confidence interval.
bWald asymptotic 95% CI is used.

- Duration of Objective Response - BICR Assessment (PPS)

Table 20: Duration of Objective Response - BICR Assessment (Per Protocol Set)

	Avastin (N=354)	FKB238 (N=352)
Number and percentage of responders	189 (53.4)	182 (51.7)
Number and percentage of responders censored [a]	63 (33.3)	58 (31.9)
Number and percentage of responders who subsequently progressed or died [a]	126 (66.7)	124 (68.1)
RECIST progression	110 (58.2)	93 (51.1)
Death [b]	16 (8.5)	31 (17.0)
Duration of response from onset of response (months) [a] [c] [d]		
Q1	3.19	4.14
Median	6.28	6.47
95% CI for median	4.86, 7.16	5.39, 7.69
Q3	10.05	11.86
Minimum - Maximum	0.0 - 23.1	0.0 - 23.0

BICR = Blinded Independent Central Review. RECIST version 1.1. Q1 = first quartile. Q3 = third quartile.
[a] Summary only includes patients with objective response. Percentages are based on the subset of responders.
[b] Death in the absence of RECIST progression.
[c] Duration of response is the time from the first documentation of CR/PR until the date of progression or death in the absence of disease progression.
[d] Calculated using the Kaplan-Meier method.

- Progression-free survival (PFS)

At data cut-off, as assessed by BIRC ***in the PPS population***, 240 (68.2%) and 247 (69.8%) patients had progressed or died in the FKB238 and EU-Avastin arms, respectively. In both treatment arms, the majority of progression events were due to progression by RECIST criteria (168 [47.7%] and 190 [53.7%] patients, respectively). The estimated hazard ratio (HR) was 0.96 (95% CI: 0.81 to 1.15). The estimated proportion of patients who were alive and progression-free at 12 months was 24.8% (95% CI: 19.8% to 30.2%) in the FKB238 arm and 24.8% (95% CI: 19.7% to 30.2%) in the EU-Avastin arm, with an estimated median PFS of 7.72 months (95% CI: 7.46 to 8.15 months) and 7.62 months (95% CI: 6.87 to 7.82 months), respectively.

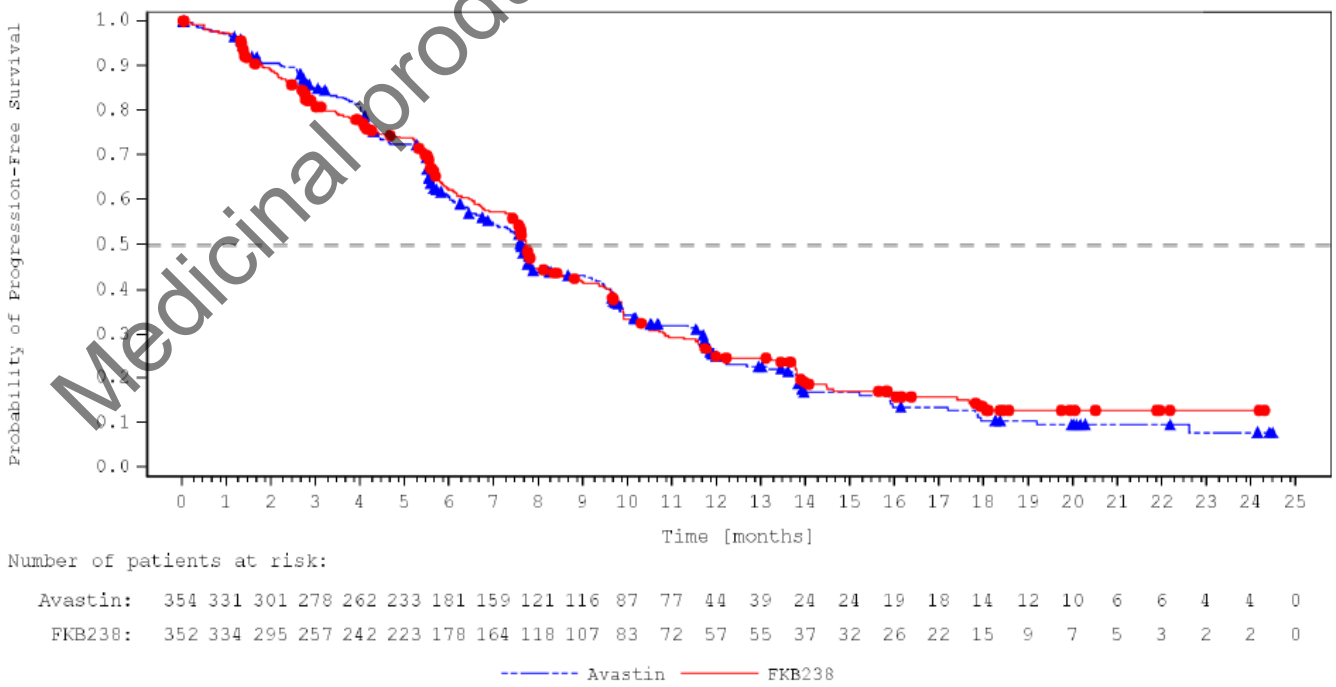


Figure 8: Kaplan-Meier Plot of Progression-Free Survival - BICR Assessment (Per Protocol Set)

- Overall survival

The estimated OS rate at 12 months was 57.7% (95% CI: 52.1% to 62.9%) in the FKB238 arm and 63.5% (95% CI: 57.9% to 68.5%) in the EU-Avastin arm for the PPS population. The estimated median OS for the PPS was 14.13 months (95% CI: 12.62 to 16.56 months) and 16.95 months (95% CI: 14.55 to 19.02 months) in the FKB238 and Avastin arms, respectively. The estimated hazard ratio (HR) was 1.19 (95% CI: 0.97 to 1.47).

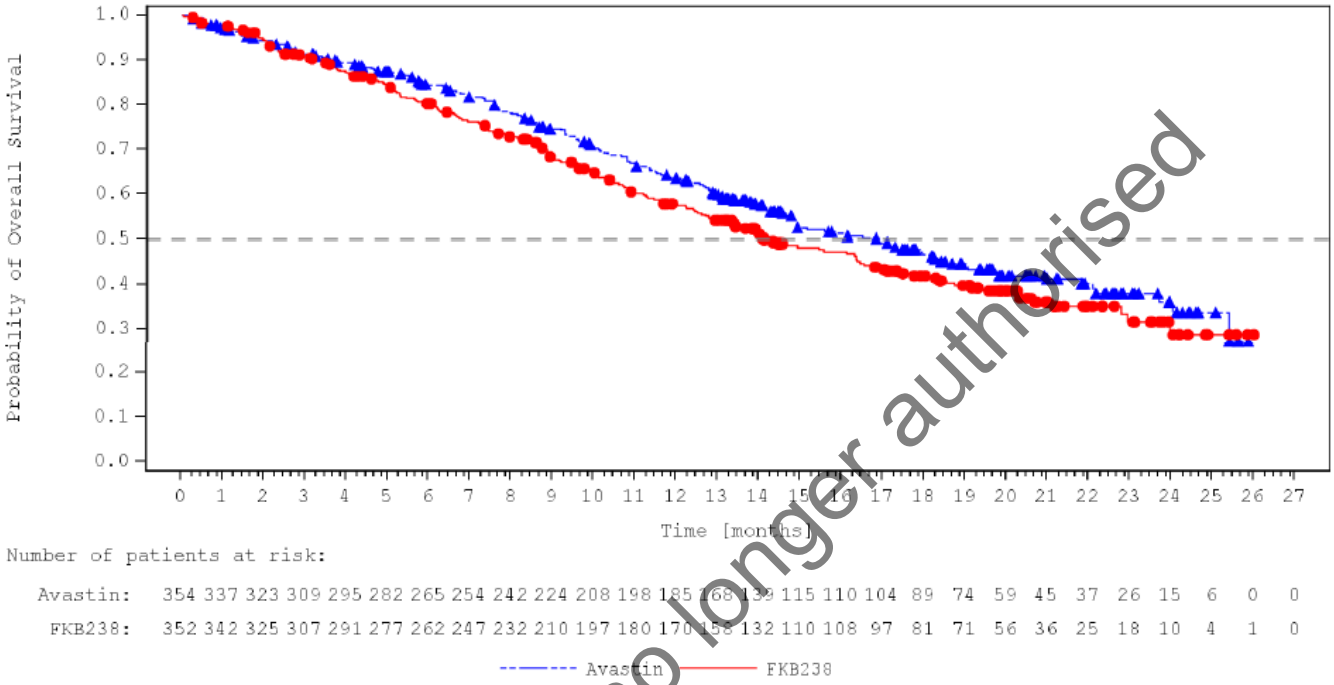


Figure 9: Kaplan-Meier Plot of Overall Survival (Per Protocol Set)

Ancillary analyses

<u>Sensitivity analyses in the ITT population:</u>

- ORR: in the ITT population (BIRC assessment) ORR was 51.6% (188 patients) for the FKB238 arm and 53.7% (197 patients) for the Avastin arm.

- ORR at Week 19: in the ITT population, the ORR at Week 19 was 47.8% (174 patients) and 51.0% (187 patients) in the FKB238 and EU-Avastin arms, respectively.

- PFS: in the ITT population, the proportion of patients having progressed or died was 67.6% vs. 69.5% in the FKB238 and Avastin groups, respectively, and the corresponding median PFS 7.72 months and 7.62 months by Kaplan-Meier analysis. The events of death in the absence of RECIST progression was slightly higher in the FKB238 group being 20.1% (73/364) vs. 16.1% (59/367) in the EU-Avastin group. The Kaplan-Meier survival curves overlapped between treatments in disease progression and the estimated hazard ratio (HR; FKB238: EU-Avastin) of 0.97 (95% CI: 0.82 to 1.16) was reached. The investigator-based sensitivity analyses and the analyses performed in the PPS population provided similar results.

Table 21: Progression status and analysis of PFS – BIRC assessment (ITT population)

	Number (%) of patients	
	FKB238	**Avastin**
	(N=364)	**(N=367)**
Progression status		
Progression[a]	246 (67.6)	255 (69.5)
RECIST progression	173 (47.5)	196 (53.4)
Death[b]	73 (20.1)	59 (16.1)
No progression	118 (32.4)	112 (30.5)
Censored RECIST progression or death[c]	28 (7.7)	18 (4.9)
Progression-free at time of analysis[d]	58 (15.9)	54 (14.7)
Lost to follow-up[e]	6 (1.6)	6 (1.6)
Withdrawal by patient[f]	25 (6.9)	32 (8.7)
Other[g]	1 (0.3)	2 (0.5)
PFS analysis		
Patients with events, n (%)	246 (67.6)	255 (69.5)
Kaplan-Meier estimates (months)		
Q1	4.40	4.34
Median	7.72	7.62
95% CI	7.46 to 7.98	6.90 to 7.82
Q3	11.96	12.02
Range	0.0 to 24.3	0.0 to 24.5
PFS rate at 12 months (%)	25.0	25.3
95% CI	20.0 to 30.3	20.3 to 30.6
Comparison between arms		
Hazard ratio[h]	0.97	
95% CI[i]	0.82 to 1.16	

BICR=blinded independent central review; CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ITT=Intent-to-treat; PFS=progression-free survival; Q1=first quartile; Q3=third quartile; RECIST=Response Evaluation Criteria in Solid Tumours

RECIST version 1.1.

[a] RECIST progression or death event not immediately following 2 or more consecutive missed tumour assessments.

[b] Death in the absence of RECIST progression.

[c] RECIST progression or death immediately after 2 or more consecutive missed tumour assessments.

[d] Defined as all patients who have no RECIST progression or death and have no Termination Status (ongoing in study or alive on data cut-off date).

[e] Defined as all patients who have no RECIST progression or death and Termination Status is 'Lost to follow-up'.

[f] Defined as all patients who have no RECIST progression or death and Termination Status is 'Withdrawal by patient'.

[g] Defined as all patients who have no RECIST progression or death and Termination Status is 'Other'.

[h] Hazard ratio and its 95% CI are calculated using the cox regression model adjusting for the listed baseline characteristics (randomisation stratification factors, ECOG Performance status at baseline, gender, smoking history and age) with ties handled by the Efron method. Treatment hazard ratio <1 favours FKB238.

[i] 95% Wald CI.

OS: in the ITT population, the proportion of patients with event was 195/364 (53.6%) and 178/367 (48.5%) in the FKB238 and EU-Avastin groups, respectively, and the estimated HR was 1.18 (95% CI: 0.96 to 1.45).

Table 22: Survival status and analysis of OS (ITT population)

	Number (%) of patients	
	FKB238	Avastin
	(N=364)	(N=367)
Survival status		
Death	195 (53.6)	178 (48.5)
Still in survival follow-up[a]	116 (31.9)	122 (33.2)
Terminated prior to death	53 (14.6)	67 (18.3)
Withdrawal by patient[b]	36 (9.9)	49 (13.4)
Lost to follow-up[c]	15 (4.1)	16 (4.4)
Other[d]	2 (0.5)	2 (0.5)
Overall survival		
Patients with events, n (%)	195 (53.6)	178 (48.5)
Kaplan-Meier estimates (months)		
Q1	7.43	8.67
Median	14.13	16.95
95% CI	12.52 to 16.56	14.65 to 19.02
Q3	NA	NA
Range	0.0 to 26.0	0.2 to 25.9
OS rate at 12 months (%)	57.4	63.7
95% CI	51.8 to 62.5	58.2 to 68.7
Comparison between arms		
Hazard ratio[e]	1.18	
95% CI[f]	0.96 to 1.45	

CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group Performance Status; ITT=Intent-to-treat; NA=not applicable; OS=overall survival; Q1=first quartile; Q3=third quartile; RECIST=Response Evaluation Criteria in Solid Tumours.

RECIST version 1.1.

[a] Includes patients known to be alive at data cut-off.

[b] Includes patients who have Termination Status of 'Withdrawal by patient'.

[c] Includes patients who have Termination Status of 'Lost to follow-up'.

[d] Includes patients who have Termination Status of 'Other' and who terminated prior to data cut-off.

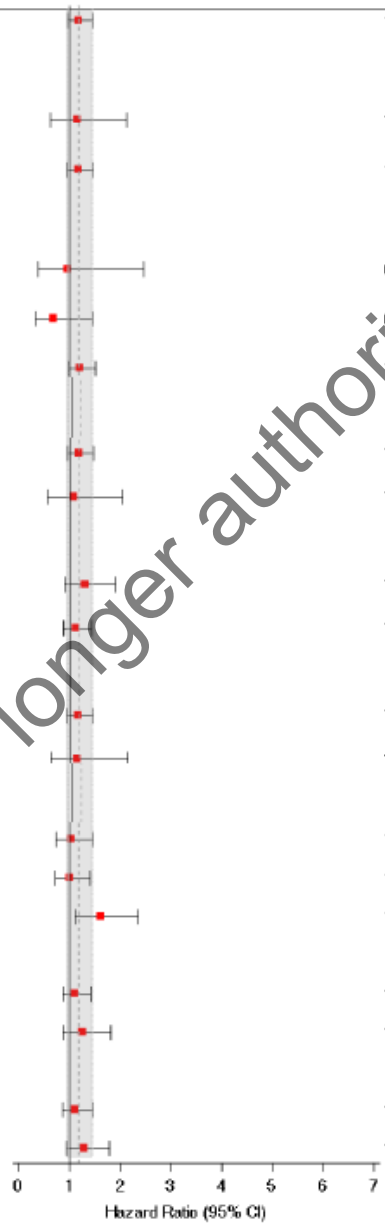
[e] Hazard ratio and its 95% CI are calculated using the Cox regression model adjusting for the listed baseline characteristics (randomisation stratification factors, ECOG PS at baseline, gender, smoking history and age) with ties handled by the Efron method. Treatment hazard ratio <1 favours FKB238.

[f] 95% Wald CI.

<u>Subgroup analyses:</u>

Subgroup analyses are shown for the ITT Population and PPS in Figure 10 and Figure 11 (for difference in ORR) and

Subgroup	Events/Subjects (%) AVA	FKB	Hazard Ratio (FKB238/Avastin) (95% CI)
Overall	178/367 (48.5)	195/364 (53.6)	1.18 (0.959, 1.446)
EGFR/ALK Status at Randomisation			
Known Negative	21/46 (45.7)	20/43 (46.5)	1.15 (0.623, 2.126)
Unknown	157/321 (48.9)	175/321 (54.5)	1.17 (0.945, 1.454)
Region			
Western Europe	9/13 (69.2)	9/13 (69.2)	0.96 (0.378, 2.456)
East Asia	18/40 (45.0)	11/38 (28.9)	0.68 (0.322, 1.446)
All Other Regions	145/306 (47.4)	169/305 (55.4)	1.21 (0.967, 1.507)
Disease Stage at Randomisation			
Advanced	160/320 (50.0)	175/315 (55.6)	1.19 (0.960, 1.475)
Recurrent	18/47 (38.3)	20/49 (40.8)	1.08 (0.569, 2.036)
ECOG Status			
0 (Normal Activity)	51/138 (37.0)	62/136 (45.6)	1.31 (0.900, 1.895)
1 (Symptomatic But Ambulatory Self-Care)	127/229 (55.5)	133/228 (58.3)	1.12 (0.882, 1.434)
Weight Loss at Baseline			
Yes	159/329 (48.3)	173/327 (52.9)	1.18 (0.948, 1.458)
No	19/38 (50.0)	22/37 (59.5)	1.16 (0.625, 2.136)
Smoker Status			
Never	66/136 (48.5)	61/127 (48.0)	1.03 (0.729, 1.462)
Former	66/128 (51.6)	65/125 (52.0)	1.00 (0.709, 1.407)
Current	46/103 (44.7)	69/112 (61.6)	1.61 (1.106, 2.343)
Sex			
Male	120/238 (50.4)	137/245 (55.9)	1.11 (0.871, 1.422)
Female	58/129 (45.0)	58/119 (48.7)	1.26 (0.872, 1.808)
Age Group			
<65	108/224 (48.2)	122/238 (51.3)	1.12 (0.861, 1.446)
>=65	70/143 (49.0)	73/126 (57.9)	1.29 (0.926, 1.786)



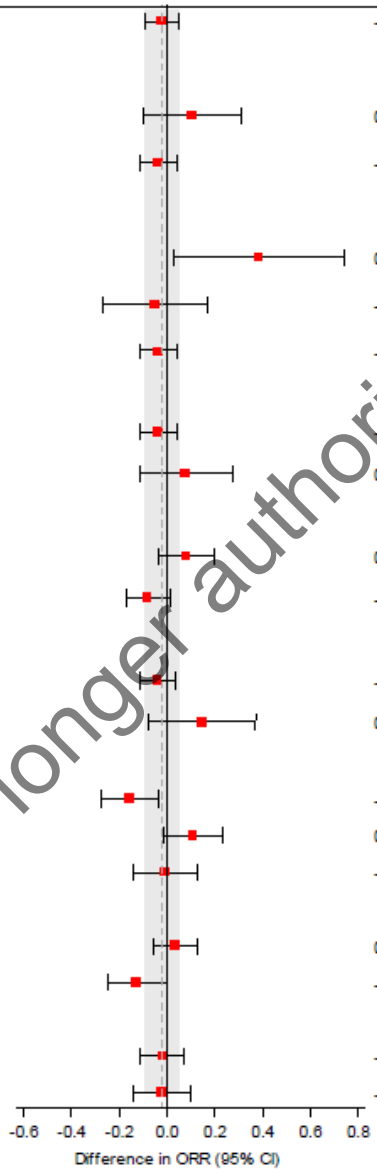
ALK=anaplastic lymphoma kinase; AVA=Avastin; CI=Confidence interval; ECOG= Eastern Collaborative Oncology Group; EGFR=epidermal growth factor receptor; FKB=FKB238; ITT=Intent-to-Treat.

Overall: Derived from Cox analysis adjusted for covariates (ties=Efron); Subgroup: Derived from unadjusted COX analysis (ties=Efron).

Subgroups with less than 10 subjects in both treatment arms are not included in the analysis.

Figure 12 and Figure 13 (for difference in OS), respectively.

Subgroup	Events/Subjects (%) AVA	FKB	Difference in ORR (FKB238/Avastin) (95% CI)
Overall	197 (53.7)	188 (51.6)	-0.02 (-0.093, 0.052)
EGFR/ALK Status at Randomisation			
Known Negative	23 (50.0)	26 (60.5)	0.10 (-0.101, 0.310)
Unknown	174 (54.2)	162 (50.5)	-0.04 (-0.115, 0.040)
Region			
Western Europe	4 (30.8)	9 (69.2)	0.38 (0.030, 0.739)
East Asia	22 (55.0)	19 (50.0)	-0.05 (-0.27[illegible], 0.171)
All Other Regions	166 (54.2)	155 (50.[illegible])	-0.03 (-0.113, 0.045)
Disease Stage at Randomisation			
Advanced	170 (53.1)	156 (49.5)	-0.04 (-0.114, 0.042)
Recurrent	27 (57.4)	32 (65.3)	0.08 (-0.116, 0.273)
ECOG Status			
0 (Normal Activity)	70 (50.7)	80 (58.8)	0.08 (-0.036, 0.198)
1 (Symptomatic But Ambulatory Self-Care)	127 (55.5)	108 (47.4)	-0.08 (-0.172, 0.010)
Prior weight loss over previous 6 months <5%			
Yes	181 (55.0)	167 (51.1)	-0.04 (-0.116, 0.037)
No	16 (42.1)	21 (56.8)	0.15 (-0.077, 0.370)
Smoker Status			
Never	79 (58.1)	54 (42.5)	-0.16 (-0.275, -0.036)
Former	61 (47.7)	73 (58.4)	0.11 (-0.015, 0.230)
Current	57 (55.3)	61 (54.5)	-0.01 (-0.142, 0.124)
Sex			
Male	120 (50.4)	132 (53.9)	0.03 (-0.054, 0.124)
Female	77 (59.7)	56 (47.1)	-0.13 (-0.250, -0.003)
Age Group			
<65	121 (54.0)	124 (52.1)	-0.02 (-0.110, 0.072)
>=65	76 (53.1)	64 (50.8)	-0.02 (-0.143, 0.096)

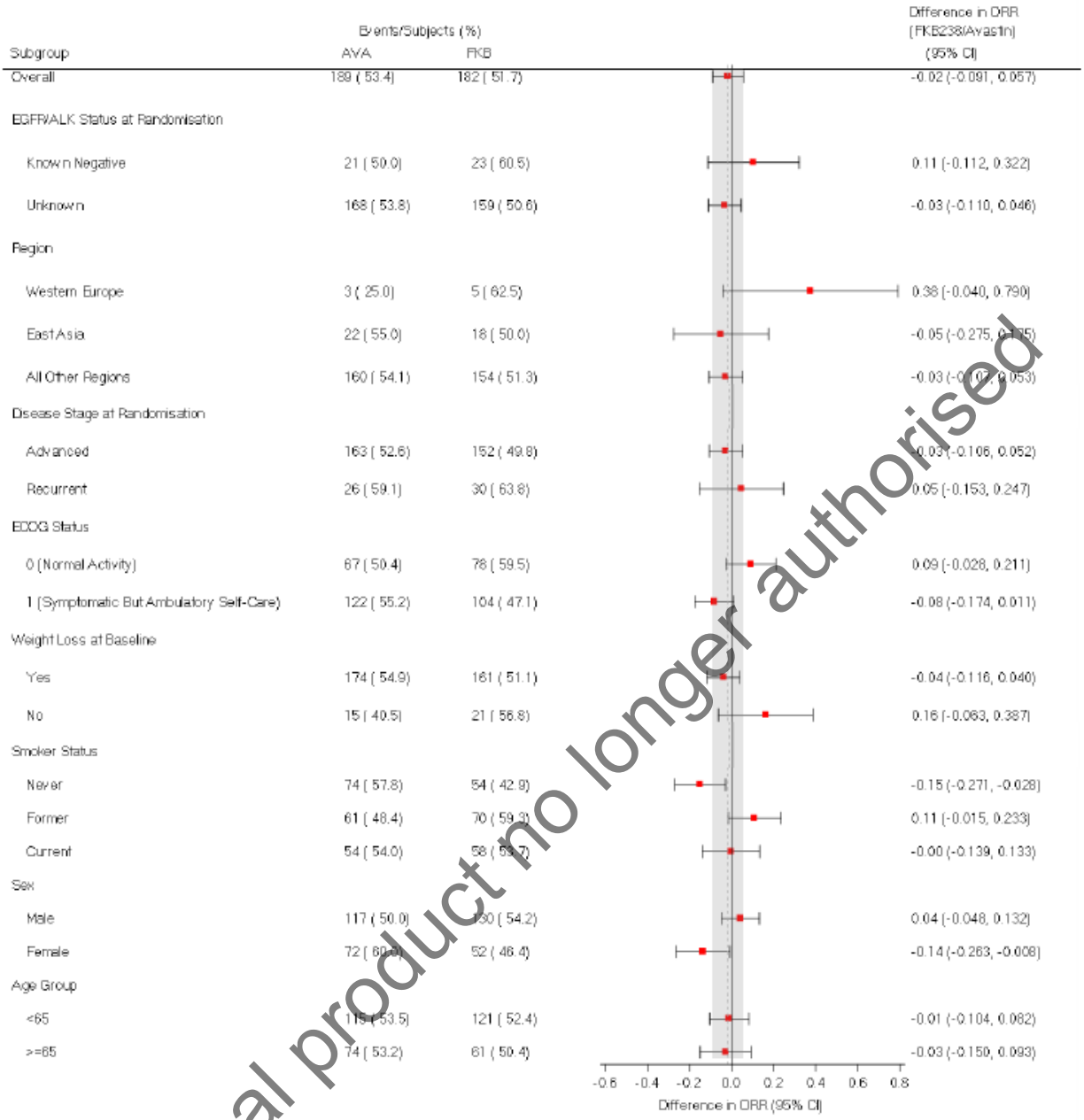


ALK=anaplastic lymphoma kinase; AVA=Avastin; CI=Confidence interval; ECOG= Eastern Collaborative Oncology Group; EGFR=epidermal growth factor receptor; FKB=FKB238; ITT=Intent-to-Treat; ORR=overall response rate

Note: Wald asymptotic 95% CI is used.

Subgroups with less than 10 subjects in both treatment arms are not included in the analysis.

Figure 10. Forest plot of overall response rate by subgroup (ITT Population)



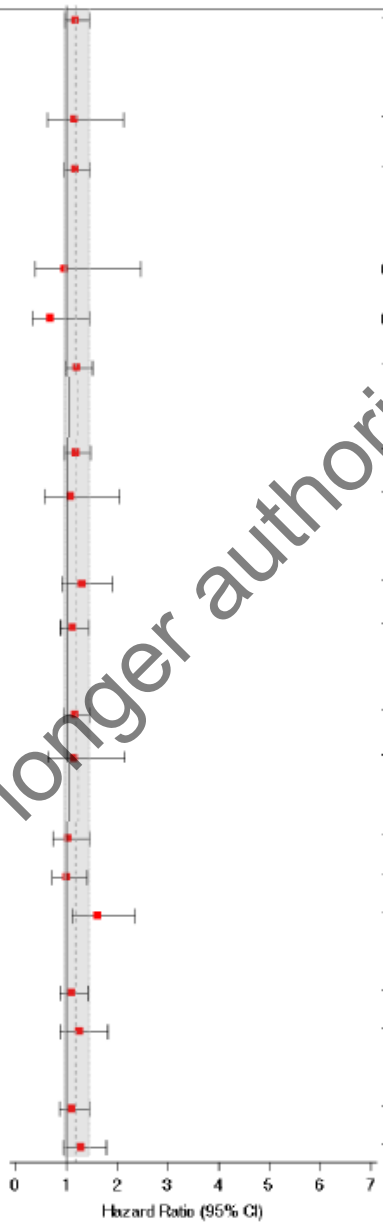
ALK=anaplastic lymphoma kinase; AVA=Avastin; CI=Confidence interval; ECOG= Eastern Collaborative Oncology Group; EGFR=epidermal growth factor receptor; FKB=FKB238; ORR=overall response rate; PPS=Per Protocol Set.

Note: Wald asymptotic 95% CI is used.

Subgroups with less than 10 subjects in both treatment arms are not included in the analysis.

Figure 11: Forest plot of overall response rate by subgroup (PPS)

Subgroup	Events/Subjects (%) AVA	FKB	Hazard Ratio (FKB238/Avastin) (95% CI)
Overall	178/367 (48.5)	195/364 (53.6)	1.18 (0.959, 1.446)
EGFR/ALK Status at Randomisation			
Known Negative	21/46 (45.7)	20/43 (46.5)	1.15 (0.623, 2.126)
Unknown	157/321 (48.9)	175/321 (54.5)	1.17 (0.945, 1.454)
Region			
Western Europe	9/13 (69.2)	9/13 (69.2)	0.96 (0.378, 2.456)
East Asia	18/40 (45.0)	11/38 (28.9)	0.68 (0.322, 1.446)
All Other Regions	145/306 (47.4)	169/305 (55.4)	1.21 (0.967, 1.507)
Disease Stage at Randomisation			
Advanced	160/320 (50.0)	175/315 (55.6)	1.19 (0.960, 1.475)
Recurrent	18/47 (38.3)	20/49 (40.8)	1.08 (0.569, 2.036)
ECOG Status			
0 (Normal Activity)	51/138 (37.0)	62/136 (45.6)	1.31 (0.900, 1.895)
1 (Symptomatic But Ambulatory Self-Care)	127/229 (55.5)	133/228 (58.3)	1.12 (0.882, 1.434)
Weight Loss at Baseline			
Yes	159/329 (48.3)	173/327 (52.9)	1.18 (0.948, 1.458)
No	19/38 (50.0)	22/37 (59.5)	1.16 (0.625, 2.136)
Smoker Status			
Never	66/136 (48.5)	61/127 (48.0)	1.03 (0.729, 1.462)
Former	66/128 (51.6)	65/125 (52.0)	1.00 (0.709, 1.407)
Current	46/103 (44.7)	69/112 (61.6)	1.61 (1.106, 2.343)
Sex			
Male	120/238 (50.4)	137/245 (55.9)	1.11 (0.871, 1.422)
Female	58/129 (45.0)	58/119 (48.7)	1.26 (0.872, 1.808)
Age Group			
<65	108/224 (48.2)	122/238 (51.3)	1.12 (0.861, 1.446)
>=65	70/143 (49.0)	73/126 (57.9)	1.29 (0.926, 1.786)

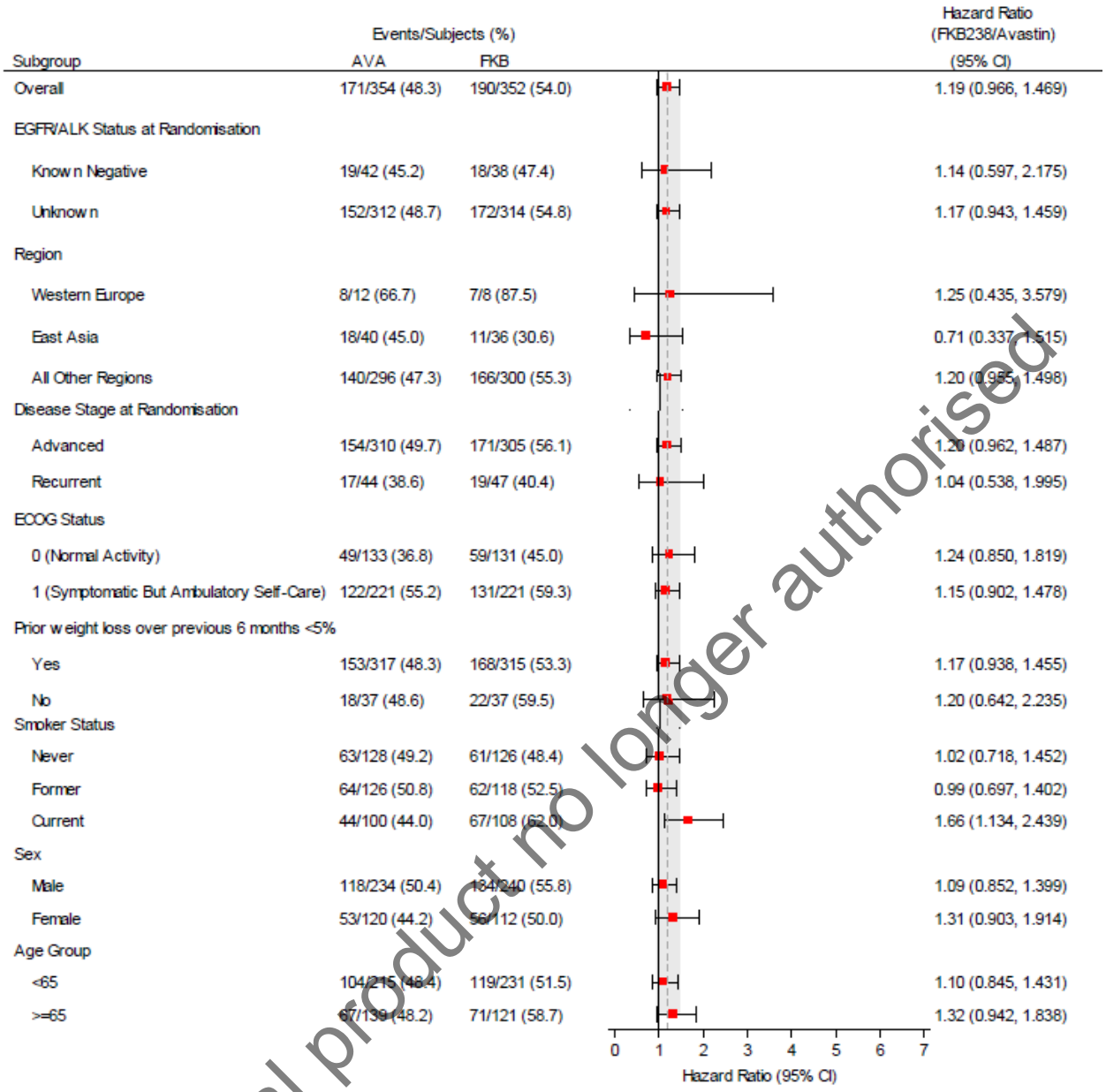


ALK=anaplastic lymphoma kinase; AVA=Avastin; CI=Confidence interval; ECOG= Eastern Collaborative Oncology Group; EGFR=epidermal growth factor receptor; FKB=FKB238; ITT=Intent-to-Treat.

Overall: Derived from Cox analysis adjusted for covariates (ties=Efron); Subgroup: Derived from unadjusted COX analysis (ties=Efron).

Subgroups with less than 10 subjects in both treatment arms are not included in the analysis.

Figure 12: Forest plot of overall survival by subgroup (ITT Population)



ALK=anaplastic lymphoma kinase; AVA=Avastin; CI=Confidence interval; ECOG=Eastern Collaborative Oncology Group; EGFR=epidermal growth factor receptor; FKB=FKB238; PPS=Per Protocol Set.

Overall: Derived from Cox analysis adjusted for covariates analysis (ties=Efron); Subgroup: Derived from unadjusted COX analysis (ties=Efron).

Subgroups with less than 10 subjects in both treatment arms are not included in the analysis.

Figure 13: Forest plot of overall survival by subgroup (PPS)

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 23: Summary of efficacy for trial FKB238-002

Title: A Randomised, Parallel, Double Blinded Study to Compare the Efficacy and Safety of FKB238 to Avastin in 1st Line Treatment for Patients with Advanced/Recurrent Non-Squamous Non-Small Cell Lung Cancer in Combination of Paclitaxel and Carboplatin (AVANA)			
Study identifier	FKB238-002 / EudraCT Number 2015-004104-33		
Design	Double-blind, randomised, parallel group, multicenter		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		21 June 2016 to 24 Jan 2019 not applicable 25 Jan 2019 – ongoing (but no further analyses of data)
Hypothesis	Equivalence		
Treatments groups	FKB238		**Treatment**: Paclitaxel 200 mg/m^2 on Day 1 for at least 4, and no more than 6 cycles, followed by Carboplatin AUC 6.0 on Day 1 for at least 4, and no more than 6 cycles followed by FKB238 15 mg/kg on Day 1 until objective PD or other criteria for treatment discontinuation are met. **Duration**: once every 21 [±3] days **Number Randomised:** 364
	Avastin		**Treatment**: Paclitaxel 200 mg/m^2 on Day 1 for at least 4, and no more than 6 cycles, followed by Carboplatin AUC 6.0 on Day 1 for at least 4, and no more than 6 cycles, followed by Avastin 15 mg/kg on Day 1 until objective PD or other criteria for treatment discontinuation are met. **Duration**: once every 21 [±3] days **Number Randomised:** 367
Endpoints and definitions	Primary: Overall Response Rate	ORR	the proportion of subjects with a best overall response (BOR) of CR or PR (by RECIST v1.1)
	Secondary: Overall Response Rate at Week 19	ORR at Week 19	the rate of the best response of CR or PR (by RECIST v1.1) assessed at Week 19
	Secondary: Progression-free Survival	PFS	the time from randomisation to the first documented disease progression (PD) or death, whichever occurred first
	Secondary: Overall Survival	OS	the time from randomisation to death due to any cause
	Secondary: Duration of Response	DOR	the time from the first documented PR or CR (by RECIST v1.1) to the first documented objective PD or death, whichever occurred first
	Secondary: Disease Control Rate	DCR	the rate of CR, PR, SD (≥6 weeks)
Database lock	02 May 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Per protocol set (PPS), defined as all patients randomised to treatment who received at least 1 dose of IP with no important protocol deviations. Patients will be included in the treatment group according to the treatment actually given.		
Descriptive statistics and estimate variability	Treatment group	FKB238	Avastin
	Number of subjects	352	354
	ORR by blinded independent central review (BICR) Number (%) 95% Confidence Interval	182(51.7) (46.35, 57.03)	189(53.4) (48.04, 58.68)
	ORR by investigator Number (%) 95% Confidence Interval	185(52.6) (47.20, 57.87)	178(50.3) (44.95, 55.61)
	ORR at Week 19 (BICR) Number (%) 95% Confidence Interval	168(47.7) (42.41, 53.09)	180(50.8) (45.51, 56.17)
	PFS (BICR) Median 95% Confidence Interval	7.72 (7.46, 8.15)	7.62 (6.87, 7.82)
	OS Median 95% Confidence Interval	14.13 (12.62, 16.56)	16.95 (14.55, 19.02)
	DOR Median 95% Confidence Interval	6.47 (5.39, 7.69)	6.28 (4.86, 7.16)
Effect estimate per comparison	Primary endpoint: ORR Primary analysis	Comparison groups	FKB238 – Avastin
		Difference in ORR (BICR)	*-0.02*
		95% Confidence Interval	(-0.0905, 0.0568)
	Sensitivity analysis	Comparison groups	FKB238 – Avastin
		Difference in ORR (Investigator)	*0.02*
		95% Confidence Interval	*(-0.0510, 0.0965)*
	Secondary endpoint: ORR (BICR) at Week 19	Comparison groups	FKB238 – Avastin
		Difference in ORR (BICR) at Week 19	*-0.03*
		95% Confidence Interval	-0.1049, 0.0425
	Secondary endpoint: PFS	Comparison groups	FKB238/Avastin
		Hazard Ratio (HR) for PFS (BICR)	0.96
		95% Confidence Interval	(0.81, 1.15)
	Secondary endpoint:	Comparison groups	FKB238/Avastin

	OS	HR for OS	1.19
		95% Confidence Interval	(0.97, 1.47)
Notes	The primary analysis for EMA was based on the PPS. Analyses based on the Intent-to-treat (ITT) population were also performed.		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable for biosimilars.

Supportive studies

Not applicable.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program to demonstrate biosimilarity between FKB238 and EU-Avastin (bevacizumab) in combination with paclitaxel and carboplatin is based on a randomised, double blind, comparative, multi-national (146 centres screened patients in 24 countries with 136 centres randomising patients), phase 3 study in first line patients with advanced or recurrent non-squamous NSCLC.

A single pivotal phase 3 equivalence trial (FKB238-002) regarding similarity on efficacy and safety is considered adequate to support this application. The study design, study population, inclusion/exclusion criteria, dose regimen, study endpoints and sample size were in general in compliance with the given CHMP scientific advice. Indeed, non-squamous NSCLC is considered a relevant and sensitive population for detection of potential differences between the two products. Study protocol amendments 3 and 4 were conducted after the first patient signed informed consent. The amendment 3 concerned a change in the handling of subjects developing toxicity and allowed these patients to continue after a delay of more than 3 weeks. This change might have had an impact on efficacy analysis in the form of possible selection bias. However, the sensitivity analysis in the ITT population showed similar result to that seen in the PPS population.

The number of patients randomised to the study was consistent with the original sample size calculations. Based on the result of a meta-analysis of available randomised clinical studies of EU-Avastin, the equivalence margin for the risk difference of ORR was defined to be ± 0.1221 which is acceptable from a statistical and clinical point of view. Randomisation was stratified using a block randomisation scheme according to EGFR mutation and ALK gene arrangement status, geographical region, prior weight loss over the previous six months and disease stage.

The study was conducted in several geographic areas and countries possibly having divergent practices and bringing variability for the data evaluation. Overall, the difference between regions had no statistically significant impact on the outcome (data not shown). The Applicant repeated the interaction test with the inclusion of the geographic regions “South America” and “Eastern Europe” previously

integrated in the "All other regions" subgroup, which showed no statistical evidence of the heterogeneity among regions (interaction p-value = 0.5164).

Inclusion/exclusion criteria are based on those of the EU-Avastin pivotal trial supporting the NSCLC indication (EMEA/H/C/000582/II/0009). In the current study, a slightly different patient population was accepted (i.e. 10-12% of the patients were Stage I to IIIA, n=82) compared to the Avastin registration study (study E4599 also stage IIIB patients with malignant pleural effusion were eligible, n=44). Nevertheless, no significant differences were observed in the ORR between the patients having lower than Stage IV disease by initial staging vs. the overall patient population. This deviation in inclusion is thus not expected to affect the overall study outcome. Patients with known sensitising EGFR mutations and ALK gene arrangements were excluded from the study as current recommendation is to treat these patients with TKIs while EGFR/ALK negative patients were included. However, the majority of patients in both treatment arms had status unknown (EGFR mutation 73 %, ALK mutation 87 %) since testing was not mandatory for this trial. Nevertheless, status unknown is deemed not to preclude demonstration of biosimilarity, and importantly, randomisation has been stratified according to EGFR mutation and ALK gene arrangement status (known negative versus status unknown for either).

The primary efficacy endpoint of the study is overall response rate (ORR) defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) by RECIST v1.1, as assessed by blinded independent central review (BICR). The secondary endpoints included ORR (by RECIST v1.1) at week 19, PFS (defined as the time from randomisation to the first documented disease progression [PD]) or death, whichever occurs first), OS (defined as the time from randomisation to death from any cause), duration of response (DoR) and disease control rate (DCR).

The choice of primary endpoint was not in line with the recommendation in the CHMP SA, which emphasised that ORR should be compared at a specific and sensitive time point and not as BOR of CR and PR. Nevertheless, ORR at Week 19 was included as a secondary endpoint and analysed using the same methods as for the primary endpoint, which is considered adequate. The other endpoints for this study are agreed. Endpoint analyses were conducted in both the PPS and the ITT populations. PPS was the primary analysis set and included all patients randomised to treatment who received at least one dose of IP and who had no important protocol deviations. Blinded independent central review assessment was used as the pivotal results of the study for both primary and secondary analyses.

Efficacy data and additional analyses

One thousand and twenty-three patients were screened, and of these, 731 were randomised to receive study treatment. The data cut-off (DCO), defined as 12 months from randomisation of the last patient enrolled in the study, was 24th of January 2019. All data up to and including this date were included in the study analyses. 89.7% (656) of patients had discontinued from study at DCO, the main reason was death, with a higher number of patients that had died in the FKB238 arm compared to the Avastin arm [195 patients [53.9%] vs. 177 patients [48.4%], respectively]). The majority of patients had no important protocol deviations (96.6% overall) with similar numbers across both arms.

There were some imbalances in demography and baseline characteristics in the overall ITT-population such as more current smokers, more patients with a past and current medical history of cardiovascular conditions, more patients with current respiratory conditions, and smaller number of patients who received subsequent anti-cancer therapy in the FKB238 arm (Refer to the Clinical Safety discussion for further details). During the study, a total of 36 patients had palliative radiotherapy. Of these, 6 patients (1 in the FKB238 arm and 5 in the Avastin arm) received it during the treatment period while the remaining received it post-treatment. In addition, 1 patient underwent surgery during study treatment (data not shown).

For the primary endpoint ORR (PPS), similar outcomes were reported across the two arms (51.7% and 53.4% in the FKB238 and EU-Avastin arms, respectively). The difference in ORR was -0.02 (95% CI: -0.095, 0.568) and was well within the pre-defined equivalence margin, supporting similar efficacy between FKB238 and EU-Avastin.

In addition, outcomes of the following endpoint and sensitivity analyses support the above-mentioned conclusions: (i) The ORR risk difference (RD) primary endpoint (BICR and investigator evaluated), and (ii) the RD for the ORR at Week 19 secondary endpoint (BICR and investigator evaluated) in the ITT population, as well as (iii) the sensitivity analysis in the PP population for the DOR (HR) (data not shown).

The Applicant has provided the requested forest plots and subgroup analyses data for the ORR and OS endpoints for both ITT and PPS populations. The data showed similar response rate and survival in each subgroup except for the Western Europe region and the current smoking status. However, these subgroups are small in sample size, and hence it is impossible to draw robust conclusions based on these data.

At week six, there was a slightly higher proportion of responders in the FKB238 arm than in the EU-Avastin arm (93 [26.4%] versus 81 [22.9%] patients). Clearly higher proportion of patients remained in response over 12 months of duration in the FKB238 group (16.5% vs. 8.6%). The median time to onset of objective response from randomisation was also shorter in the FKB238 arm than in the EU-Avastin arm (6.93 weeks versus 11.29 weeks, respectively). However, this might be due to a sampling artefact of the different response assessment timings (i.e. 6 weeks and 12 weeks). The mean time to response was 10.4 and 10.5 weeks for the FKB238 and Avastin arms, respectively.

The estimated proportion of patients who were alive and progression-free at 12 months was 24.8% (95% CI: 19.8% to 30.2%) in the FKB238 arm and 24.8% (95% CI: 19.7% to 30.2%) in the EU-Avastin arm. The estimated median PFS was 7.72 months (95% CI: 7.46 to 8.15 months) and 7.62 months (95% CI: 6.87 to 7.82 months), respectively.

The estimated OS rate at 12 months was 57.7% (95% CI: 52.1% to 62.9%) in the FKB238 arm and 63.5% (95% CI: 57.9% to 68.5%) in the EU-Avastin arm in the overall PPS. The Kaplan-Meyer (KM) survival curves in the overall PPS were overlapping until 3 months, at which time point the survival curves showed a slight separation between the treatment arms. However, the KM survival curves did not show any tendency of time-dependent increase in the death rate difference between the treatment groups, implying similarity in the progression of the disease by time. The estimated median OS for the PPS was 14.13 months (95% CI: 12.62 to 16.56 months) and 16.95 months (95% CI: 14.55 to 19.02 months) in the FKB238 and Avastin arms, respectively (HR 1.19 [95% CI: 0.97 to 1.47]). Nevertheless, the estimated HR was not significantly different from 1, and the 95% CI contained value 1 although the margins were skewed in favour of the reference product. Besides, the study FKB238-002 was not powered to draw any firm conclusions on the efficacy based on OS, and no type 1 error control was included. Furthermore, survival status of 14 subjects in the Avastin group is unknown due to withdrawal of consent and subsequently lost information on survival. Therefore, some deaths in the Avastin group might possibly not have been recorded (refer to Discussion on Clinical Safety).

According to the post-hoc subgroup analysis provided (data not shown), the events of deaths in the absence of RECIST progression were slightly higher in the FKB238 group being 20.1% (73/364) vs. 16.1% (59/367) in the EU-Avastin arm. Based on the KM curves in patients without PD (by BICR) who died in the ITT population, the survival curves were almost overlapping until 10 months, including at the 3-month time point. Therefore, the slightly lower survival in the overall FKB238 group cannot be explained by the difference in patients who discontinued without PD. Of note, the comparison and the causality evaluation of the deaths in this analysis (in patients who died without PD) is hampered due to the following: (i) After randomisation was broken, the comparisons did not include the initially randomised groups, and (ii) the treatment groups were no longer comparable in terms of anticancer

treatments after the discontinuation or the completion of study. Although slightly more events of deaths were reported as a reason for discontinuation in the FKB238 group in the absence of RECIST progression by BICR, the large part of these were considered not necessarily due to AEs related to the treatment investigated.

As indicated in the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) OS may not be sensitive enough for establishing comparability of a biosimilar mAb to a reference mAb, since they may be influenced by various factors not attributable to differences between the biosimilar mAb and the reference mAb, but by factors like tumour burden, performance status, previous lines of treatments, underlying clinical conditions, subsequent lines of treatment, etc. The observed imbalances in baseline characteristics (including patients with possibly worse prognosis due to several confounding factors) may likely be reflecting that the patients in the biosimilar arm might have been a more vulnerable patient group, potentially contributing to the noted difference. Importantly, the potential OS-difference is not reflected by an effect in PFS, DoR and DCR, hazard and odds ratios. In addition, the types of deaths were very variable including treatment-related and non-treatment-related deaths, with no clear pattern or accumulation of certain causes. Finally, one important factor potentially misbalancing the groups or their disease characteristics is the fact that EGFR and ALK status was unknown in 2/3 and 4/5 of patients, respectively. Therefore, it is difficult to compare the patient heterogeneity with regards to the type and severity of disease.

Overall, considering the totality of evidence, the OS-results should be interpreted with caution. It has to be taken into consideration that the study was neither adequately powered to demonstrate equivalence nor to detect differences in OS, and no type 1 error control was included. In addition, the 95% CI contained value 1 although the margins were skewed in favour of the reference product. The KM survival curves do not indicate any tendency of the time-dependent increase in the death rate difference, which speaks against the differences in disease progression between the study arms. The divergence seen early, only at 3-month time point in KM survival curve (being similar thereafter) might be due to patient heterogeneity and/or a random data variation rather than a real treatment effect. Taken together, several confounding and potentially contributing factors may have had an impact on the numerical OS-differences, and there is no indication of a difference in real treatment effect that may compromise biosimilarity.

2.5.4. Conclusions on the clinical efficacy

The presented data on the primary endpoint from study FKB238-002 support similar efficacy between FKB238 and its reference product, EU-Avastin.

2.6. Clinical safety

The applicant is seeking approval of FKB238 as a biosimilar bevacizumab product to the reference medicinal product European Union (EU)-approved, Avastin.

Comparative safety data of FKB238 was derived from three clinical studies.The study designed to contribute key safety data was a randomised, double-blind, parallel study, conducted in 24 countries to compare the efficacy and safety of FKB238 to EU-Avastin when used in combination with paclitaxel and carboplatin in the first-line treatment of patients with advanced/recurrent non-squamous non-small cell lung cancer (NS-NSCLC; Study **FKB238-002**).

Prior to that, a single-dose PK study was conducted in the United Kingdom (UK) in healthy male subjects to compare the PK properties and safety of FKB238 with US-Avastin and EU-Avastin (Study

FKB238-001). An additional PK study has been conducted, to meet the requirements of the Japanese Pharmaceuticals and Medical Devices Agency, to compare the PK characteristics and safety of FKB238 with those of EU-Avastin in Japanese healthy male subjects (Study **FKB238-003**).

Safety data are presented by study with no combined or integrated analyses of safety across studies planned or performed due to different treated study populations (NSCLC subjects versus healthy subjects) and different dosing regimens (single-dose versus multiple-dose).

Patient exposure

Comparative clinical study FKB238-002

A summary of exposure, by study treatment, is presented for study FKB238-002 in Table 24.

A total of 728 patients received at least 1 dose of IP (FKB238 or Avastin). Across both the FKB238 and Avastin arms, approximately half of patients had either an IP dose interruption or delay (184 [50.8%] and 198 [54.1%] patients, respectively. Most of these were IP delays, which were reported in 184 (50.8%) and 197 (53.8%) patients in the FKB238 and Avastin arms, respectively, with the majority of these having <3 delays.

Table 24: Extent of exposure: Safety Population (Study FKB238-002)

	Bevacizumab exposure		Paclitaxel exposure		Carboplatin exposure	
	FKB238 (N=362)	Avastin (N=366)	FKB238 (N=362)	Avastin (N=366)	FKB238 (N=362)	Avastin (N=366)
Number of cycles						
Mean (SD)	11.4 (8.42)	11.5 (8.26)	4.7 (1.59)	4.8 (1.57)	4.7 (1.58)	4.8 (1.57)
Range	1 to 35	1 to 37	1 to 6	1 to 6	1 to 6	1 to 6
Duration of exposure[a] [weeks]						
Mean (SD)	35.36 (26.03)	35.87 (25.34)	14.74 (5.28)	15.14 (5.24)	14.81 (5.25)	15.13 (5.25)
Range	0.3 to 110.6	0.9 to 111.4	0.3 to 23.6	0.9 to 28.4	0.3 to 23.6	0.9 to 28.4
Dose intensity[b] [mg/kg/3 weeks (FKB238 and Avastin); mg/m^2/3 weeks (paclitaxel); AUC/3 weeks (carboplatin)]						
Mean (SD)	14.46 (0.75)	14.35 (0.91)	190.17 (16.94)	190.02 (15.09)	5.62 (0.61)	5.60 (0.55)
Range	10.6 to 15.8	10.0 to 15.4	10.8 to 223.2	118.2 to 213.9	3.2 to 9.4	3.7 to 8.1
Relative dose intensity[c] [n (%)]						
<60%	0	0	1 (0.3)	1 (0.3)	3 (0.8)	0
≥60% to <80%	6 (1.7)	12 (3.3)	16 (4.4)	22 (6.0)	32 (8.8)	33 (9.0)
≥80% to <90%	31 (8.6)	36 (9.8)	56 (15.5)	59 (16.1)	69 (19.1)	72 (19.7)
≥90% to <100%	207 (57.2)	208 (56.8)	193 (53.3)	177 (48.4)	169 (46.7)	185 (50.5)
≥100% to <110%	118 (32.6)	110 (30.1)	94 (26.0)	107 (29.2)	84 (23.2)	73 (19.9)
≥110%	0	0	2 (0.6)	0	5 (1.4)	3 (0.8)

AUC=area under the curve; CSR=clinical study report; SD=standard deviation.
a Duration of exposure=(last dosing date - first dosing date + 21) / 7. For patients who died, were discontinued, or lost to follow-up prior to the end of the 21 days from last dose, duration was defined as (censoring date – first dosing date + 1) / 7, with censoring date as the earliest of the following dates (date of death, date of study discontinuation, date last known to be alive), as applicable.
b Dose intensity=Cumulative dose level / ((last dosing date – first dosing date + 21) / 21).
c Relative dose intensity was calculated as the dose intensity divided by the planned dose per cycle.

Pharmacokinetic Studies FKB238-001 and FKB238-003

A total of 139 healthy male subjects received a single dose of FKB238 or Avastin, including 99 subjects in Study FKB238-001 (33 FKB238, 34 EU-Avastin, 32 US-Avastin) and 40 subjects in Study FKB238-003 (20 FKB238, 20 EU-Avastin).

Baseline Demographics

Please refer to Table 14 and Table 15, Baseline section in the Clinical efficacy part for a tabular overview of Baseline demographics.

The proportion of patients with any previous medical history was slightly higher in the FKB238 arm (27.2%) than in the Avastin arm (22.9%), with slight imbalances in the frequencies of previous medical history SOCs between the treatment arms. Slightly more patients in the FKB238 arm than in the Avastin arm had a previous medical history pertaining to cardiac disorders, (15 [4.1%] patients versus 9 [2.5%] patients, respectively). On the other hand, slightly fewer patients in the FKB238 arm than in the Avastin arm had a previous medical history of respiratory, thoracic and mediastinal disorders (9 [2.5%] patients versus 19 [5.2%] patients, respectively).

The proportion of patients with any current medical history was slightly higher in the FKB238 arm (89.8%) than in the Avastin arm (85.8%), with small imbalances in the frequencies of current medical history SOCs between the treatment arms. Of note, more patients in the FKB238 arm than in the Avastin arm had current medical histories in the SOC of respiratory, thoracic and mediastinal disorders (178 [48.9%] versus 139 [37.9%] patients, respectively). At the PT level, individual current medical histories were balanced across treatment arms, with the exceptions of cough (FKB238, 59 [16.2%]; Avastin, 31 [8.4%]) and dyspnoea (FKB238, 55 [15.1%]); Avastin, 31 [8.4%]).

Adverse events

Comparative clinical Study FKB238-002

An overall summary of AEs for Study FKB238-002 is presented in Table 25.

Table 25: Overall summary of adverse events: Safety Population (Study FKB238-002)

Characteristic	FKB238 (N=362)	Avastin (N=366)
Number (%) of patients[a] with at least one:		
TEAE	341 (94.2)	348 (95.1)
Causally related to IP[b]	148 (40.9)	174 (47.5)
Causally related to any combination drugs[b]	298 (82.3)	309 (84.4)
Causally related to study treatment[b]	309 (85.4)	315 (86.1)
CTCAE grade 3 or higher TEAE	194 (53.6)	203 (55.5)
Causally related to IP[b]	40 (11.0)	50 (13.7)
Causally related to any combination drugs[b]	121 (33.4)	124 (33.9)
Causally related to study treatment[b]	132 (36.5)	138 (37.[illegible])
TEAE leading to discontinuation of IP	36 (9.9)	41 ([illegible])
Causally related to IP[b]	14 (3.9)	18 (4.9)
TEAE leading to discontinuation of any combination drugs	42 (11.6)	37 (10.1)
Causally related to any combination drugs[b]	34 (9.4)	25 (6.8)
TEAE leading to discontinuation of study treatment	55 (15.2)	58 (15.8)
Causally related to study treatment[b]	41 ([illegible])	41 (11.2)
TESAE	9[illegible]	95 (26.0)
Causally related to IP[b]	26 (7.2)	21 (5.7)
Causally related to any combination drugs[b]	40 (11.0)	43 (11.7)
Causally related to study treatment[b]	51 (14.1)	54 (14.8)
TEAE leading to death	30 (8.3)	23 (6.3)
Causally related to IP[b]	3 (0.8)	2 (0.5)
Causally related to any combination drugs[b]	2 (0.6)	3 (0.8)
Causally related to study treatment[b]	4 (1.1)	4 (1.1)

CSR=clinical study report; CTCAE=Common Terminology Criteria for Adverse Events; IP=investigational product; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.
a Patients with multiple events in the same category are counted only once in that category. Patients with events in ≥1 category are counted once in each of those categories.
b As assessed by the investigator.

An overall summary of AEs for Studies FKB238-001 and FKB238-003 is presented in the table below.

Table 26: Overall summary of adverse events: Safety Population (Studies FKB238-001 and FKB238-003)

Characteristic	Study FKB238-001			Study FKB238-003	
	FKB238 (N=33)	EU-Avastin (N=34)	US-Avastin (N=32)	FKB238 (N=20)	EU-Avastin (N=20)
Number (%) of subjects with at least one:					
TEAE	32 (97.0)	26 (76.5)	23 (71.9)	12 (60.0)	6 (30.0)
SAE	0	0	0	0	0
Grade 3 or higher TEAE	1 (3.0)	0	0	0	0
TEAE leading to premature study discontinuation	0	0	0	0	0
TEADR	15 (45.5)	11 (32.4)	12 (37.5)	2 (10.0)	1 (5.0)

CSR=clinical study report; EU=European Union; SAE=serious adverse event; TEADR=treatment-emergent adverse drug reaction; TEAE=treatment-emergent adverse event; US=United States.
TEADRs are defined as TEAEs where the relationship to study medication was recorded as 'related' or 'possibly related'.

Common adverse events

Comparative clinical Study FKB238-002

A summary of TEAEs, by SOC and PT, is presented for Study FKB238-002 in Table 27.

Table 27: Treatment-emergent adverse events reported for ≥5% of patients in either treatment group: Safety Population (Study FKB238-002)

SOC PT	FKB238 (N=362)	Avastin (N=366)
	Number (%) of patients	
Number (%) of patients with ≥1 TEAE	341 (94.2)	348 (95.1)
Blood and lymphatic system disorders	**200 (55.2)**	**216 (59.0)**
Anaemia	105 (29.0)	119 (32.5)
Leukopenia	43 (11.9)	50 (13.7)
Neutropenia	109 (30.1)	145 (39.6)
Thrombocytopenia	44 (12.2)	66 (18.0)
Gastrointestinal disorders	**115 (31.8)**	**108 (29.5)**
Constipation	19 (5.2)	21 (5.7)
Diarrhoea	35 (9.7)	35 (9.6)
Nausea	52 (14.4)	45 (12.3)
Vomiting	24 (6.6)	18 (4.9)
General disorders and administration site conditions	**114 (31.5)**	**133 (36.3)**
Asthenia	37 (10.2)	59 (16.1)
Fatigue	41 (11.3)	45 (12.3)
Pyrexia	15 (4.1)	21 (5.7)
Non-cardiac chest pain	18 (5.0)	11 (3.0)
Infections and infestations	**77 (21.3)**	**88 (24.0)**
Pneumonia	18 (5.0)	20 (5.5)
Investigations	**160 (44.2)**	**169 (46.2)**
Alanine aminotransferase increased	38 (10.5)	35 (9.6)
Aspartate aminotransferase increased	32 (8.8)	35 (9.6)
Blood alkaline phosphatase decreased	19 (5.2)	27 (7.4)
Gamma-glutamyltransferase increased	38 (10.5)	31 (8.5)
Neutrophil count decreased	24 (6.6)	25 (6.8)
Platelet count decreased	30 (8.3)	25 (6.8)
Weight decreased	41 (11.3)	56 (15.3)
White blood cell count decreased	24 (6.6)	26 (7.1)
Metabolism and nutrition disorders	**89 (24.6)**	**109 (29.8)**
Decreased appetite	43 (11.9)	42 (11.5)
Hyperglycaemia	14 (3.9)	22 (6.0)
Musculoskeletal and connective tissue disorders	**94 (26.0)**	**102 (27.9)**
Arthralgia	32 (8.8)	36 (9.8)
Back pain	22 (6.1)	15 (4.1)
Myalgia	29 (8.0)	32 (8.7)

SOC PT	FKB238 (N=362)	Avastin (N=366)
	Number (%) of patients	
Nervous system disorders	**159 (43.9)**	**162 (44.3)**
Headache	18 (5.0)	23 (6.3)
Neuropathy peripheral	58 (16.0)	52 (14.2)
Paraesthesia	24 (6.6)	22 (6.0)
Peripheral sensory neuropathy	28 (7.7)	25 (6.8)
Polyneuropathy	16 (4.4)	23 (6.3)
Renal and urinary disorders	**39 (10.8)**	**56 (15.3)**
Proteinuria	24 (6.6)	41 (11.2)
Respiratory, thoracic and mediastinal disorders	**88 (24.3)**	**101 (27.6)**
Cough	17 (4.7)	25 (6.8)
Dyspnoea	18 (5.0)	[illegible]
Epistaxis	16 (4.4)	23 (6.3)
Skin and subcutaneous tissue disorders	**168 (46.4)**	**176 (48.1)**
Alopecia	154 (42.5)	159 (43.4)
Vascular disorders	**57 (15.7)**	**61 (16.7)**
Hypertension	42 (11.6)	44 (12.0)

CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
TEAEs were coded using MedDRA Version 21.1.

A summary of TEAEs, by SOC and PT, is presented for Studies FKB238-001 and FKB238-003 in Table 28.

Table 28: Treatment-emergent adverse events reported for ≥5% of subjects in any treatment group/study Safety Population (Studies FKB238-001 and FKB238-003)

SOC PT	Study FKB238-001			Study FKB238-003	
	FKB238 (N=33)	EU-Avastin (N=34)	US-Avastin (N=32)	FKB238 (N=20)	EU-Avastin (N=20)
	Number (%) of subjects				
Number (%) of subjects with ≥1 TEAE	32 (97.0)	26 (76.5)	23 (71.9)	12 (60.0)	6 (30.0)
Nervous system disorders	**16 (48.5)**	**7 (20.6)**	**12 (37.5)**	**1 (5.0)**	**1 (5.0)**
Headache	16 (48.5)	6 (17.6)	10 (31.3)	1 (5.0)	1 (5.0)
Dizziness	0	1 (2.9)	2 (6.3)	0	0
Respiratory, thoracic and mediastinal disorders	**11 (33.3)**	**7 (20.6)**	**12 (37.5)**	**1 (5.0)**	**0**
Oropharyngeal pain	3 (9.1)	2 (5.9)	5 (15.6)	0	0
Epistaxis	3 (9.1)	3 (8.8)	3 (9.4)	0	0
Rhinorrhoea	1 (3.0)	3 (8.8)	3 (9.4)	0	0
Nasal congestion	2 (6.1)	1 (2.9)	3 (9.4)	0	0
Cough	3 (9.1)	2 (5.9)	0	0	0
Musculoskeletal and connective tissue disorders	**10 (30.3)**	**8 (23.5)**	**4 (12.5)**	**2 (10.0)**	**1 (5.0)**
Back pain	3 (9.1)	4 (11.8)	1 (3.1)	0	0
Arthralgia	2 (6.1)	3 (8.8)	0	0	0
Myalgia	2 (6.1)	0	1 (3.1)	2 (10.0)	0
Gastrointestinal disorders	**2 (6.1)**	**9 (26.5)**	**7 (21.9)**	**0**	**0**
Tooth ache	1 (3.0)	4 (11.8)	2 (6.3)	0	0
Dyspepsia	0	3 (8.8)	0	0	0
Mouth ulceration	0	0	2 (6.3)	0	0
Infections and infestations	**7 (21.2)**	**6 (17.6)**	**5 (15.6)**	**9 (45.0)**	**0**
Nasopharyngitis	3 (9.1)	4 (11.8)	2 (6.3)	7 (35.0)	0
Tooth infection	2 (6.1)	0	0	0	0
General disorders and administration site conditions	**3 (9.1)**	**5 (14.7)**	**5 (15.6)**	**0**	**0**
Fatigue	1 (3.0)	3 (8.8)	1 (3.1)	0	0
Influenza like illness	1 (3.0)	1 (2.9)	2 (6.3)	0	0
Skin and subcutaneous tissue disorders	**1 (3.0)**	**4 (11.8)**	**1 (3.1)**	**0**	**1 (5.0)**
Dry skin	1 (3.0)	3 (8.8)	0	0	0
Investigations	**1 (3.0)**	**0**	**0**	**3 (15.0)**	**3 (15.0)**
Alanine aminotransferase increased	1 (3.0)	0	0	0	3 (15.0)

CSR=clinical study report; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; US=United States.
Events ordered per overall SOC and PT frequency in Study FKB238-001.
TEAEs were coded using MedDRA Version 17.1 and Version 21.1 in Studies FKB238-001 and FKB238-003, respectively.
Source: Table 10 and Table 14.3.1.2.2.1, Study FKB238-001 CSR (Module 5.3.3.1); Table 10 and Errata Table 14.3.1.2.2.1, Study FKB238-003 CSR (Module 5.3.5.4).

There was an imbalance in reported TEAEs between treatment arms in both PK-studies. Headache was a commonly reported TEAE and with highest frequency in the FKB238 arm (48.5% compared to 17.6% in

the EU-Avastin arm and 31.3% in the US-Avastin arm). Headache was also the most common reported TEADR although with less prominent difference between the treatment arms. Regarding to the frequency of headache, elevations in the diastolic blood pressure were observed in the morning and in the evening across all treatment arms without a pattern. Other measurements (laboratory values, ECG, vital signs) were well balanced as well.

Treatment-related adverse events

Comparative clinical Study FKB238-002

A summary of TEADRs (considered causally related to IP, FKB238 or Avastin, by the investigator), by SOC and PT, is presented for Study FKB238-002 in Table 29.

Table 29: Treatment-emergent adverse drug reactions reported for ≥5% of patients in either treatment group: Safety Population (Study FKB238-002)

SOC PT	FKB238 (N=362)	Avastin (N=366)
	Number (%) of patients	
Number (%) of patients with ≥1 TEADR	148 (40.9)	174 (47.5)
Investigations	**45 (12.4)**	**50 (13.7)**
Blood and lymphatic system disorders	**41 (11.3)**	**59 (16.1)**
Anaemia	21 (5.8)	28 (7.7)
Neutropenia	14 (3.9)	29 (7.9)
Vascular disorders	**29 (8.0)**	**32 (8.7)**
Hypertension	23 (6.4)	26 (7.1)
Skin and subcutaneous tissue disorders	**28 (7.7)**	**40 (10.9)**
Alopecia	18 (5.0)	30 (8.2)
Gastrointestinal disorders	**25 (6.9)**	**28 (7.7)**
Respiratory, thoracic and mediastinal disorders	**25 (6.9)**	**29 (7.9)**
General disorders and administration site conditions	**23 (6.4)**	**43 (11.7)**
Asthenia	13 (3.6)	23 (6.3)
Nervous system disorders	**22 (6.1)**	**29 (7.9)**
Metabolism and nutrition disorders	**21 (5.8)**	**18 (4.9)**
Renal and urinary disorders	**21 (5.8)**	**33 (9.0)**
Proteinuria	17 (4.7)	28 (7.7)

CSR=clinical study report; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEADR=treatment-emergent adverse drug reaction; TEAE=treatment-emergent adverse event.
Events ordered per frequency in the FKB238 arm.
TEADRs are defined as TEAEs considered causally related to IP (FKB238 or Avastin), as assessed by the investigator.
TEAEs were coded using MedDRA Version 21.1. Source: Table 14.3.2.7, Study FKB238-002 CSR (Module 5.3.5.1).

A summary of TEADRs by SOC and PT, is presented for Studies FKB238-001 and FKB238-003 in Table 30.

Table 30: Treatment-emergent adverse drug reactions reported for ≥5% of subjects in any treatment group in either study: Safety Population (Studies FKB238-001 and FKB238-003)

SOC PT	Study FKB238-001			Study FKB238-003	
	FKB238 (N=33)	EU-Avastin (N=34)	US-Avastin (N=32)	FKB238 (N=20)	EU-Avastin (N=20)
	Number (%) of subjects				
Number (%) of subjects with ≥1 TEADR	15 (45.5)	11 (32.4)	12 (37.5)	2 (10.0)	1 (5.0)
Nervous system disorders	**8 (24.2)**	**3 (8.8)**	**7 (21.9)**	**0**	**0**
Headache	8 (24.2)	2 (5.9)	6 (18.8)	0	0
Respiratory, thoracic and mediastinal disorders	**2 (6.1)**	**3 (8.8)**	**4 (12.5)**	**0**	**0**
Epistaxis	2 (6.1)	3 (8.8)	3 (9.4)	0	0
General disorders and administration site conditions	**1 (3.0)**	**3 (8.8)**	**3 (9.4)**	**0**	**0**
Fatigue	1 (3.0)	3 (8.8)	1 (3.1)	0	0
Musculoskeletal and connective tissue disorders	**4 (12.1)**	**2 (5.9)**	**1 (3.1)**	**1 (5.0)**	**0**
Back pain	2 (6.1)	1 (2.9)	0	0	0
Myalgia	1 (3.0)	0	0	1 (5.0)	0
Skin and subcutaneous tissue disorders	**1 (3.0)**	**3 (8.8)**	**1 (3.1)**	**0**	**1 (5.0)**
Dry skin	1 (3.0)	3 (8.8)	0	0	0
Nail bed bleeding	0	0	0	0	1 (5.0)
Investigations	**0**	**0**	**0**	**1 (5.0)**	**0**
Gamma-glutamyltransferase increased	0	0	0	1 (5.0)	0

CSR=clinical study report; EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEADR=treatment-emergent adverse drug reaction; TEAE=treatment-emergent adverse event; US=United States.
Events ordered per overall SOC frequency in Study FKB238-001.
TEADRs are defined as TEAEs where the relationship to study medication was recorded as 'related' or 'possibly related'.
TEADRs were coded using MedDRA Version 17.1 and Version 21.1 in Studies FKB238-001 and FKB238-003, respectively. Source: Table 11 and Table 14.3.1.2.2.2, Study FKB238-001 CSR (Module 5.3.3.1); Table 12 and Table 14.3.1.2.2.2, Study FKB238-003 CSR (Module 5.3.5.4).

Adverse events of special interest

AEs of special interest were identified using a prospectively compiled list of medical concepts aligned with the list of important identified risks in the Avastin EU Risk Management Plan (RMP; Version 28.1), in order to reflect the expected class-related toxicities for an Avastin biosimilar.

<u>Comparative clinical Study FKB238-002: Analysis of adverse events by organ system or syndrome:</u>

Table 31: Summary of TEAEs of special interest: Safety Population (Study FKB238-002)

Medical concept	Number (%) of patients[a]		
	FKB238 (N=362)	Avastin (N=366)	Total (N=728)
Patients with any TEAE of special interest	266 (73.5)	280 (76.5)	546 (75.0)
Arterial thromboembolic events	5 (1.4)	2 (0.5)	7 (1.0)
Bleeding / Haemorrhage	44 (12.2)	55 (15.0)	99 (13.6)
Cardiac disorders (excluding CHF and ATE)	17 (4.7)	24 (6.6)	41 (5.6)
Congestive heart failure	13 (3.6)	13 (3.6)	26 (3.6)
Embryo-foetal development disturbance	0	3 (0.8)	3 (0.4)
Fistula (excluding gastrointestinal)	2 (0.6)	1 (0.3)	3 (0.4)
Gallbladder perforation	0	1 (0.3)	1 (0.1)
Gastrointestinal perforation	3 (0.8)	4 (1.1)	7 (1.0)
Hypersensitivity reactions / Infusion reactions	48 (13.3)	43 (11.7)	91 (12.5)
Hypertension	42 (11.6)	53 (14.5)	95 (13.0)
Neutropenia	141 (39.0)	174 (47.5)	315 (43.3)
Osteonecrosis of the jaw	1 (0.3)	5 (1.4)	6 (0.8)
Peripheral sensory neuropathy	134 (37.0)	132 (36.1)	266 (36.5)
Posterior reversible encephalopathy syndrome	1 (0.3)	0	1 (0.1)
Proteinuria	27 (7.5)	41 (11.2)	68 (9.3)
Pulmonary haemorrhage	3 (0.8)	2 (0.5)	5 (0.7)
Pulmonary hypertension	22 (6.1)	29 (7.9)	51 (7.0)
Surgery and wound healing complications	0	2 (0.5)	2 (0.3)
Venous thromboembolic events	13 (3.6)	8 (2.2)	21 (2.9)

AE=adverse event; ATE=arterial thromboembolic events; CHF=congestive heart failure; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
MedDRA version 21.1.
Number (%) of patients are sorted alphabetically by TEAE of special interest.
[a]Patients with multiple AEs are counted once for each medical concept.
Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Arterial thromboembolic events

TEAEs pertaining to the medical concept of arterial thromboembolic events are shown in Table 32.

CTCAE ≥grade 3 TEAEs were experienced by 3 (0.8%) patients in the FKB238 arm and 2 (0.5%) patients in the Avastin arm, respectively. TEAEs considered related to IP were experienced by 3 (0.8%) and 1 (0.3%) patients, respectively, and TEAEs considered related to study treatment (IP and/or any combination drugs) were experienced by 3 (0.8%) and 1 (0.3%) patients, respectively. One (0.3%) patient in each of the treatment arms discontinued IP due to arterial thromboembolic events, and 1 (0.3%) patient in each of treatment arms discontinued study treatment due to arterial thromboembolic events. One (0.3%) patient in each of the treatment arms experienced arterial thromboembolic events leading to death.

Table 32: Summary of TEAEs pertaining to the medical concept of arterial thromboembolic events: Study FKB238-002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Arterial thromboembolic events	**5 (1.4)**	**2 (0.5)**
Acute myocardial infarction	1 (0.3)	0
Amaurosis fugax	1 (0.3)	0
Ischaemic stroke	0	1 (0.3)
Lacunar infarction	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Transient ischaemic attack	1 (0.3)	1 (0.3)

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event. MedDRA version 21.1.

Number (%) of patients with AEs are sorted alphabetically by preferred term. a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.

Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Bleeding/haemorrhage

CTCAE ≥grade 3 bleeding/haemorrhage TEAEs were experienced by 6 (1.7%) patients in the FKB238 arm and 3 (0.8%) patients in the Avastin arm, respectively. TEAEs considered related to IP were experienced by 26 (7.2%) and 33 (9.0%) patients, respectively, and TEAEs considered related to study treatment (IP and/or any combination drugs) were experienced by 29 (8.0%) and 37 (10.1%) patients, respectively. Four (1.1%) patients in each of the treatment arms discontinued IP due to TEAEs pertaining to the medical concept of bleeding/haemorrhage, with 4 (1.1%) patients in each of the treatment arms also discontinuing study treatment due to bleeding/haemorrhage TEAEs. Two (0.6%) and 1 (0.3%) patients in the FKB238 and Avastin arms, respectively, experienced bleeding/haemorrhage TEAEs leading to death.

Table 33: Summary of TEAEs pertaining to the medical concept of bleeding/haemorrhage: Study FKB238-002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Bleeding/haemorrhage	**44 (12.2)**	**55 (15.0)**
Activated partial thromboplastin time prolonged	1 (0.3)	1 (0.3)
Anal haemorrhage	2 (0.6)	2 (0.5)
Blood urine present	0	1 (0.3)
Conjunctival haemorrhage	0	1 (0.3)
Contusion	1 (0.3)	0
Disseminated intravascular coagulation	1 (0.3)	0
Diverticulum intestinal haemorrhagic	1 (0.3)	0
Ecchymosis	1 (0.3)	1 (0.3)
Epistaxis	16 (4.4)	23 (6.3)
Gastric haemorrhage	1 (0.3)	0
Gastrointestinal haemorrhage	0	1 (0.3)
Gingival bleeding	1 (0.3)	1 (0.3)
Haematemesis	1 (0.3)	0
Haematochezia	3 (0.8)	1 (0.3)
Haematocrit decreased	2 (0.6)	3 (0.8)
Haematuria	6 (1.7)	12 (3.3)
Haemoglobin decreased	2 (0.6)	1 (0.3)
Haemoptysis	8 (2.2)	9 (2.5)
Haemorrhagic stroke	1 (0.3)	1 (0.3)
Haemorrhoidal haemorrhage	0	1 (0.3)
International normalised ratio increased	2 (0.6)	0
Lower gastrointestinal haemorrhage	1 (0.3)	2 (0.5)
Menorrhagia	1 (0.3)	0
Mouth haemorrhage	0	1 (0.3)
Petechiae	0	1 (0.3)
Prothrombin time prolonged	1 (0.3)	0
Purpura	0	1 (0.3)
Rectal haemorrhage	1 (0.3)	1 (0.3)
Red blood cell count decreased	2 (0.6)	3 (0.8)
Reticulocyte count increased	2 (0.6)	0
Traumatic haematoma	0	1 (0.3)
Uterine haemorrhage	0	1 (0.3)
Upper gastrointestinal haemorrhage	0	2 (0.5)
Vaginal haemorrhage	0	1 (0.3)

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.
Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Coagulation laboratory data were similar in both treatment arms.

Cardiac disorders (excluding congestive heart failure and arterial thromboembolic events)

CTCAE ≥grade 3 TEAEs were experienced by 1 (0.3%) patient in the FKB238 arm and 3 (0.8%) patients in the Avastin arm, respectively. TEAEs considered related to IP were experienced by 2 (0.6%) and 9 (2.5%) patients, respectively, with TEAEs considered related to study treatment (IP and/or any combination drugs) experienced by 5 (1.4%) and 13 (3.6%) patients, respectively. One (0.3%) patient in each of the treatment arms discontinued IP due to TEAEs pertaining to the medical concept of cardiac disorders, with 1 (0.3%) patient in each of the treatment arms also discontinuing study treatment due to such events. No patients in the FKB238 arm and 1 (0.3%) patient in the Avastin arm experienced cardiac disorder TEAEs leading to death.

Table 34: Summary of TEAEs pertaining to the medical concept of cardiac disorders (excluding congestive heart failure and arterial thromboembolic events): Study FKB238-002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Cardiac disorders (excluding congestive heart failure and arterial thromboembolic events)	**17 (4.7)**	**24 (6.6)**
Arrythmia	2 (0.6)	0
Atrial fibrillation	0	2 (0.5)
Bundle branch block left	1 (0.3)	1 (0.3)
Bundle branch block right	2 (0.6)	0
Cardiac disorder	0	1 (0.3)
Electrocardiogram QT prolonged	2 (0.6)	3 (0.8)
Electrocardiogram repolarisation abnormality	3 (0.8)	4 (1.1)
Extrasystoles	0	3 (0.8)
Sinus arrhythmia	0	1 (0.3)
Sinus bradycardia	0	1 (0.3)
Sinus tachycardia	8 (2.2)	7 (1.9)
Supraventricular extrasystoles	1 (0.3)	2 (0.5)
Supraventricular tachycardia	1 (0.3)	0
Tachyarrhythmia	0	1 (0.3)
Ventricular extrasystoles	0	2 (0.5)

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities;
TEAE=treatment-emergent adverse event.
MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.

Fistula (excluding gastrointestinal)

Two patients in the FKB238 arm experienced serious CTCAE grade 2 events of oesophagobronchial fistula that were considered related to IP and combination drugs and led to permanent discontinuation of both IP and combination drugs. The events were reported as not resolved in 1 patient and recovered/resolved with sequelae in the other patient. One patient in the Avastin arm experienced a non-serious CTCAE grade 1 event of tracheo-oesophageal fistula that was not considered related to IP or combination drugs, but led to dose delay for both IP and combination drugs. The event was reported as not recovered/resolved.

Table 35: Summary of TEAEs pertaining to the medical concept of fistula (excluding gastrointestinal): Study FKB238-002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Fistula (excluding gastrointestinal)	**2 (0.6)**	**1 (0.3)**
Oesophagobronchial fistula	2 (0.6)	0
Tracheo-oesophageal fistula	0	1 (0.3)

AE=adverse event; ; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities;
TEAE=treatment-emergent adverse event.
MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.
Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Gallbladder perforation

The only reported event relating to gallbladder perforation was a non-serious CTCAE grade 3 event of gallbladder abscess in the Avastin arm, which was not considered related to IP or combination drugs, but led to permanent discontinuation of IP. The outcome for the event was recovered/resolved.

Gastrointestinal perforation

CTCAE ≥grade 3 gastrointestinal perforation TEAEs were experienced by 1 (0.3%) patient in the FKB238 arm and 3 (0.8%) patients in the Avastin arm, respectively. TEAEs considered related to IP were experienced by 2 patients in each of the treatment arms (0.6% and 0.5%, respectively), and TEAEs considered related to study treatment (IP and/or any combination drugs) were experienced by 2 patients in each of the treatment arms (0.6% and 0.5%, respectively). Three (0.8%) and 4 (1.1%) patients, respectively, discontinued IP due to TEAEs pertaining to the medical concept of gastrointestinal perforation, with 3 (0.8%) and 4 (1.1%) patients also discontinuing study treatment due to such events. One patient (0.3%) in each of the treatment arms experienced gastrointestinal perforation TEAEs leading to death.

Table 36: Summary of TEAEs pertaining to the medical concept of gastrointestinal perforation: Study FKB238-002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Gastrointestinal perforation	**3 (0.8)**	**4 (1.1)**
Anal fistula	0	1 (0.3)
Colonic abscess	0	1 (0.3)
Ileal perforation	0	1 (0.3)
Oesophagobronchial fistula	2 (0.6)	0
Peritonitis	1 (0.3)	1 (0.3)
Small intestinal perforation	0	1 (0.3)

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities;
TEAE=treatment-emergent adverse event.
MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.

Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Hypersensitivity reactions/infusion reactions

CTCAE ≥grade 3 TEAEs were experienced by 7 (1.9%) patients in the FKB238 arm and 5 (1.4%) patients in the Avastin arm, respectively. TEAEs considered related to IP were experienced by 12 (3.3%) and 10 (2.7%) patients, respectively, and TEAEs considered related to study treatment (IP and/or any combination drugs) were experienced by 37 (10.2%) and 28 (7.7%) patients, respectively. Two (0.6%) and 1 (0.3%) patients, respectively, discontinued IP due to TEAEs pertaining to the medical concept of hypersensitivity reactions/infusion reactions, with 3 (0.8%) and 1 (0.3%) patients also discontinuing study treatment due to such TEAEs. Two (0.6%) and 3 (0.8%) patients in the FKB238 and Avastin arms, respectively, experienced hypersensitivity reactions/infusion reactions TEAEs leading to death.

Table 37: Summary of TEAEs pertaining to the medical concept of hypersensitivity reactions /infusion reactions: Study FKB238-002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Hypersensitivity reactions/infusion reactions	**48 (13.3)**	**43 (11.7)**
Acute respiratory failure	2 (0.6)	0
Bronchospasm	1 (0.3)	0
Contrast media allergy	1 (0.3)	0
Dermatitis	2 (0.6)	0
Dermatitis acneiform	2 (0.6)	0
Dermatitis allergic	1 (0.3)	1 (0.3)
Drug eruption	2 (0.6)	1 (0.3)
Drug hypersensitivity	2 (0.6)	2 (0.5)
Eczema	1 (0.3)	0
Eosinophilia	1 (0.3)	1 (0.3)
Erythema	1 (0.3)	0
Flushing	2 (0.6)	3 (0.8)
Hypersensitivity	7 (1.9)	2 (0.5)
Infusion related reaction	2 (0.6)	2 (0.5)
Pneumonitis	2 (0.6)	0
Pruritus	5 (1.4)	7 (1.9)
Pruritus generalised	1 (0.3)	1 (0.3)
Rash	7 (1.9)	5 (1.4)
Rash erythematous	0	1 (0.3)
Rash maculo-papular	6 (1.7)	7 (1.9)
Rash pruritic	1 (0.3)	0

Respiratory failure	2 (0.6)	3 (0.8)
Rhinitis allergic	1 (0.3)	1 (0.3)
Skin erosion	1 (0.3)	0
Stomatitis	8 (2.2)	10 (2.7)
Urticaria	2 (0.6)	2 (0.5)
Wheezing	1 (0.3)	0

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities;
TEAE=treatment-emergent adverse event.
MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.
Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

There were slightly more patients in the FKB238 arm compared to Avastin arm that experienced hypersensitivity/IRR events (48 vs 43 patients respectively).

Hypertension

CTCAE ≥grade 3 TEAEs were experienced by 14 (3.9%) patients in the FKB238 arm and 21 (5.7%) patients in the Avastin arm, respectively. TEAEs considered related to IP were experienced by 24 (6.6%) and 27 (7.4%) patients, respectively, and TEAEs considered related to study treatment (IP and/or any combination drugs) were experienced by 24 (6.6%) and 27 (7.4%) patients, respectively. One (0.3%) and 4 (1.1%) patients, respectively, discontinued IP due to TEAEs pertaining to the medical concept of hypertension, with 1 (0.3%) and 4 (1.1%) patients also discontinuing study treatment due to such TEAEs. No patients in either treatment arm experienced TEAEs pertaining to the medical concept of hypertension that led to death.

Table 38: Summary of TEAEs pertaining to the medical concept of hypertension: Study FKB238-002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Hypertension	**42 (11.6)**	**53 (14.5)**
Blood pressure diastolic increased	0	1 (0.3)
Blood pressure increased	2 (0.6)	5 (1.4)
Hypertension	42 (11.6)	44 (12.0)
Hypertensive crisis	0	2 (0.5)
Prehypertension	0	1 (0.3)

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities;
TEAE=treatment-emergent adverse event. MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.
Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Vital signs evaluations, which included assessments of blood pressure, were similar in both treatment arms. Thus, the slight imbalance in the reporting of hypertension events between the treatment arms was not supported by the objective data.

Necrotising fasciitis

No TEAEs were retrieved using this search.

Neutropenia

CTCAE ≥grade 3 TEAEs were experienced by 80 (22.1%) patients in the FKB238 arm and 93 (25.4%) in the Avastin arm, respectively. TEAEs considered related to IP were experienced by 23 (6.4%) and 41 (11.2%) patients, respectively, and TEAEs considered related to study treatment (IP and/or any combination drugs) were experienced by 135 (37.3%) and 165 (45.1%) patients, respectively. One (0.3%) and 0 patients, respectively, discontinued IP due to TEAEs pertaining to the medical concept of neutropenia, with 6 (1.7%) and 1 (0.3%) patients discontinuing study treatment due to such TEAEs. No patients in either treatment arm experienced TEAEs pertaining to the medical concept of neutropenia leading to death.

Table 39: Summary of TEAEs pertaining to the medical concept of neutropenia: Study FKB238 002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients	
	FKB238 (N=362)	Avastin (N=366)
Neutropenia	**141 (39.0)**	**174 (47.5)**
Febrile neutropenia	11 (3.0)	7 (1.9)
Neutropenia	109 (30.1)	145 (39.6)
Neutrophil count decreased	24 (6.6)	25 (6.8)
Neutrophil percentage decreased	[illegible]	1 (0.3)
White blood cell count decreased	24 (6.6)	26 (7.1)

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event. MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.
Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Osteonecrosis of the jaw

TEAEs pertaining to the medical concept of osteonecrosis of the jaw were experienced by 1 (0.3%) patient (PT: pain in jaw) in the FKB238 arm and 5 (1.4%) patients in the Avastin arm. All of the events were non-serious and of CTCAE grade 1 or 2, and none led to discontinuation of study treatment. None of these events are considered to be consistent with the medical concept of osteonecrosis of the jaw.

Ovarian failure

Of the pre-specified PTs for this medical concept, none was reported in Study FKB238-002.

Peripheral sensory neuropathy

CTCAE ≥grade 3 TEAEs were experienced by 10 (2.8%) patients in the FKB238 arm and 3 (0.8%) patients in the Avastin arm, respectively. TEAEs considered related to IP were experienced by 13 (3.6%) and 14 (3.8%) patients, respectively, with TEAEs considered related to study treatment (IP and/or any combination drugs) experienced by 125 (34.5%) and 124 (33.9%) patients, respectively. One (0.3%) and 0 patients, respectively, discontinued IP due to TEAEs pertaining to the medical concept of peripheral sensory neuropathy, with 10 (2.8%) and 12 (3.3%) patients also discontinuing study treatment due to such events. No patients in either treatment arm experienced TEAEs pertaining to the medical concept of peripheral sensory neuropathy that led to death.

Table 40: Summary of TEAEs pertaining to the medical concept of peripheral sensory neuropathy: Study FKB238-002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Peripheral sensory neuropathy	**134 (37.0)**	**132 (36.1)**
Central pain syndrome	1 (0.3)	0
Formication	1 (0.3)	0
Hypoaesthesia	9 (2.5)	9 (2.5)
Muscular weakness	0	1 (0.3)
Neuralgia	0	1 (0.3)
Neuropathy peripheral	58 (16.0)	51 (14.2)
Neurotoxicity	3 (0.8)	1 (0.3)
Paraesthesia	24 (6.6)	22 (6.0)
Peripheral sensorimotor neuropathy	1 (0.3)	0
Peripheral sensory neuropathy	28 (7.7)	25 (6.8)
Polyneuropathy	16 (4.4)	23 (6.3)

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities;
TEAE=treatment-emergent adverse event.
MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.
Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Posterior reversible encephalopathy syndrome

Only 1 patient in the FKB238 arm experienced a TEAE pertaining to the medical concept of PRES. This was a serious CTCAE grade 3 event which was considered related to IP but not to combination drugs and led to permanent discontinuation of IP. The event started 107 days from the first dose of IP and had an outcome of recovered/resolved with sequelae. This patient had clinically relevant high blood pressure 85 days prior to the event, but not on the day prior to the event. Vital signs assessments were not recorded for this patient during the event.

Proteinuria

CTCAE ≥grade 3 TEAEs were experienced by 1 (0.3%) patient in the FKB238 arm and 6 (1.6%) patients in the Avastin arm, respectively. TEAEs considered related to IP were experienced by 17 (4.7%) and 28 (7.7%) patients, respectively, with TEAEs considered related to study treatment (IP and/or any combination drugs) experienced by 17 (4.7%) and 30 (8.2%) patients, respectively. One (0.3%) and 2 (0.5%) patients, respectively, discontinued IP due to proteinuria TEAEs, with 1 (0.3%) and 2 (0.5%) patients discontinuing study treatment due to such events. No patients in either treatment arm experienced TEAEs pertaining to the medical concept of proteinuria that led to death.

Table 41: Summary of TEAEs pertaining to the medical concept of proteinuria: Study FKB238 002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Proteinuria	**27 (7.5)**	**41 (11.2)**
Albuminuria	1 (0.3)	0
Haemoglobinuria	1 (0.3)	0
Protein urine	1 (0.3)	0
Proteinuria	24 (6.6)	41 (11.2)

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.
Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Pulmonary haemorrhage

TEAEs pertaining to the medical concept of pulmonary haemorrhage were experienced by 3 (0.8%) patients in the FKB238 arm and 2 (0.5%) patients in the Avastin arm (all reported under the PT of pulmonary haemorrhage). Four of the patients experienced serious events of CTCAE grade 5, with the remaining patient (Avastin arm) experiencing a non-serious CTCAE grade 1 event which led to permanent discontinuation of IP.

Pulmonary hypertension

CTCAE ≥grade 3 TEAEs were experienced by 4 (1.1%) patients in the FKB238 arm and 6 (1.6%) patients in the Avastin arm, respectively.

TEAEs considered related to IP were experienced by 1 (0.3%) and 4 (1.1%) patients, respectively, with TEAEs considered related to study treatment (IP and/or any combination drugs) experienced by 6 patients in each treatment arm (1.7% and 1.6% of patients, respectively). No patients in either treatment arm discontinued IP or study treatment due to TEAEs pertaining to the medical concept of pulmonary hypertension. Three (0.8%) and 1 (0.3%) patients in the FKB238 and Avastin arms, respectively, experienced TEAEs pertaining to the medical concept of pulmonary hypertension that led to death.

Table 42: Summary of TEAEs pertaining to the medical concept of pulmonary hypertension: Study FKB238-002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Pulmonary hypertension	**22 (6.1)**	**29 (7.9)**
Cor pulmonale	1 (0.3)	0
Diastolic dysfunction	1 (0.3)	0
Dyspnoea	18 (5.0)	29 (7.9)
Dyspnoea exertional	1 (0.3)	0
Hypoxia	0	1 (0.3)
Pulmonary hypertension	1 (0.3)	1 (0.3)

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities;
TEAE=treatment-emergent adverse event.
MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.
Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Surgery and wound healing complications

Only 2 patients (in the Avastin arm) experienced TEAEs pertaining to the medical concept of surgery and wound healing complications. Both patients experienced non-serious CTCAE grade 2 events of impaired healing. One of the events was considered related to IP and led to a dose delay of IP.

Thrombotic microangiopathy

This pre-specified PT was not reported in this study.

Venous thromboembolic events

CTCAE ≥grade 3 TEAEs were experienced by 10 (2.8%) patients in the FKB238 arm and 8 (2.2%) patients in the Avastin arm, respectively. TEAEs considered related to IP were experienced by 6 (1.7%) and 2 (0.5%) patients, respectively, with TEAEs considered related to study treatment (IP and/or any combination drugs) experienced by 8 (2.2%) and 2 (0.5%) patients, respectively. Three (0.8%) and 1 (0.3%) patients, respectively, discontinued IP due to venous thromboembolic events, with 3 (0.8%) and 1 (0.3%) patients, discontinuing study treatment due to such events. Two (0.6%) and 3 (0.8%) patients in the FKB238 and Avastin arms experienced venous thromboembolic events leading to death.

Table 43: Summary of TEAEs pertaining to the medical concept of venous thromboembolic events: Study FKB238-002 (Safety Population)

Medical concept MedDRA preferred term	Number (%) of patients[a]	
	FKB238 (N=362)	Avastin (N=366)
Venous thromboembolic events	**13 (3.6)**	**8 (2.2)**
Brachiocephalic vein thrombosis	1 (0.3)	0
Deep vein thrombosis	2 (0.6)	1 (0.3)
Pulmonary embolism	10 (2.8)	7 (1.9)
Thrombophlebitis	1 (0.3)	0
Venous thrombosis limb	1 (0.3)	0

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities;
TEAE=treatment-emergent adverse event.
MedDRA version 21.1.
Number (%) of patients with AEs are sorted alphabetically by preferred term.
a Patients with multiple AEs are counted once for each medical concept and for each preferred term within each medical concept.
Source: Table 14.3.6.1, Study FKB238-002 CSR (Module 5.3.5.1).

Serious adverse event/deaths/other significant events

Deaths

Pharmacokinetic Studies FKB238-001 and FKB238-003

There were no deaths during Studies FKB238-001 and FKB238-003.

Comparative clinical Study FKB238-002

Overall summary of deaths

All deaths in Study FKB238-002 are presented for the Safety Population in Table 44, and TEAEs leading to death are summarised by SOC and PT in Table 45.

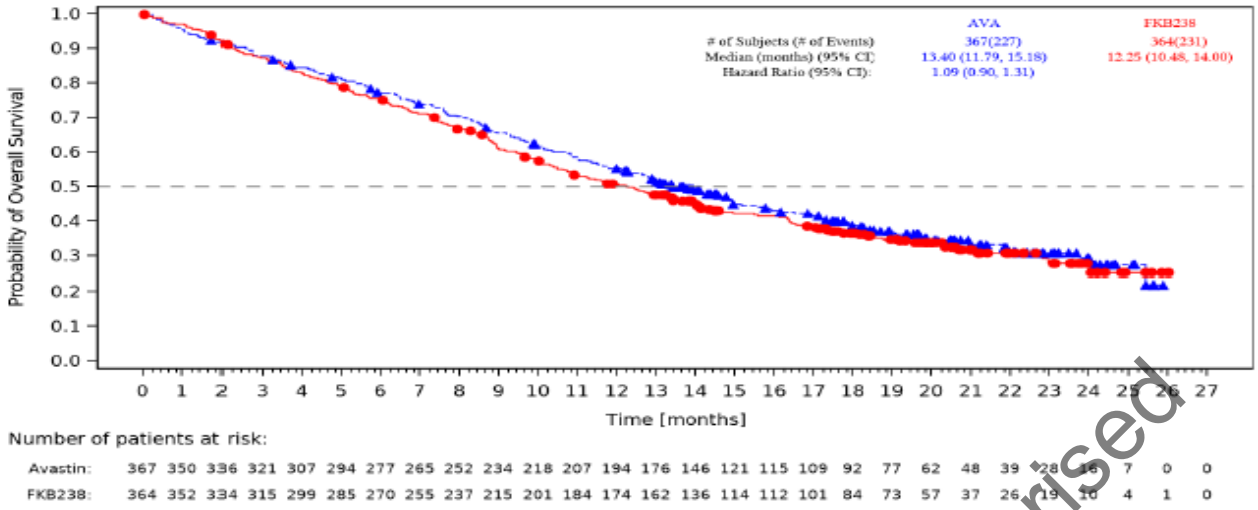
As of data cut-off, there was a numeric imbalance in the number of deaths observed between the FKB238 arm (195 [53.9%] patients) and the Avastin arm (177 [48.4%] patients).

Several factors contributed to the imbalance in deaths between the treatment arms.

Baseline data for the ITT-population show some imbalances in demography and baseline characteristics (more current smokers, more patients with a past and current medical history of cardiovascular conditions, more patients with current respiratory conditions, and smaller number of patients who received subsequent anti-cancer therapy in the FKB238 arm), indicating that patients in the FKB238 arm had a higher background risk of death than those in the Avastin arm.

Fewer patients withdrew consent to follow-up in the FKB238 arm compared to the Avastin arm, 36 [9.9%] patients versus 49 [13.4%] patients, respectively. TEAEs leading to discontinuation of study treatment were reported for a higher proportion of withdrawal of consent (WoC)-patients in the Avastin arm than in the FKB238 arm (8 [16.3%] versus 2 [5.7%] patients, respectively), as were TEAEs with Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher (24 [49.0%] versus 14 [40.0%] patients, respectively) and treatment-emergent SAEs (11 [22.4%] versus 5 [14.3%] patients, respectively). Baseline characteristics for the 85 patients who discontinued due to WoC (FKB238, 36; Avastin, 49) showed that a higher proportion of patients had AJCC stage IV disease at diagnosis in the Avastin arm than in the FKB238 arm (47 [95.9%] versus 31 [86.1%] patients, respectively). Additionally, a higher proportion of patients were aged ≥65 years in the Avastin arm than in the FKB238 arm (18 [36.7%] versus 10 [27.8%] patients, respectively), with 6 (12.2%) patients in the Avastin arm aged between 75 and 84 years compared to no patients in the FKB238 arm. The proportion of current smokers for this group of patients was also slightly higher in the Avastin arm than in the FKB238 arm (19 [38.8%] versus 12 [33.3%] patients, respectively), as was the proportion of patients with an ECOG PS of 1 (24 [49.0%] versus 17 [47.2%] patients, respectively). More patients in the Avastin arm than the FKB238 arm withdrew following AEs and PD. Overall, patients in the Avastin arm who withdrew consent to the study had a worse AE profile and worse prognostic factors than those in the FKB238 arm.

In order to investigate the impact of the missing survival data on the reliability of the OS estimation, the MAH performed a post-hoc sensitivity analysis in which discontinuation from the study due to WoC was considered as a death event. The results of this sensitivity analysis are shown in the KM plot below.



AVA=Avastin; CI=confidence interval; ITT=Intent-to-Treat; OS=overall survival; WoC=withdrawal of consent.

Figure 14: Kaplan-Meier plot of OS considering patients who discontinued study due to WoC as event (ITT Population)

Table 44: All deaths: Safety Population (Study FKB238-002)

Category	FKB238 (N=362)	Avastin (N=366)
	Number (%) of patients	
Total number of deaths	195 (53.9)	177 (48.4)
Death related to disease under investigation only[a]	156 (43.1)	148 (40.4)
AE with outcome of death only	17 (4.7)	12 (3.3)
Death related to disease under investigation and AE with outcome of death	14 (3.9)	11 (3.0)
Other deaths[b]	8 (2.2)	6 (1.6)
Deaths on the last study treatment administration date	0	0
Deaths within 30 days of last study treatment dose	44 (12.2)	40 (10.9)
Deaths more than 30 days after last study treatment dose	151 (41.7)	137 (37.4)

AE=adverse event; CSR=clinical study report; IP=investigational product.
Study treatment=IP and/or any combination drugs (paclitaxel and carboplatin).
a As assessed by the investigator.
b Deaths not related to the disease under investigation for which no AE with an outcome of death was recorded and deaths with an unknown relationship to the disease under investigation.
Source: Table 34, Study FKB238-002 CSR (Module 5.3.5.1).

TEAEs with a fatal outcome

Table 45: Treatment-emergent adverse events leading to death: Safety Population (Study FKB238-002)

SOC PT	FKB238 (N=362)	Avastin (N=366)
	Number (%) of patients	
Number (%) of patients with ≥1 TEAE leading to death	30 (8.3)	23 (6.3)
Cardiac disorders	**6 (1.7)**	**2 (0.5)**
Acute coronary syndrome	2 (0.6)	1 (0.3)
Acute myocardial infarction	1 (0.3)	0
Cardiac disorder	0	1 (0.3)
Cardio-respiratory arrest	2 (0.6)	0
Cor pulmonale	1 (0.3)	0
General disorders and administration site conditions	**7 (1.9)**	**5 (1.4)**
Death	5 (1.4)	3 (0.8)
General physical health deterioration	0	2 (0.5)
Pyrexia	1 (0.3)	0
Sudden death	1 (0.3)	0
Hepatobiliary disorders	**0**	**1 (0.3)**
Cholecystitis	0	1 (0.3)
Infections and infestations	**1 (0.3)**	**1 (0.3)**
Peritonitis	1 (0.3)	1 (0.3)
Nervous system disorders	**5 (1.4)**	**5 (1.4)**
Cerebral arteriosclerosis	1 (0.3)	0
Cerebrovascular accident	2 (0.6)	3 (0.8)
Epilepsy	1 (0.3)	0
Haemorrhagic stroke	1 (0.3)	1 (0.3)
Ischaemic stroke	0	1 (0.3)
Renal and urinary disorders	**0**	**1 (0.3)**
Acute kidney injury	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	**12 (3.3)**	**8 (2.2)**
Acute respiratory failure	1 (0.3)	0
Dyspnoea	2 (0.6)	1 (0.3)
Haemoptysis	1 (0.3)	0
Pneumonia aspiration	1 (0.3)	0
Pulmonary embolism	2 (0.6)	3 (0.8)
Pulmonary haemorrhage	3 (0.8)	1 (0.3)
Pulmonary oedema	1 (0.3)	0
Respiratory failure	1 (0.3)	3 (0.8)

CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
TEAEs were coded using MedDRA Version 21.1.
Source: Table 35, Study FKB238-002 CSR (Module 5.3.5.1).

The PTs reported in the cardiac disorders SOC are consistent with the expected safety profile of Avastin (acute coronary syndrome, acute myocardial infarction) or were found to represent terminal events in patients with lung cancer (cardio-respiratory arrest, cor pulmonale).

Fatal events in the SOC of general disorders and administration site conditions were mainly driven by deaths that were reported conservatively as AEs by the investigator because the patient died unattended

at home without any preceding AEs or objective evidence of disease progression. Autopsies were not performed in any of these cases. The Study FKB238-002 protocol states "Events, which are unequivocally due to disease progression, should not be reported as an AE during the study". In each case where death was reported as a SAE due to underlying disease the investigator was asked if they considered the event to be unequivocally due to disease progression. If the event was due to underlying disease but there was no objective evidence of progression the event was to be reported as an SAE according to the protocol. It is acknowledged that there are challenges in assessing the cause of death and the causality to the given study treatment in the absence of autopsies, and especially in the cases of sudden death at home.

The fatal PTs reported in the respiratory, thoracic and mediastinal disorders SOC are mainly consistent with the expected safety profile of Avastin (pulmonary embolism, pulmonary haemorrhage, haemoptysis), or the underlying lung cancer can cause the events (acute respiratory failure, dyspnoea, respiratory failure).

The 53 patients who experienced TEAEs leading to death were analysed in detail for any factors that could support interpretation of the event and grouped into mutually exclusive categories accordingly.

In 6 cases, the report describes death of unknown cause (e.g. AE of 'Death' or 'Sudden death') where no further information is available. A further 6 case reports describe death due to NSCLC only, and in 16 cases the report describes an event that is consistent with a terminal event in advanced NSCLC (e.g., respiratory failure, general deterioration, dyspnoea, cor pulmonale, pneumonia aspiration, cardio-respiratory arrest, pulmonary haemorrhage). In 17 reports, the event is completely consistent with the known safety profile of Avastin. For the 8 remaining case reports (4 FKB238, 4 Avastin), no clear alternative causal factors were identified and they described events that were not contained in the SmPC for Avastin. Narratives for these 8 cases were provided.

<u>TEAEs with a fatal outcome: overall conclusions</u>

Due to the fact that 18 more deaths overall were observed in the FKB238 arm during the study, the TEAEs with a fatal outcome were thoroughly reviewed to identify any potential safety concerns.

The baseline and disease characteristics of the patients who experienced a TEAE with a fatal outcome were fairly balanced between study arms with observed differences in both directions. Compared to the overall study population, there is a trend that patients experiencing TEAE with fatal outcome included more current smokers, more patients with a past and current medical history of cardiovascular conditions, more patients with current respiratory conditions, and smaller number of patients who received subsequent anti-cancer therapy in the FKB238 arm, indicating that patients in the FKB238 arm had a higher background risk of death than those in the Avastin arm. It is common that the performance status declines faster during anticancer treatments in patients with advanced cancer and with overall poor performance status at baseline.

A summary of narratives for all fatal TEAEs was submitted and the Applicant did not amend (upgrade or downgrade) the investigator's causality assessment for any event. Also individual summary narratives were provided.

Of the 6 patients with death of unknown cause, none had progressive disease and none were considered related to IP. Two patients in the FKB238 arm had a current respiratory medical history, and no patient had a current or past cardiovascular medical history or past respiratory medical history. Of the 16 patients categorized to terminal events in the context of advanced non-small cell lung cancer, all the reported PT were in accordance with the symptoms and conditions belonging to terminal phase. Most of the patients had current cardiovascular and/or respiratory conditions. In 15 of the 16 patients, fatal TEAE was considered causally not to be related to IP. The cases were accordingly reported as TEAEs.

Of the 6 patients categorized as death due to underlying NSCLC, all 6 had Stage IV disease at original diagnosis. Of them only 2 patients in the FKB238 arm had PD prior to death. Most of the patients had current cardiovascular and/or respiratory conditions. In 4 of the 6 cases, fatal TEAE was considered causally not to be related to IP.

Of the 17 patients categorized as fatal TEAEs consistent with safety profile of bevacizumab, two patients had PD prior to death and 15 patients experienced fatal TEAEs considered not to be related to IP. Most of the patients had current cardiovascular and/or respiratory conditions. The reported PTs (Acute coronary syndrome, Acute myocardial infarction, Cerebrovascular accident, Haemorrhagic stroke, Ischemic stroke and Pulmonary embolism) were balanced between the study arms. Even though some of the TEAEs with fatal outcome labelled as "death due to underlying NSCLC" and terminal events in advanced NSCLC" are also possibly events consistent with known safety profile of Avastin, such as "dyspnoea" and pulmonary haemorrhage", the distribution over treatment arms remain relatively similar

Of the 8 patients with fatal TEAEs with no clear alternative causal factors, 2 patients had PD prior to death and all cases were considered not to be related to IP. Most of the patients had current cardiovascular and/or respiratory conditions.

The FKB238-002 was a multi-centre study conducted in several geographic areas in 146 centres in 24 countries, of which 136 centres randomised patients. The distribution of TEAEs, TESAEs and fatal TEAEs were balanced across the study sites and by region and centre.

Serious adverse events

Pharmacokinetic Studies FKB238-001 and FKB238-003

No SAEs were reported in Studies FKB238-001 and FKB238-003.

Comparative clinical Study FKB238-002

Table 46: Treatment-emergent serious adverse events reported in at least 3 patients in either treatment group: Safety Population (Study FKB238-002)

SOC PT	FKB238 (N=362)	Avastin (N=366)
	Number (%) of patients	
Number (%) of patients with ≥1 TESAE	91 (25.1)	95 (26.0)
Blood and lymphatic system disorders	**19 (5.2)**	**32 (8.7)**
Anaemia	5 (1.4)	9 (2.5)
Febrile neutropenia	7 (1.9)	5 (1.4)
Neutropenia	7 (1.9)	18 (4.9)
Cardiac disorders	**9 (2.5)**	**4 (1.1)**
Acute coronary syndrome	3 (0.8)	1 (0.3)
Gastrointestinal disorders	**8 (2.2)**	**9 (2.5)**
Diarrhoea	1 (0.3)	3 (0.8)
Vomiting	3 (0.8)	2 (0.5)
General disorders and administration site conditions	**10 (2.8)**	**6 (1.6)**
Death	5 (1.4)	3 (0.8)
Infections and infestations	**14 (3.9)**	**16 (4.4)**
Pneumonia	10 (2.8)	9 (2.5)
Investigations	**4 (1.1)**	**3 (0.8)**
Neutrophil count decreased	3 (0.8)	2 (0.5)
Nervous system disorders	**13 (3.6)**	**8 (2.2)**
Cerebrovascular accident	2 (0.6)	3 (0.8)
Respiratory, thoracic and mediastinal disorders	**23 (6.4)**	**17 (4.6)**
Dyspnoea	2 (0.6)	3 (0.8)
Pneumothorax	0	4 (1.1)
Pulmonary embolism	6 (1.7)	5 (1.4)
Pulmonary haemorrhage	3 (0.8)	1 (0.3)
Respiratory failure	1 (0.3)	3 (0.8)

CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TESAE=treatment-emergent serious adverse event.
TESAEs were coded using MedDRA Version 21.1.
Source: Table 36, Study FKB238-002 CSR (Module 5.3.5.1).

The incidence of individual TEAEs was similar between the treatment arms, although slightly more patients experienced TEAEs of neutropenia in the Avastin arm (18 [4.9%] patients) than in the FKB238 arm (7 [1.9%] patients).

Laboratory findings

Comparative clinical Study FKB238-002

Haematology

Across both the FKB238 and Avastin treatment arms, there were minor fluctuations in mean haematology values over time, particularly in the first cycles when chemotherapy was administered concomitantly. Values for each haematological parameter were generally similar across both treatment arms.

For most haematology parameters, only small proportions (<10%) of patients with CTCAE grade 0 or 1 at baseline worsened to CTCAE grade 3 or 4 on treatment in both treatment arms. A notable exception was for decreased neutrophil count, in which 19 (5.3%) and 42 (11.7%) patients in the FKB238 and Avastin arms, respectively, with CTCAE grade 0 at baseline shifted to CTCAE grade 4 on treatment. A total of 68 (19.0%) and 61 (17.0%) patients, respectively, with CTCAE grade 0 at baseline shifted to CTCAE grade 3 on treatment.

Clinically relevant abnormal haematology values were common during the study in both treatment arms, with a similar incidence of TEAEs pertaining to abnormal haematology values reported in both treatment arms, with the exception of neutropenia (reported for 109 [30.1%] and 145 [39.6%] patients, the FKB238 and Avastin arms, respectively) and thrombocytopenia (44 [12.2%] and 66 [18.0%] patients, respectively). Other common abnormal haematology values with similar distribution between treatment arms were anaemia (reported for 105 [29.0%] and 119 [32.5%] patients, respectively) and leukopenia (reported for 43 [11.9%] and 50 [13.7%] patients, respectively).

Clinical chemistry

Across both the FKB238 and Avastin treatment arms, generally minor fluctuations in mean clinical chemistry values over time were observed.

For all clinical chemistry parameters, only small proportions (<10%) of patients with CTCAE grade 0 or 1 at baseline worsened to CTCAE grade 3 or 4 on treatment in both treatment arms.

Clinically relevant abnormal clinical chemistry values were common during the study, with a similar incidence of TEAEs pertaining to abnormal clinical chemistry values reported in both treatment arms, with the exception of blood lactate dehydrogenase increased, which was reported for fewer patients in the FKB238 arm than in the Avastin arm (6 [1.7%] versus 18 [4.9%] patients, respectively).

Other common abnormal clinical chemistry values with similar distribution between treatment arms were alanine aminotransferase increased (reported for 38 [10.5%] and 35 [9.6%] patients, respectively) and gamma glutamyltransferase increased (reported for 38 [10.5%] and 31 [8.5%] patients, respectively).

In each of the FKB238 and Avastin treatment arms, 1 SAE of potential Hy's Law was identified based on reported AE verbatim terms of "Hys law" (PTs of drug-induced liver injury were reported).

Laboratory results of 2 additional patients fulfilled Hy's law criteria on 1 or more occasions (one in each treatment arm); however, AEs of Hy's law were not reported for either of these patients.

Vital signs

In Study FKB238-002, across both the FKB238 and Avastin treatment arms, there were only minor changes in vital signs parameters over time. The incidence of clinically relevant vital signs values was low in both treatment arms, with a similar incidence of TEAEs pertaining to abnormal vital sign values reported in both treatment arms.

Electrocardiogram

In Study FKB238-002, there were no notable differences between the treatment arms in ECG findings. Only small proportions of patients in the FKB238 and Avastin treatment arms with a normal ECG at baseline had an ECG that worsened to an abnormal, clinically relevant finding at the end of treatment (6/223 [2.7%] and 4/193 [2.1%] patients, respectively). The incidence of clinically relevant ECG values was low in both treatment arms, with a similar incidence of TEAEs pertaining to abnormal ECG values reported in both treatment arms. These included TEAEs of electrocardiogram QT prolonged (0.6% and 0.8% of patients in the FKB238 and Avastin arms, respectively), electrocardiogram QT shortened (0.3% and 0%), and electrocardiogram repolarisation abnormality (0.8% and 1.1%). Additional reported TEAEs within the SOC of cardiac disorders are discussed under the TEAE of special interest medical concepts.

Physical examination

In Study FKB238-002, the majority of patients in both treatment arms had normal findings on physical examination at baseline. The only notable exception was for the respiratory system, for which approximately half of patients had an abnormal baseline assessment in both treatment arms. In both treatment arms, only small numbers of patients (<16%) with a normal baseline physical examination had an abnormal finding during treatment. Of note, per the protocol any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment was to be reported as an AE.

Left ventricular ejection fraction

In Study FKB238-002, there were no notable differences between the treatment arms in LVEF findings. Of the patients with a post-baseline LVEF assessment, only 1 patient (in the Avastin arm) had an LVEF decrease of ≥10 percentage points and an absolute value of <50%, and across both treatment arms, small numbers of patients had an LVEF decrease of ≥15 percentage points and an absolute value of ≥50% (7 [1.9%] and 3 [0.8%] patients, respectively).

Pharmacokinetic Studies FKB238-001

No notable trends were observed in clinical laboratory data in Study FKB238-001. There were a few variations in the mean values for the haematology, biochemistry, and urinalysis parameters when compared to baseline evaluations, but no notable trends were observed across the 3 treatment groups.

Safety in special populations

The effect of intrinsic factors on the safety of FKB238 has not been formally investigated.

Immunogenicity

The applicant submitted an Integrated Summary of Immunogenicity (ISI).
The extent of the evaluation of relative immunogenicity was based on the following considerations:
• Nature of risks identified for the reference medicinal product bevacizumab (Avastin) in different populations.
• Sensitivity of methodology to detect clinically relevant differences in immunogenicity between the biosimilar and reference medical product, particularly in terms of the need to apply suitably drug and target tolerant ADA (anti-drug antibodies) and Nab (neutralising Anti-drug antibody) assays.
• Scale of product quality differences and the associated uncertainty about impact on immunogenicity-related risks.
• Responses received from concerned regulatory agencies during clinical development of FKB238.

FKB238-002 study in NS-NSCLC patients

Table 47: ADA sampling time-points in study FKB238-002

Day	Study Treatment Period (all visits within ± 3 days of schedule)									Study treatment discontinuation (±7 days)	Follow-up
	Cycle 1			Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5 Day 1	Cycle 6 Day 1	Cycle 7 & sub-sequent cycles Day 1		
	Day 1	Day 8	Day 15								
Visit	2	3	4	5	6	7	8	9	Visit 10 onwards		
Drug admin.	X			X	X	X	X	X	X		
ADA [1,2]	X			X		X		X		X	X[2]
Drug conc. [2,3,4]	X			X[4]		X[4]		X		X	X[2]

Abbreviations: ADA=Anti-Drug Antibody; conc. = Concentration
1 Pre-dose at Cycles 1, 2, and 4, Cycle 6, study treatment discontinuation visit, and Follow-up period.
2 Follow-up samples scheduled every 12 weeks (up to 1 year [± 14 days] after randomization) until death, or loss of patient to follow-up, whichever occurred first.
3 Pre-dose at Cycles 1, 2, and 4, Cycle 6, study treatment discontinuation visit, and Follow-up period.
4 Additional samples immediately after completion of IP infusion on Cycles 1 and 4 were required.

A total of 731 eligible patients were randomly assigned in a 1:1 ratio to receive either:

- FKB238 group: paclitaxel + carboplatin (combination drugs) + FKB238; or
- Avastin group: paclitaxel + carboplatin (combination drugs) + EU-Avastin

Number of subjects for whom ADA samples were available (table below).

Table 48: ADA test results for study FKB238-002 as proportion of number of patients treated

Time-point	No. Patients that had Protocolled Sampling Visits	No. of patients ADA sample received at central lab	Number of samples available with ADA test result (% of total)		
			FKB238	EU-Avastin	Total
Cycle 1 Day 1	731	721	328	328	656
Cycle 2 Day 1	686	677	312	310	622
Cycle 4 Day 1	610	592	273	275	548
Cycle 6 Day 1	535	519	240	245	485
Study discontinuation	653	430	200	200	400
Follow-up Week 12	123	110	53	55	108
Follow-up Week 24	56	53	24	26	50
Follow-up Week 36	22	19	5	12	17
Follow-up Week 48	4	4	1	3	4
Unscheduled visit	N/A	N/A	6	3	9
Total	3420	3125	1442	1457	2899

Abbreviations: N/A=Not Applicable.
Source: Quality issue report 174758, Table 14.1.1 Patient Disposition, CSR Study FKB238-002, Module 5.3.5.1, adis,sas7bdat.

Proportion of false positives in ADA sample testing

Based on the assay cut points shown, the overall (i.e. including pre- and post-treatment samples) False Positive Error Rate (FPER) was 60.5% in the FKB238 treatment group and 61.3% in the EU-Avastin treatment group respectively (as shown in the table below).

Table 49: False positive rate for ADA test results in study FKB238-002

Statistics	Treatment group		Overall
	FKB238	EU-Avastin	
Total number of samples screened	1442	1457	2899
Number of samples screened Positive	884	906	1790
Number of samples confirmed Positive	11	13	24
Number samples confirmed Negative	871	891	1762
Screening False Positive Rate [a]	98.5%	98.3%	98.4%
FPER [b, c]	60.5%	61.3%	60.9%

a Screening False Positive rate = (No. of samples confirmed negative / No. of samples screened positive) x 100

b FPER = [(# of samples screened positive - # of samples confirmed positive) / Total sample #] x 100

c Confirmatory cut point was based on a 1% false positive rate with modified outlier exclusion approach

Source: CSR Study FKB238-002, Module 5.3.5.1, adis,sas7bdat. Samples with no reportable value are removed from this calculation; 6 samples for screening assay, 4 samples for confirmatory assay due to insufficient volume.

The false positive error rate (FPER) was much lower for the pre-dose samples (5.6%) compared with the post-dose samples (approx. 60%), consistent with the putative VEGF interference effect only in the post-dose samples. A modified outlier approach was used to calculate a confirmatory cut point using a 1% false positive rate applied to the pre-study validation cut point dataset. Based on application of the confirmatory cut point of 50.9% inhibition to the results for the 656 pre-dose samples tested in the ADA assay, of which 41 samples screened positive, 4 pre-dose samples (0.6% of total) were confirmed as positive.

ADA results

Confirmed ADA positive signals were detected in nine subjects (3.0% of the ADA Evaluable Population) in both the FKB238 and EU-Avastin treatment groups. Treatment-emergent ADA was detected in seven subjects (2.3% of the ADA evaluable population) in each group. Only one (0.3% of the ADA evaluable population) of these confirmed positive samples in the FKB238 treatment group, and three (1.0% of the ADA evaluable population) samples in the EU-Avastin treatment group, met the criteria of "persistent positive". The highest treatment-emergent ADA titer was 16, and ADA titer distribution was similar for the FKB238 and EU-Avastin treatment groups.

The table below provides a summary of the results from ADA and NAb testing of clinical samples from study FKB238-002. The results are from the clinical analyses dataset and are based on the assay cut points using the modified approach for outlier exclusion.

Table 50: Summary of ADA and NAb responses during study FKB238-002 by treatment group (ADA Evaluable Population)

Category	EU-Avastin (N=305)	FKB238 (N=305)
ADA prevalence (any ADA positive, baseline or post-baseline)		
n (%) [e]	9 (3.0)	9 (3.0)
Median of maximum titer [a]	2	3
Min - Max	<2 – 4	<2 - 64
Treatment-emergent ADA positive (ADA incidence) [d]		
n (%) [e]	7 (2.3)	7 (2.3)
Median of maximum titer [a]	3	2
Min - Max	<2 – 4	<2 - 16
ADA positive post-baseline and positive at baseline		
n (%) [e]	0	1 (0.3)
Median of maximum titer [a]		64
Min - Max		64 - 64
Treatment-induced ADA (ADA positive post-baseline only)		
n (%) [e]	7 (2.3)	7 (2.3)
Median of maximum titer [a]	3	2
Min - Max	<2 – 4	<2 - 16
ADA positive at baseline only		
n (%) [e]	2 (0.7)	1 (0.3)
Median of maximum titer [a]	<2	4
Min - Max	<2 - 2	4 - 4
Treatment-boosted ADA [c]		
n (%) [e]	0	0
Median of maximum titer [a]		
Min - Max		
Persistent positive [b]		
n (%) [e]	3 (1.0)	1 (0.3)
Median of maximum titer [a]	4	16
Min - Max	2 - 4	16 - 16
Transient positive [b]		
n (%) [e]	4 (1.3)	7 (2.3)
Median of maximum titer [a]	2	2
Min - Max	<2 - 4	<2 - 64
NAb positive at any visit		
n (%) [e]	1 (0.3)	1 (0.3)
Median of maximum titer [a]	4	64
Min - Max	4 - 4	64 - 64

Abbreviations: ADA=Anti-Drug Antibody; NAb=Neutralizing Antibody; min=Minimum; max=Maximum

Note: Baseline is defined as the last non-missing result prior to the first dosing. ADA prevalence is defined as the proportion of patients with positive ADA result at any time, baseline or post-baseline. [a] If a patient has more than one titer result, the maximum titer result is used whether it is baseline or post-baseline. A titer value of <2 denotes a sample which was tested positive in the confirmatory assay but failed to register a titer above the first dilution of 2. [b] Persistent positive is defined as positive at >=2 post-baseline assessments (with >=16 weeks between first and last positive) or positive at last post-baseline assessment. Transient positive is defined as having at least on post-baseline ADA positive assessment and not fulfilling the conditions of persistent positive. [c] Treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to a 4-fold or higher level following drug administration. [d] Treatment-emergent ADA positive is defined as either treatment-induced ADA or treatment-boosted ADA. ADA incidence is the percentage of treatment-emergent ADA positive patients. [e] Denominator is the number of ADA evaluable subjects in the treatment group.

Impact of ADA on systemic drug concentration

The number of subjects with confirmed ADA positive results was low in each treatment group. The results are summarised in the table below.

Table 51: Summary of serum concentrations (µg/mL) of FKB238 and Avastin by ADA Category - Subgroup - ADA Evaluable Population (Pharmacokinetics Population)

Visit	EU-Avastin (N=305)			FKB238 (N=305)		
	ADA positive	Treatment-emergent ADA positive	ADA negative	ADA positive	Treatment-emergent ADA positive	ADA negative
Cycle 1 day 1 Pre-infusion						
n	9	7	296	9	7	294
Mean	BLQ	BLQ	NC	NC	NC	NC
SD	NC	NC	NC	NC	NC	NC
Median	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
(Min, Max)	(BLQ, BLQ)	(BLQ, BLQ)	(BLQ, BLQ)	(BLQ, BLQ)	(BLQ, BLQ)	(BLQ, BLQ)
Cycle 2 day 1 Pre-infusion						
n	9	7	290	9	7	291
Mean	34.772	33.487	58.096	37.397	36.117	50.732
SD	16.5449	16.3629	32.7664	21.7115	23.0876	22.3465
Median	28.340	28.340	56.295	41.280	41.280	50.110
(Min, Max)	(12.16, 62.67)	(12.16, 62.67)	(0.05, 373.58)	(0.76, 62.54)	(0.76, 62.54)	(0.1, 129.22)
Cycle 4 day 1 Pre-infusion						
n	7	5	257	8	6	255
Mean	71.977	72.080	98.449	79.133	77.717	86.266
SD	31.2715	29.9491	48.8408	26.7297	31.4014	32.6832
Median	62.830	62.830	96.010	85.870	86.165	86.260
(Min, Max)	(37.96, 106.04)	(43.82, 106.04)	(0.1, 513.72)	(31.27, 114.24)	(31.27, 114.24)	(0.1, 235.8)
Cycle 6 day 1 Pre-infusion						
n	4	2	231	7	5	227
Mean	73.535	88.715	123.161	87.930	86.804	105.574
SD	26.7104	26.0710	54.7605	20.2324	24.2572	48.6940
Median	72.525	88.715	117.840	84.410	84.330	99.480
(Min, Max)	(41.94, 107.15)	(70.28, 107.15)	(0.1, 449.96)	(55.52, 111.01)	(55.52, 111.01)	(0.1, 347.6)

Abbreviations: ADA=Anti-Drug Antibody; BLQ=Below Lower Limit of Quantification; NC=Not Calculable; SD=Standard Deviation; min=Minimum; max=Maximum

Note: n = number of subjects in ADA evaluable population with at least one serum drug concentration value, excluding pre-dose values after cycle 1 without IP dose in previous cycle, excluding post-dose values without IP dose in this cycle.

ADA positive population includes subjects who do have any ADA positive results at baseline or post-baseline. Treatment-emergent ADA positive is defined as either treatment-induced ADA (post-baseline ADA positive only) or treatment-boosted ADA. Treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to a 4-fold or higher level following drug administration.

ADA negative population includes subjects who do not have any ADA positive results at baseline or post-baseline.

Study FKB238-001

The chosen dose level of FKB238 and Avastin (5 mg/kg given intravenously) was the lowest recommended therapeutic dose for the licensed indications. This dose has a well-established safety profile in patients and according to the applicant was appropriate to give to healthy subjects (in accordance with EMA Guideline EMA/CHMP/BMWP/403543/2010).

Confirmed ADA positive samples were detected in only four subjects: in pre-treatment samples from one subject in the FKB238 treatment group and from two subjects in the EU-Avastin treatment group; and in the Day 15 post-treatment samples from one subject in the US-Avastin treatment group (Table 52).

Table 52: Summary of subjects with confirmed ADA positive results in at least one of the ADA assay formats used for study FKB238-001 sample analysis

		Confirmatory ADA assay			ADA titer assay			NAb assay		
Subject No.	Day	FKB238	EU-Avastin	US-Avastin	FKB238	EU-Avastin	US-Avastin	FKB238	EU-Avastin	US-Avastin
Treatment = FKB238										
043	Pre-dose	P	P	P	1	4	1	P	N	N
Treatment = EU-Avastin										
027	Pre-dose	P	P	N	1	1	-	P	N	-
085	Pre-dose	P	P	P	1	1	1	P	N	N
Treatment = US-Avastin										
082	15	P	P	P	4	16	16	P	N	N

Abbreviations: ADA=Anti-Drug Antibody; NAb=Neutralising Antibody; P=Positive; N=Negative

Source: Tables 1, 2 and 3 in Bioanalytical Study Report, No. 238-CA14-008, Appendix 16.1.10 of CSR Module 5.3.3.1

Study FKB238-003

The bioanalytical study in Japanese healthy volunteers, FKB238-003, where the PK-profile of FKB238 were compared to EU-Avastin, confirmed the low immunogenicity potential of FKB 238.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

No TEAEs led to the premature discontinuation of subjects from Studies FKB238-001 and FKB238-003.

In Study FKB238-002, similar proportions of patients in the FKB238 and Avastin arms experienced TEAEs leading to discontinuation of IP (9.9% and 11.2%, respectively), discontinuation of any combination drugs (11.6% and 10.1%), and discontinuation of study treatment overall (IP and/or any combination drugs) (15.2% and 15.8%). Likewise, similar proportions of patients in the FKB238 and Avastin arms experienced TEAEs leading to discontinuation of IP that were considered related to IP (3.9% and 4.9%, respectively), TEAEs leading to discontinuation of any combination drugs considered related to any combination drugs (9.4% and 6.8%), and TEAEs leading to discontinuation of study treatment considered related to study treatment (11.3% and 11.2%).

Of the 20 patients with an IP dose interruption, 13 patients interrupted IP due to an AE. Of the 381 patients with an IP cycle delay, 219 patients delayed due to an AE and 43 patients delayed due to delayed haematological recovery. The incidence of patients who interrupted or delayed IP due to an AE or due to delayed haematological recovery was similar between the treatment arms.

Of the patients who had a dose interruption, reduction, or delay for any combination drugs (248 and 232 patients for paclitaxel and carboplatin, respectively), the majority did so due to an AE. The incidence of patients who had any combination drug dose interruption, reduction, or delay due to an AE was similar between the treatment arms.

The number of discontinuations due to AEs causally related to treatment was slightly higher in the EU-Avastin arm, and the number of fatal TEAEs was higher in the FKB238 arm.

Post marketing experience

FKB238 is not yet approved in any country worldwide in any indication. Thus, there are no post-marketing data available for the use of FKB238.

2.6.1. Discussion on clinical safety

Comparative safety data of FKB238 was derived from two PK studies in healthy volunteers (study FKB238-001 and study FKB238-003) and one phase III study in 1st line treatment for patients with advanced/recurrent non-squamous non-small cell lung cancer in combination of paclitaxel and carboplatin (FKB238-002)

Overall, these studies constitute a total safety database for FKB238 of 415 subjects, including 33 healthy male subjects who received a single dose of FKB238 in Study FKB238-001, 20 Japanese healthy male subjects who received a single dose of FKB238 in Study FKB238-003 and 362 patients treated for advanced/recurrent NS-NSCLC.

In study FKB238-002, four protocol amendments were conducted of which the third protocol amendment was conducted on 12th April 2017 after the enrolment of the study participants. The amendments were justified and did not interfere with the safety assessment.

The overall duration of exposure to investigational product [IP; FKB238 or Avastin] in Study FKB238-002 was mean 35.61 weeks, range 0.3 to 111.4 weeks.

Adverse events:

In the PK- study FKB238-001, more subjects experienced TEAEs in the FKB238 arm (32; 97.0 %) compared to the Avastin arms (26; 76.5 % EU-Avastin and 23; 71.9 % US-Avastin). The TEAE PT reported for the highest proportion of subjects was headache (32.3% of subjects overall). There was a rather large imbalance in the incidence of headache events across the treatment arms, which were reported for 16 (48.5%), 6 (17.6%), and 10 (31.3%) subjects in the FKB238, Avastin, and US-Avastin arms, respectively. The safety concerns regarding the relatively high proportion of reported AEs of headache have been addressed adequately. The reported AEs of headache were transient and non-serious, and no connection or clinical pattern could be detected to any serious development of a medical condition. Of note, in Study FKB238-002, the PT of headache was reported for a similar proportion between treatment arms; 18 (5.0%) and 23 (6.3%) in the FKB238 and Avastin arms, respectively.

The number of subjects reporting TEAEs in PK-study FKB238-003 was also higher in the FKB238-arm compared to the Avastin-arm (12; 60% vs. 6; 30%, respectively). A thorough examination of reported TEAEs and TEADRs for studies FKB238-001 and -003 have been provided. Considering the small numbers of subjects in each treatment arm of this study, a small number of events can make a large apparent difference in reporting rate, and in particular when multiple events are reported by the same patient.

The two PK-studies are small studies not primarily designed for safety evaluations, and the observed differences between treatment groups are most likely chance findings.

Overall in the main study FKB238-002, similar proportion of patients experienced at least 1 TEAE between the FKB238 and Avastin treatment arms (94.2% and 95.1% of patients, respectively).

TEAEs considered causally related to IP (FKB238 or Avastin) were most frequently reported in the SOCs of blood and lymphatic system disorders (13.7% of patients overall), investigations (13.0%), skin and subcutaneous tissue disorders (9.3%), and general disorders and administration site conditions (9.1%). The incidence of any TEAEs causally related to IP was somewhat lower in the FKB238 arm than in the

Avastin arm (40.9% versus 47.5% of patients, respectively), as was the incidence of TEAEs causally related to any combination drugs (82.3% versus 84.4% of patients, respectively). Overall, the incidence of TEAEs causally related to study treatment (IP and/or any combination drugs) was balanced between the treatment arms (85.4% and 86.1% of patients, respectively) and no clinically meaningful differences were seen.

A clearly higher frequency of anaemia and neutropenia was reported in the EU-Avastin arm compared to the FKB238 arm. Also, asthenia and proteinuria were more commonly seen in this EU-Avastin arm.

No TEADRs were reported with a difference in incidence between the treatment arms of >5%. The greatest difference between the treatment arms was seen for TEADRs of neutropenia, which were reported as IP-related for more patients in the Avastin arm than in the FKB238 arm (29 [7.9%] versus 14 [3.9%] patients, respectively). The proportion of patients receiving combination chemotherapy at each cycle was higher in the Avastin arm compared to the FKB238 arm and concomitant chemotherapy might influence both neutrophil count and reduce renal function (leading to proteinuria).

The proportions of patients with CTCAE ≥grade 3 TEAEs (53.6% and 55.5% of patients, respectively) and CTCAE ≥grade 3 TEAEs considered related to IP (11.0% and 13.7% of patients, respectively) were also similar between the treatment arms.

TEAEs leading to discontinuation of IP were reported for 36 (9.9%) and 41 (11.2%) patients in the FKB238 and Avastin arms, respectively, with TEAEs leading to discontinuation of IP considered related to IP for 14 (3.9%) and 18 (4.9%) patients, respectively.

Overall, in the pivotal study FKB238-002, only slight numeric imbalances in reporting of individual TEAEs were observed. For example, the incidence of TEAEs in the SOC of blood and lymphatic disorders was lower in the FKB238 arm (55.2%) than in the Avastin arm (59.0%), whereas the incidence of TEAEs in the SOC of gastrointestinal disorders was higher in the FKB238 arm than in the Avastin arm (31.8% versus 29.5%, respectively). For most SOCs, there seem to be slightly more patients reporting TEAEs in the Avastin-arm compared to the FKB238-arm. However, there was no clear pattern in the most commonly reported TEAEs (≥5%) to suggest any difference in the safety profile between FKB238 and Avastin.

Adverse events of special interest derived from the Avastin SmPC were investigated. The overall incidence of TEAEs of special interest was generally similar between the FKB238 and Avastin treatment arms (266 [73.5%] and 280 [76.5%] patients, respectively), and in line with frequency stated for Avastin SmPC, but some differences were observed.

Slightly more patients in the FKB238 arm compared to Avastin arm experienced hypersensitivity/IRR events (48 vs 43 patients respectively). The events that were reported within a relevant timeframe for a hypersensitivity/IRR had a similar distribution over treatment arms (17 in the FKB238-arm and 13 in the Avastin-arm). None of the events was serious AEs.

Deaths and serious adverse events:

There were no SAEs, including deaths, during Studies FKB238-001 and FKB238-003.

Overall, the frequency of SAEs in study FKB238-002 is similar between treatment arms. Small differences are seen on the SOC/PT level but are considered not to be clinically meaningful.

As of data cut-off, there were 18 more deaths observed in the FKB238 arm (195 [53.9%] patients) compared to the Avastin arm (177 [48.4%] patients). Approximately 40% of patients' deaths in both the FKB238 and Avastin arms occurred more than 30 days after the last study treatment (IP and/or any combination drugs) (151 [41.7%] and 137 [37.4%] patients, respectively). The majority of deaths were related to the disease under investigation: 156 and 148 patients in the FKB238 and Avastin arms,

respectively. The number of TEAEs with a fatal outcome was 30 (8.3%) versus 23 (6.3%) for FKB238 and Avastin, respectively.

Due to the difference in deaths between study arms, the applicant has performed a thorough evaluation of all deaths in study FKB238-002.

Baseline data for the ITT-population show imbalances in demography and baseline characteristics ($\Delta \approx$ 3-11% with regards to more current smokers, more patients with a past and current medical history of cardiovascular conditions, more patients with current respiratory conditions, and smaller number of patients who received subsequent anti-cancer therapy in the FKB238 arm) indicating that patients in the FKB238 arm had a higher background risk of death than those in the Avastin arm.

Fewer patients withdrew consent to follow-up in the FKB238 arm compared to the Avastin arm, 36 [9.9%] patients versus 49 [13.4%] patients, respectively. The survival status of 13 more subjects in the Avastin arm as compared to the FKB238 arm is unknown due to withdrawal of consent and subsequently lost information on survival. Therefore, some deaths in the Avastin group might possibly not have been recorded. TEAEs leading to discontinuation of study treatment were reported for a higher proportion of withdrawal of consent (WoC)-patients in the Avastin arm than in the FKB238 arm (8 [16.3%] versus 2 [5.7%] patients, respectively), as were TEAEs with CTCAE grade 3 or higher (24 [49.0%] versus 14 [40.0%] patients, respectively) and treatment-emergent SAEs (11 [22.4%] versus 5 [14.3%] patients, respectively). Baseline characteristics for the 85 patients who discontinued due to WoC (FKB238, 36; Avastin, 49) showed that a higher proportion of patients had AJCC stage IV disease at diagnosis in the Avastin arm than in the FKB238 arm (47 [95.9%] versus 31 [86.1%] patients, respectively). Additionally, a higher proportion of patients were aged ≥65 years in the Avastin arm than in the FKB238 arm (18 [36.7%] versus 10 [27.8%] patients, respectively), with 6 (12.2%) patients in the Avastin arm aged between 75 and 84 years compared to no patients in the FKB238 arm. The proportion of current smokers for this group of patients was also slightly higher in the Avastin arm than in the FKB238 arm (19 [38.8%] versus 12 [33.3%] patients, respectively), as was the proportion of patients with an ECOG PS of 1 (24 [49.0%] versus 17 [47.2%] patients, respectively).

Overall, patients in the Avastin arm who withdrew consent to the study had a worse AE profile, worse prognostic factors and thereby a higher risk of death, than those in the FKB238 arm. More patients in the Avastin arm than the FKB238 arm withdrew following AEs and PD. Thus, some deaths might not have been recorded.

In order to investigate the impact of the missing survival data on the reliability of the OS estimation, the MAH performed a post-hoc sensitivity analysis in which discontinuation from the study due to WoC was considered as a death event.

The estimated hazard ratio (HR) from this sensitivity analysis is 1.09 (95% confidence interval [CI]: 0.90 to 1.31), which is lower than the value obtained in the pre-specified analysis (1.18 [95% CI: 0.96 to 1.45]). Median OS in the FKB238 and Avastin treatment arms using the sensitivity analysis were 12.25 months and 13.40 months, respectively. This sensitivity analysis shows that the higher numbers of WoC in the Avastin arm relative to the FKB238 arm could have introduced non-negligible bias into the pre-specified OS analysis, thereby resulting in an overestimated HR.

<u>Immunogenicity:</u>

The bioanalytical methods regarding ADAs are considered of good quality and appropriately validated.

Immunogenicity of FKB-238 versus EU-Avastin was low with a similar number of ADA positives in each arm. No ADA positive samples were detected after cycle six (or EoT), with most treatment–emergent ADA being transient in both groups.

A substantial number of patients with missing ADA results at different time points conferred uncertainty to the similarity between arms regarding immunogenicity. The applicant has adequately justified that the missing ADA samples would not have had any impact on the biosimilarity assessment, and that ADA measurements were balanced between treatment arms.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of FKB238 is comparable to EU-Avastin and is in line with the safety profile for bevacizumab (SmPC Avastin).

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Not applicable as there are no safety concerns

Risk minimisation measures

Not applicable as there are no safety concerns

Conclusion

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

2.8. 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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Equidacent (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

Equidacent, FKB238 (bevacizumab), has been developed as a biosimilar to the reference product Avastin. The administration and posology are according to the reference product, as described in the Avastin SmPC.

FKB238 is claiming the same indications as authorised for the reference product Avastin, except for one indication concerning platinum-resistant ovarian cancer, which was excluded due to patent restrictions:

- Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.
- Bevacizumab 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 (HER2) status.
- Bevacizumab in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine.
- Bevacizumab, 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.
- Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.

- Bevacizumab in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer.
- Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynaecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- Bevacizumab, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.
- Bevacizumab, 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.

Summary of analytical comparability (quality data)

Both FKB238 active substance lots and FKB238 finished product lots were used for similarity studies, which is considered acceptable as high comparability between the active substance and the finished product has been demonstrated. Furthermore, the same formulation is used for both active substance and finished product, only the concentrations and the containers differ. FKB238 was compared to both EU-approved Avastin lots and US-licensed Avastin lots at 100 mg and 400 mg concentrations. The analytical comparability studies included comparisons of primary, secondary and higher order structures, post-translational modifications (charge variants and glycan profiles), purity and impurities, quantity, biological activity for Fab and Fc related functions, and comparative stability studies.

Summary of non-clinical data

The FKB238 non-clinical programme consisted of a number of *in vitro* assays, an *in vivo* study in SCID mice, a single dose toxicity study in mice and a 2-week repeat-dose toxicity study in Cynomolgus monkeys. All studies were done in comparison with Avastin. In addition, a 2-week repeat dose toxicity study with only FKB238 were performed in rats.

Summary of clinical comparability data

The PK similarity between FKB238 and both EU- and US-sourced bevacizumab (Avastin) was investigated in a pivotal phase I clinical trial in healthy male subjects (FKB238-001). In addition, PK similarity of FKB238 and EU-Avastin was also investigated in a phase I trial in healthy Japanese males (FKB238-003).

A total of 99 healthy males were randomised to receive FKB238, EU-Avastin and US-Avastin in FKB238-001, and 40 healthy Japanese males were randomised to FKB238 or EU-Avastin in FKB238-003. The co-primary endpoints were that 90% CIs of log ratio test/reference of AUC0-∞ and AUC0-t were between 80-125%.

The clinical efficacy and safety program to demonstrate equivalence between FKB238 and the reference product EU-Avastin (bevacizumab) in combination with paclitaxel and carboplatin is based on a single randomised, double blind, comparative, phase 3 study in first line patients with advanced or recurrent non-squamous NSCLC, FKB238-002.

731 patients were randomised to receive FKB238 or EU-Avastin in combination with 4-6 cycles of chemotherapy (paclitaxel/carboplatin). After chemotherapy was completed the investigational product was continued as monotherapy until PD or other criteria for treatment discontinuation are met. At data cut-off, all patients had been followed for at least 12 months. The primary endpoint was ORR defined as BOR. The equivalence margin for the risk difference of ORR was defined to be ± 0.1221. Other endpoints were secondary efficacy outcomes, safety, immunogenicity and pharmacokinetics.

The design of the phase 1 and phase 3 studies has been discussed in two CHMP scientific advice (SA) from 2015 (EMA/CHMP/SAWP/169264/2015 and EMA/CHMP/SAWP/819725/2015). From a PK, efficacy and safety point of view the applicant mostly followed the CHMP SA.

3.2. Results supporting biosimilarity

Quality data

Both FKB238 active substance lots and FKB238 finished product lots were used for similarity studies and high comparability between the active substance and the finished product has been demonstrated. Furthermore, the same formulation is used for both active substance and finished product, only the concentrations and the containers differ. FKB238 was compared to both EU-approved Avastin lots and US-licensed Avastin lots at 100 mg and 400 mg concentrations. The analytical comparability studies included comparisons of primary, secondary and higher order structures, post-translational modifications (charge variants and glycan profiles), purity and impurities, quantity, biological activity for Fab and Fc related functions, and comparative stability studies.

FKB238 is considered to be highly similar to EU-licensed Avastin with respect to the presented physicochemical and biological characteristics.

Non-clinical data

A number of in vitro functional assays were conducted to substantiate similarity between FKB238 and the European reference product Avastin. The assays included binding to VEGF isoforms, Fcγ receptors, FcRn and C1q, neutralisation of VEGF signal transduction (reporter gene assay) and neutralisation of VEGF induced cell proliferation of HUVEC. In addition, ADCC and CDC activities were investigated. Further, pharmacokinetic and toxicological properties of FKB238 and bevacizumab (EU and US) were characterised in rats (single dose), SCID mice (US Avastin only) and in a GLP 4-week repeat dose toxicity study in cynomolgus monkey. A 2-week repeat dose toxicity study were also performed in rats, which only evaluated TK parameters of FKB238.

Generally, the data presented by the applicant indicate similarity between FKB238 and Avastin.

Clinical data

Pharmacokinetics

In the two PK similarity trials, the PK ratios of the co-primary endpoints ($AUC_{0-\infty}$ and AUC_{0-T}) and secondary endpoints (C_{max} and $t_{1/2}$) were within the predefined 90% CI of the log ratio FKB238/EU-Avastin within 80 to 125%.

Efficacy

For the primary endpoint ORR (BIRC assessment of PPS), similar outcomes were reported across the two arms (51.7 % [95% CI: 46.35 to 57.03] and 53.4% [95% CI: 48.04 to 58.68] in the FKB238 and EU-Avastin arms, respectively). The difference in ORR was -0.02 and inside the pre-defined equivalence margin of ±0.1221.

The ORR by BICR assessment for the ITT population and ORR by investigator assessment (PPS) showed similar outcome as the primary analysis.

Secondary endpoints ORR at week 19, PFS, DOR and DCR (BIRC assessment of PPS) were all in line with the outcome of the primary analysis.

Safety

For the pivotal study FKB238-002, some slight numeric imbalances in reporting of individual TEAEs were observed. The incidence of TEAEs in the SOC of blood and lymphatic disorders was lower in the FKB238 arm (55.2%) than in the Avastin arm (59.0%), whereas the incidence of TEAEs in the SOC of gastrointestinal disorders was higher in the FKB238 arm than in the Avastin arm (31.8% versus 29.5%, respectively). For the other SOCs, small differences were observed. In conclusion, there was no clear pattern in the most commonly reported TEAEs (≥5%) to suggest any difference in the safety profile between FKB238 and Avastin.

As of data cut-off, there were 18 more deaths observed in the FKB238 arm (195 [53.9%] patients) compared to the Avastin arm (177 [48.4%] patients). Baseline data for the ITT-population show imbalances in demography and baseline characteristics ($\Delta \approx$ 3-11% with regards to more current smokers, more patients with a past and current medical history of cardiovascular conditions, more patients with current respiratory conditions, and smaller number of patients who received subsequent anti-cancer therapy in the FKB238 arm).

Immunogenicity

The ADA prevalence was 3.0% in both treatment arms (9 out of 305 ADA evaluable patients in each arm tested positive for ADA at any visit). The detected ADA incidence (FKB238-001,-002, -003) seems to correspond to what was reported by the originator company for EU-Avastin in earlier clinical studies, and the titres measured in confirmed ADA positive samples in the phase 3 patient study (FKB238-002), seem relatively low (maximum titre value = 64).

Overall, there were no apparent differences in any of the immunogenicity-related parameters that were evaluated in study FKB238-002.

3.3. Uncertainties and limitations about biosimilarity

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

3.4. Discussion on biosimilarity

The Applicant has analysed the similarity between FKB238 and EU-approved Avastin in a comprehensive comparability exercise. High similarity was demonstrated for most of the physicochemical parameters. Some minor differences were detected for some of the parameters, which were appropriately discussed and justified by the applicant not to have a clinical impact. High similarity was demonstrated for most of the *in vitro* functional parameters, including for critical parameters such as binding to target VEGF-A and neutralisation of VEGF activities. Differences were noted in binding affinity of FKB238 to FcγRIIIa (F, V) and FcγRIIIb (NA1, NA2) in comparison to EU-approved Avastin. These binding differences are likely caused by the different levels of afucosylated glycan species, and the applicant conducted a risk analysis for the differences in binding activity against FcγRIIIa. The lack of ADCC and CDC effector functions was demonstrated in FKB238, similar to EU-approved Avastin. Taking into consideration the mode of action for bevacizumab and similar PK profile, the observed differences in binding affinity are not considered clinically meaningful.

PK similarity between FKB238 and EU-Avastin has been demonstrated in two PK similarity ("bioequivalence") trials.

The pivotal phase 3 clinical efficacy and safety study was adequately designed and the primary and secondary efficacy outcomes and equivalence criteria are deemed acceptable. The primary efficacy data was supportive of biosimilarity between FKB238 and EU-Avastin and sustained by the majority of secondary endpoints. Furthermore, the safety data pivotal study of the most commonly reported TEAEs (≥5%) was not suggestive of any difference in the safety profile between FKB238 and Avastin. There was an imbalance in the number of deaths between treatment arms FKB238 arm (n=195 [53.9%] FKB238 arm, n=177 [48.4%] Avastin arm). At the same time the baseline data for the ITT-population showed imbalances in demography and baseline characteristics and a smaller number of patients who received subsequent anti-cancer therapy in the FKB238 arm which could indicate that patients in the FKB238 arm had a higher background risk of death than those in the Avastin arm.

Fewer patients withdrew consent to follow-up in the FKB238 arm compared to the Avastin arm, 36 [9.9%] patients versus 49 [13.4%] patients, respectively. Patients in the Avastin arm who withdrew consent to the study had a worse AE profile, worse prognostic factors and thereby a higher risk of death, than those in the FKB238 arm. Thus, some deaths might not have been recorded and the risk of this was higher in the Avastin arm.

Post-hoc sensitivity analyses to investigate the impact of the withdrawal of consent (WoC) patients on OS were presented, and the resulting HR is brought closer to 1. This sensitivity analysis indicates that the higher numbers of WoC in the Avastin arm relative to the FKB238 arm could have introduced non-negligible bias into the pre-specified OS analysis, thereby resulting in an overestimated HR. Also, separation of the OS-Kaplan-Meier curves in these patients who withdrew consent seemed to occur approximately at the same time point (at 3-4 months) as seen in the Kaplan-Meier curve for the OS in the overall ITT population, hence being a possible contributing factor for the numerical OS-difference.

In conclusion, the numerical difference in deaths between study arms might be explained by several confounding factors and is not considered a real difference in biosimilarity.

Overall, the Applicant has provided a thorough comparative exercise in terms of quality, non-clinical, and clinical parameters in line with the EU guidance to demonstrate biosimilarity between FKB238 and Avastin. Biosimilarity has been demonstrated in quality, non-clinical and clinical (PK, efficacy and safety, including immunogenicity) data.

3.5. Extrapolation of safety and efficacy

The indications granted for the reference product Avastin were applied for Equidacent, except for one indication concerning platinum-resistant ovarian cancer, which was excluded due to patent restrictions. All indications that are applied for share the same mechanism of action. In addition, posology and route of administration are the same across all indications. Based on this, extrapolation to all EU-Avastin approved indications can be supported.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Equidacent is not similar to Zejula within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Outcome

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

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

Bevacizumab 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.

Bevacizumab in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline- containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Equidacent in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1.

Bevacizumab, 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.

Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.

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

Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Bevacizumab, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

Bevacizumab, 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.

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.

Appendix

1. CHMP AR on similarity dated 23 July 2020