28 January 2021
EMA/112177/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alymsys

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/005286/0000

Note

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

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Table of contents

List of abbreviations

µDSC	Micro Differential Scanning Calorimetry
aa	Amino Acid
ADA	Anti-drug antibody
ADCC	Antibody Dependent Cell Mediated Cytotoxicity
AE	Adverse event
AESI	Adverse events of special interest
AEX	Anion Exchange Chromatography
ALB	Albumin
ALK	Anaplastic lymphoma kinase
ALP	Aspartate aminotransferase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AT	All Treated
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve from time zero to infinity
AUC_{last}	Area under the concentration-time curve from time zero to the last quantifiable concentration
$\%AUC_{extrap}$	Area under the concentration-time curve from time t to infinity as a percentage of total AUC
BDS	Bulk Drug Substance
BLI	Biolayer interferometry
BSA	Body surface area
BPD	Biological product development
CR	Clinical complete response
CCr	Creatinine clearance
CCIT	Container Closure Integrity Test
CD	Circular Dichroism
CDC	Complement Dependent Cytotoxicity
CE	Capillary Electrophoresis
CE-SDS	Capillary Electrophoresis in Sodium Dodecyl Sulfate
CFU	Colony Forming Units
CHF	Congestive heart failure
CHMP	Committee for medicinal products for human use
CHO	Chinese Hamster Ovary

CI	Confidence interval
cIEF	Capillary Isoelectric Focusing
CIEX/CEX	Cation Exchange Chromatography
CL	Clearance
Cmax	Maximum observed concentration at tmax
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTD	Common technical document
Ctrough	Serum concentration at baseline and prior to dosing
CV	Coefficient of variation
Cys	Cysteine
df	Degree of freedom
DF/UF	Diafiltration / Ultrafiltration
DLS	Dynamic Light Scattering
DoE	Design of Experiment
DOR	Duration of response
DP	Drug Product
DS	Drug Substance
DSC	Differential Scanning Microcalorimetry
ECL	Electrochemiluminescence
ECOG	Eastern cooperative oncology group
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EoPCB	End of Production Cell Bank
EOS	End of study
EOT	End of treatment
EPAR	European public assessment report
ESI	ElectroSpray Ionisation
EU	Endotoxin Unit
ERK	Extracellular signal regulated kinases
EU	European union
FA2	Glycoform diantennary w/o 2 β-Gal w Fuc or G0F
FAS	Full analysis set
Fab	Fragment Antigen Binding

Fc	Fragment Crystallisable
FcRn	Fc Receptor Neonatal
FcγR	Fc Gamma Receptor
FcR	Fc receptor
FcRn	Neonatal Fc receptor
FcγRIa	Fc gamma receptor Ia
FcγRIIa	Fc gamma receptor IIa
FcγRIIb	Fc gamma receptor IIb
FcγRIIIa	Fc gamma receptor IIIa
FcγRIIIb	Fc gamma receptor IIIb
FDA	Food and Drug Administration
FLR	Fluorescence (detection)
FMEA	Failure Mode and Effects Analysis
F/T	Freeze-Thaw
FOLFOX-4	5-fluorouracil/leucovorin/oxaliplatin
5-FU/FA	5-fluorouracil/folinic acid
GC	Gas Chromatography
Geo	Geometric
GeoLSMean	Geometric least squares mean
GH	GH GENHELIX S.A.
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GPP	General Process Parameter
HC	Heavy Chain
HCCF	Harvested Cell Culture Fluid
HCP	Host Cell Protein
HDPE	High Density Polyethylene
HDX	Hydrogen/deuterium exchange
HHL	Heavy Heavy Light (chain fragment)
HILIC-UPLC	Hydrophilic Interaction Ultra Performance Liquid Chromatography
HLA	Human leukocyte antigen
HMW	High Molecular Weight
HQC	High quality control
HPC	High positive control
HPLC	High Performance Liquid Chromatography
HR	Hazard ratio
HRP	Horseradish peroxidase
HV	Healthy volunteers
HUVEC	Human Umbilical Vein Endothelial Cells

ICH	The international council for harmonization of technical requirements for pharmaceuticals for human use
ICF	Informed consent form
IEX	Ion Exchange Chromatography
Ig	Immunoglobulin
IgG	Immunoglobulin G
IL	Interleukin
INN	International non-proprietary name
IMP	Investigational medicinal product
IPC	In-Process Control
IPP	In-Process Parameter
IPT	In-Process Testing
ITT	Intent-to-treat
i.v. or IV	Intravenous
kDa	Kilo Dalton
kel	Elimination rate constant
λz	Terminal rate constant
LC	Light Chain
LLOQ	Lower limit of quantitation
LMV	Low Molecular Weight
LOQ	Limit of Quantitation
LSMean	Least squares mean
LTS	Long term stability
MA	Material Attribute
MAA	Marketing authorisation application
mAb	Monoclonal Antibody
Man5	Mannose 5
MB02 DS	mAbxience Drug Substance
MB02 DP	mAbxience Drug Product
MCB	Master Cell Bank
mCRC	Metastatic carcinoma of the colon or rectum
MedDRA	Medical dictionary for regulatory activities
MFI	Microflow Imaging
MHC	Major histocompatibility complex
MI	Multiple Imputation
MMV/MVM	Mouse Minute Virus
MOA	Mechanism of action
MQC	Medium quality control
MRD	Minimum required dilution

MRI	Magnetic resonance imaging
MS	Mass Spectrometry
N/A	Not available or not applicable
NAb	Neutralizing antibody
NCI CTCAE	National cancer institute common terminology criteria for adverse events
NCPP	Non-Critical Process Parameter
NeuAc	N-Acetylneuraminic acid
NeuGc	N-Glycolylneuraminic acid
NGHC	Non-glycosylated heavy chains
NHS	Normal human serum
NR	Non-Reduced
NSCLC	Non-small cell lung cancer
OFAT	One Factor At Time
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PAR	Proven Acceptable Range
PD	Pharmacodynamics
PD	Progressive disease
PETG	Polyethylene Terephthalate Glycol
PFS	Progression-free survival
PIP	Pediatric investigation plan
PK	Pharmacokinetics
PlGF	Placenta Growth Factor
PO	Polyolefin
PP	Process Parameter
PP	Per-protocol
PPQ	Process Performance Qualification
PPS	Per-protocol set
PR	Partial response
PT	Preferred term
QA	Quality Attribute
QbD	Quality by Design
QC	Quality Control
QTPP	Quality Target Product Profile
R	Reduced
RECIST	Response evaluation criteria in solid tumors version 1.1
RLU	Relative luminescence Unit
RMP	Risk management plan

RMP	Reference Medicinal Product
RP HPLC	Reverse Phase High Performance Liquid Chromatography
RPLC	Reverse Phase Liquid Chromatography
RRS	Research reference standard
SA	Scientific advice
SA	Streptavidin
SAE	Serious adverse event
SAF	Safety set
SD	Stable disease
SD	Standard Deviation
SDM	Scale-Down Model
SDS-PAGE	Sodium Dodecyl Sulphate – Polyacrylamide Gel Electrophoresis
SEC	Size Exclusion Chromatography
SE HPLC	Size Exclusion High Performance Liquid Chromatography
SmPC	Summary of product characteristics
SOC	System organ class
SPR	Surface Plasmon Resonance
SST	System Suitability Test
svAUC	Sedimentation Velocity Analytical Ultracentrifugation
t½	Terminal half life
t1/2β	Beta half life
TEAE	Treatment-emergent adverse event
Tmax	Time to reach maximum (peak) plasma concentration (Cmax)
TOF	Time-of-flight
TTP	Time to progression
TVCN	Total Viable Cell Number
Tyr	Tyrosine
TAMC	Total Aerobic Microbial Count
TSE	Transmittable Spongiform Encephalopathy
TYMC	Total Yeast and Mould Count
UF/DF	Ultrafiltration/Diafiltration
UHPLC	Ultrahigh Performance Liquid Chromatography
US(A)	United States (of America)
UV	Ultraviolet
UV/VIS	Ultraviolet/visible spectroscopy
VEGF	Vascular Endothelial Growth Factor
WCB	Working Cell Bank
WC-CPP	Well Controlled-Critical Process Parameter
WFI	Water For Injections

Vz	Volume of distribution during the terminal phase

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mabxience Research SL submitted on 9 January 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Alymsys, 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:

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

Alymsys 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 of the SmPC.

Alymsys 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 of the SmPC.

Alymsys, 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.

Alymsys, 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.

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

Alymsys, 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 III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Alymsys, 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.

Alymsys, in combination with topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents (see Section 5.1).—indication added during the evaluation procedure.

Alymsys, 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 legal basis for this application refers to:

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

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

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with Zejula, an authorised orphan medicinal product.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 February 2017	EMEA/H/SA/3471/1/2017/III	Prof. Dieter Deforce, Dr Kirstine Moll Harboe
22 June 2017	EMEA/H/SA/3471/1/FU/1/2017/II	Dr Ferran Torres, Dr Sheila Killalea
28 March 2019	EMEA/H/SA/3471/1/FU/2/2019/I	Dr Juha Kolehmainen, Prof Andrea Laslop

The Scientific Advice pertained to quality, pre-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Christian Gartner Co-Rapporteur: Filip Josephson

The application was received by the EMA on	9 January 2020
The procedure started on	30 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 April 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 April 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 May 2020

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 May 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 October 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	09 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	25 November 2020
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	10 December 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 January 2021
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 Alymsys on	28 January 2021
The CHMP adopted a report on similarity of Alymsys with Zejula authorised orphan medicinal product(s) on (Appendix 1)	28 January 2021

2. Scientific discussion

2.1. Problem statement

About the product

Alymsys (Company code MB02) has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Avastin, which contains bevacizumab as the active substance.

MB02 (bevacizumab) belongs to the pharmacotherapeutic group: "monoclonal antibodies" (ATC code: L01XC07).

Bevacizumab is a recombinant humanised monoclonal antibody, which specifically binds to human vascular endothelial growth factor (VEGF), preventing its interaction with VEGF receptors (VEGFRs) on the surface of endothelial cells. As a result, the VEGFR-dependent signalling pathways required to promote and maintain blood vessel formation (angiogenesis) are inhibited. Through this mechanism,

bevacizumab can potentially reduce tumour size by promoting regression of existing tumour vasculature and inhibit tumour growth by inhibiting the formation of new tumour blood vessels.

The Applicant claims the same therapeutic indications for MB02 as granted for Avastin in the EU, except for the treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer with paclitaxel. Alymsys is intended for the treatment of carcinoma of the colon or rectum, breast cancer, non-small cell lung cancer, renal cell cancer, epithelial ovarian, fallopian tube or primary peritoneal cancer, and carcinoma of the cervix (see section 1). The recommended posology and method of administration correspond to those of Avastin.

Alymsys 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

Alymsys has been developed as biosimilar to the reference medicinal product Avastin (EMA product number EMEA/H/C/000582). The finished product is presented as concentrate for solution for infusion containing 25 mg/mL of bevacizumab as active substance. The product is supplied in two presentations, i.e. 100 mg/4 mL and 400 mg/16 mL single-use vials (8 mL and 20 mL, respectively).

Other ingredients are: trehalose dihydrate, sodium phosphate (monobasic sodium phosphate monohydrate and disodium phosphate), polysorbate 20, and water for injections.

The product is available in Type I glass vials closed with a chlorobutyl stopper and an aluminium seal with a polypropylene flip-off cap.

2.2.2. Active Substance

General Information

The active substance of Alymsys (also referred to as MB02) is bevacizumab (INN), a recombinant humanised IgG1 kappa monoclonal antibody directed against VEGF-A. Binding of bevacizumab to VEGF-A neutralises the biological activity of VEGF-A by blocking binding of VEGF-A to its receptors. Bevacizumab does not display Fc effector functions. Alymsys is produced from a mammalian Chinese hamster ovarian (CHO) cell line. It consists of 2 heavy chains (HC) of the lgG1 subclass (453 aa) and 2 light chains (LC) of the kappa subclass (214 aa) connected by intra- and interchain disulphide bonds. The N-glycosylation site is located at amino acid position Asn303 on the heavy chain. The theoretical molecular mass of the fully assembled antibody is 149199.86 Da (main glycoform G0F/G0F).

Manufacture, process controls and characterisation

Manufacturers

GH Genhelix S.A. (Armunia, León, Spain) manufactures MB02 active substance in accordance with current good manufacturing practices (GMP).

Description of manufacturing process and process controls

MB02 is expressed in a CHO cell line using a fed-batch process. Manufacture of a batch starts from a single vial of the working cell bank (WCB). After thawing, the cells are expanded under controlled

conditions in multiple steps to obtain sufficient cells for inoculation of single-use production bioreactors. The unprocessed bulk from the end of production bioreactors step is clarified through a series of depth filters.

MB02 is purified by a series of column chromatography steps. The manufacturing process includes two dedicated, orthogonal virus clearance steps, i.e. virus inactivation and virus removal. The formulated MB02 active substance is filtered, filled into bottles and stored.

Overall, the process parameters and in-process controls in combination with the other control measures appear sufficient to ensure quality and safety of MB02 and to monitor process consistency. The process parameters, which are classified into critical process parameters (CPP), well-controlled critical process parameters (WC-CPP), non-critical (NCPP) process parameters, and general process parameters (GPP), are based on enhanced knowledge gained by process experience throughout process development, manufacture of clinical batches, and process characterisation at small scale. Three categories of in-process tests, i.e. in-process controls, in-process parameters, and in-process testing, have been defined by the Applicant. The in-process tests and their limits have been derived from process understanding and under consideration of safety aspects.

Control of materials

Raw materials are of compendial quality or adequate in-house specifications have been established. Composition and preparation of cell culture media and buffer solutions are sufficiently described. Significant single-use materials as well as relevant processing materials are registered. No direct animal-derived materials but some materials of indirect animal origin are used during manufacture of MB02 active substance (please refer to section on adventitious agents below).

The construction of the expression vector and its genetic elements are described in sufficient detail. The origin of the antibody sequence is briefly described; the correct nucleotide and amino acid sequence was confirmed. The information provided on the origin and history of the parental CHO cell line and generation of the final production clone is acceptable. The applicant has established a two-tiered cell bank system with Master Cell Bank (MCB) and Working Cell Bank (WCB). Cell banking procedures are adequately described. A protocol describing manufacture and qualification of new WCBs has been registered. Characterisation of the expression construct and cell substrate including MCB, WCB, and end of production cell bank (EoPCB) is in line with ICH guidelines Q5A, Q5B and Q5D.

Control of critical steps and intermediates

The Applicant followed an enhanced development approach using existing knowledge, process development and manufacturing experience, risk assessment tools, and process characterisation studies to develop a control strategy as outlined in ICH Q11 and EMA/CHMP/BWP/187338/2014.

A comprehensive set of product variants, process-related impurities and so called `obligatory´ quality attributes (i.e. protein content, general and microbial attributes) that cover the relevant attributes of MB02 was assessed and an impact score based on impact on biological activity, PK/PD, immunogenicity and safety was assigned to each quality attribute. The criticality score was determined from the impact score and the uncertainty score using a quantitative risk ranking matrix. The relevant CQA of bevacizumab have been identified; the individual impact and uncertainty scores as well as justifications for the scoring are agreeable.

Process characterisation studies were used to systematically evaluate process parameters with regard to their impact on process performance and product quality and inform regression models for determination of proven acceptable ranges (PAR).

Process validation

The Applicant follows a process validation lifecycle strategy as described in Guideline EMA/CHMP/BWP/187338/2014 comprising process characterisation, process verification/process performance qualification (PPQ), and ongoing process verification throughout the lifecycle. The prospective process verification encompassed manufacture of process validation batches according to the intended commercial process at the intended commercial manufacturing site and scale. Confirmation of adequate removal of process- and product related impurities and of hold times for process intermediate pools were part of the validation activities. The validation results, which were all within their specified acceptance criteria, demonstrate that the process performs consistently and delivers active substance complying with the release specifications under commercial operating conditions. The results confirm that the process-related impurities are consistently reduced to low levels/below the LOQ and that product-related impurities are controlled at low level. Potential leachables originating from single-use equipment have been addressed. Overall, the data on re-use of the chromatography resins support the proposed lifetime. A summary of the shipping validation has been added to the dossier.

Manufacturing process development

Early development was performed at 500 L scale and comprehensively presented. Based on experience gained the process was further developed, optimized and scaled-up to the intended scale at the intended manufacturing site for the European market GH Genhelix S.A. (Armunia, León, Spain). Prior to manufacture of active substance for the pivotal clinical trials (comparative PK, safety, and immunogenicity study MB02-A-02-17; comparative efficacy, safety, and immunogenicity study MB02-C-01-17) the process was further optimised. In addition, during production of active substance for the pivotal phase III study MB02-C-01-17 the UF/DF step was optimised to improve the adjustment of the protein concentration.

Comparability of MB02 active substance from the 500 L and the commercial process was not directly evaluated but finished product from the site used to manufacture clinical material or intended commercial site using active substance from the 500 L and commercial process, respectively, was shown to be comparable (please refer to finished product section). The pivotal clinical phase I and phase III studies were performed with active substance manufactured with the intended commercial process (except for the modified UF/DF step which was implemented during the pivotal comparative phase III study).

Characterisation

The Applicant comprehensively characterised the structure and biological properties of MB02 using orthogonal, state-of-the art analytical methods. The amino acid sequence of MB02 was experimentally confirmed by peptide mapping with 100% sequence coverage. Presence of C- and N-terminal variants (pyroglutamate, Lys-clipping), oxidation, and deamidation is presented. The higher order structure was evaluated by a combination of disulphide bridge mapping, far-UV CD, hydrogen/deuterium exchange mass spectrometry, µDSC, and DLS. Charge and size variants were determined using complementary analytical methods (CEX-HPLC, cIEF and CE-SDS, SE-HPLC, respectively). Glycoanalysis comprised the identification of the oligosaccharide pattern and site occupancy by peptide mapping and HILIC-UPLC-FLR; in addition, sialic acid content (NeuAc and NeuGc) was determined by UHPL-FLR. The absence of alpha-1,3-galactose structures has been demonstrated. The biological characterisation included an assessment of binding to VEGF variant and PlGF and to VEGF-A_{165} by ELISA as well as of functional activity in cell-based assays (HUVEC). In addition, absence of Fc effector functions (ADCC and CDC) was confirmed in cell-based assays. The presented data confirm the expected structural and functional characteristics of bevacizumab.

Product-related variants and impurities detected by SEC- and CEX-HPLC were identified and characterised using relevant orthogonal methods. Functional characterisation of the variants/impurities included determination of VEGF binding by competitive ELISA.

The levels of HHL fragments, as observed by non-reducing CE-SDS, were demonstrated to be higher in MB02 active substance as compared to Avastin. Detailed analyses by peptide mapping and mass spectrometry revealed amino acid substitutions, with relevant substitution levels (>1%) only occurring at position HC226. Extensive experiments support the Applicant´s conclusion that the amino acid substitution is metabolic. As demonstrated in the analytical similarity assessment (please refer to discussion of analytical similarity) higher order structure and biological activity was highly comparable between MB02 and the reference product further indicating that the amino acid replacements have no impact on efficacy. Immunogenicity may potentially be affected by the replacement; however, the clinical data do not indicate immunogenicity issues with MB02. Absolute quantitation based on stable isotope labelling revealed relative levels of amino acid substitution at HC226 of 1.29±0.23%. The chemistry behind the change and the related information has been sufficiently discussed by the Applicant.

The Applicant described future options to minimise the amino acid substitution in the commercial process and submitted a corresponding post approval change management protocol (PACMP) for implementation of an optimised active substance manufacturing process. The initially submitted PACMP has been revised and is now acceptable.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The proposed set of quality attributes included in the specifications for release and stability testing of MB02 active substance complies with ICH Q6B, Ph. Eur. 2031 and EMA/CHMP/BWP/532517/2008 and is acceptable. The release specification for MB02 active substance comprises tests for identity, purity and impurities, potency, quantity, microbiological attributes and general attributes.

In addition to manufacturing process capability, batch release and stability data (including the clinical batches), data from the analytical similarity exercise, and characterisation data, the Applicant took into account regulatory requirements from the Ph. Eur. and relevant guidelines to justify the specifications.

From a current perspective, the proposed specification limits are agreeable. The limits for several specification parameters were tightened upon request. The Applicant committed to re-evaluate several limits after at least 30 commercial batches have been manufactured (See "Recommendations for future quality development").

Analytical Methods

The analytical methods are sufficiently described and considered adequate. For determination of HCP, a commercial generic test kit is currently used; however, the Applicant intend to implement a process specific HCP ELISA method: a time plan for implementation has been provided (See "Recommendations for future quality development"). The implemented system suitability tests (SST) and sample acceptance criteria appear suitable to provide adequate control over analytical method performance.

Overall, the presented analytical method validations are adequate and demonstrate the suitability of the analytical procedures for their intended use. The relevant analytical method parameters have been assessed in accordance with ICH Q2(R1). Robustness of the methods has been sufficiently demonstrated by extensive robustness data.

Potency is determined by a combination of a competitive VEGF-binding ELISA and a relevant cell-based assay that measures inhibition of proliferation.

Reference Standards

The history of reference standards used throughout development of MB02 is presented. Recently, a two-tiered system with primary reference standard and secondary reference standards has been implemented. The reference materials were adequately qualified according to the development phase using release and additional characterisation tests. The procedures for assignment and stability monitoring of potency of the reference standards are acceptable.

Batch Analyses

Batch release data are presented for active substance batches manufactured according to the intended commercial manufacturing process at the intended commercial site GH Genhelix S.A., Spain. The batches were used in the pivotal clinical studies, for demonstration of analytical similarity, in stability studies as well as for process validation purposes. All results comply with the specifications at time of testing and the commercial specifications. The presented results demonstrate that the manufacturing process reliably delivers MB02 active substance with consistent quality.

Container closure

MB02 active substance is stored in bottles with screw cap closures. The materials comply with Ph. Eur. and/or USP requirements and Commission Regulation (EU) No. 10/2011 on plastic materials and articles in contact with food. Compatibility has been demonstrated by stability studies and additional compatibility studies.

Stability

Based on the updated stability data, the Applicant presented a shelf life claim.

The ongoing stability studies are conducted at long-term storage conditions as well as under accelerated conditions using MB02 active substance batches that were manufactured according to the intended commercial manufacturing process at the intended commercial site. In addition, forced degradation studies applying several stress conditions were performed.

The design of the studies is in accordance with ICH Q5C. The samples are stored in bottles representative of the commercial container closure system and were filled to the same level as the commercial container closure. Overall, the analytical programme follows the proposed active substance specifications and includes stability indicating methods. Results were statistically evaluated for trends.

At long-term and accelerated conditions, all results comply with the acceptance criteria for the studies as well as the proposed commercial specification limits. No obvious relevant trends are present at long-term conditions.

No major effects on quality of MB02 were observed in the forced degradation studies. Further comparative stress stability studies were conducted as part of the analytical similarity exercise. The presented data support the proposed shelf life in the defined container closure system.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is a sterile, preservative-free concentrate for solution for infusion containing 25 mg/mL of bevacizumab as active substance and is supplied in two presentations: MB02 100 mg/4 mL and MB02 400 mg/16 mL single-use vials.

Bevacizumab is formulated with trehalose dihydrate, sodium phosphate (as monobasic sodium phosphate monohydrate and as disodium phosphate), polysorbate 20 and water for injections. The formulation is identical to that of the reference medicinal product.

MB02 finished product does not contain any overages. To ensure that each vial contains a volume sufficient for withdrawal, the Applicant is proposing a target fill volume of 4.30 mL and 16.60 mL for the 100 mg and 400 mg strength, respectively. The proposed target fill volume appears sufficiently justified.

The excipients used for MB02 active substance and finished product are of compendial quality and the same as the excipients used in the EU-authorised reference product (Avastin). The excipients include a buffering agent to stabilise pH, non-reducing disaccharide as lyo/cryo-protectant and stabiliser against thermal stress, and a surfactant for preventing aggregation upon mechanical and freeze-thaw stresses.

The formulation of MB02 is identical to that of the reference product Avastin. The suitability of the formulation for MB02 was justified by data derived from stability studies. Furthermore, formulation robustness was assessed under accelerated/stress/freeze-thaw conditions. The proposed formulation is considered suitable for MB02.

Manufacturing process development

Manufacture of the finished product includes thawing and pooling of active substance, sterile filtration, aseptic filling into vials and packaging.

The process development activities addressed defining the quality target product profile (QTPP), identifying critical quality attributes (CQAs), risk assessment and identification of critical process parameters (CPPs), and establishing a process control strategy to ensure that CQAs are met.

The process control strategy was based on the evaluation of CQAs and CPPs. The following control elements are included: control of excipients and raw materials, in-process testing, release testing, characterization of impurities, stability monitoring, process performance qualification, and control of environmental factors and adventitious agents. A clear link of each control element to each CQA has been provided. Taken together, the control strategy appears adequate.

The Applicant has outlined a summary of manufacturing process changes that occurred between early phase clinical development and late phase clinical development and commercial production. The potential impact of manufacturing process changes to the quality of MB02 has been evaluated in comparability studies.

Comparability study 1 and 2 compared early phase clinical material to late phase/pivotal clinical finished product development. Comparability study 1 includes extensive physicochemical and biological characterization studies while Comparability study 2 includes forced/stressed degradation studies. Full comparability reports including batch data have been provided. The presented data indicate that early phase clinical material is comparable to late phase clinical material.

Comparability Study 3 compared MB02 manufactured at the proposed commercial manufacturing site using the filling Line 1 versus filling Line 2. Comparability was assessed by evaluating release data and

extended characterization. The provided data indicate comparability of material manufactured using filling Line 1 vs. filling Line 2.

Container closure system

The container closure system consists of 8 mL vials for MB02 100 mg/4 mL presentation and 20 mL vials for MB02 400 mg/16 mL presentation. These containers comprise a clear, sterilized Type I borosilicate glass vial, closed with Type I chlorobutyl rubber stopper and an aluminium seal fitted with a plastic flip-off cap. The vial, stopper and seal components are compliant with appropriate Ph. Eur. monographs for primary containers and closures.

The suitability of the container closure system used for storage, transportation and use of MB02 finished product was demonstrated by the studies assessing the appropriateness of materials (compliance to standards and extractable assessment), compatibility of materials of construction with dosage form (leachable assessment), functional performance, and container closure integrity. The long-term compatibility of MB02 finished product with the container closure system is demonstrated from stability data.

The Applicant committed to present the results of the ongoing leachables study when the study is finalized (See "Recommendations for future quality development"). MB02 finished product is intended to be diluted in sodium chloride 0.9% w/v. Compatibility has been evaluated for polyolefin (PO) bags as well as polyvinyl chloride (PVC) bags Results demonstrate in-use stability of MB02 in infusion bags up to 30 days at 2-8°C followed by 48h at 30°C. This is appropriately reflected in the SmPC.

Manufacture of the product and process controls

The finished product is manufactured, packaged, controlled and released in accordance with the current Good Manufacturing Practices (GMP). Certificates confirming GMP compliance have been provided or are available via EudraGMDP.

EU batch release is performed at GH, Genhelix S.A., Parque Tecnológico de León, Edificio GENHELIX, C/Julia Morros, s/n, Armunia, 24009 León, Spain.

MB02 finished product is manufactured according to a standard manufacturing process including active substance thawing and pooling (Step 1 and Step 2), bioburden reduction filtration (Step 3), sterilizing filtration/aseptic filling (Step 4), visual inspection (Step 5), and secondary packaging & storage (Step 6).

The control strategy has been established to ensure that CQAs consistently remain within acceptable limits. Critical in-process parameters are either controlled via in-process controls (IPCs) or in-process tests (IPTs). Critical process parameters are controlled or monitored with an acceptable range, which has been defined based on product development studies and existing product knowledge.

Process validation

The process validation studies were performed according to a classical approach. Batches were manufactured for each of the two presentations. Minimum and maximum batch sizes were considered for both presentations. Process parameters were set based on results obtained in manufacturing process development studies according to normal operating ranges.

The in-process test results met pre-defined acceptance criteria in most instances; excursions have been adequately investigated and addressed.

Analytical release testing was performed in line with specifications proposed for release of commercial batches. The release test results were well within pre-defined specifications for all process validation batches.

The process validation data overall indicate that the finished product manufacturing process consistently yields finished product meeting its pre-determined quality attributes.

Furthermore, the Applicant provided a risk assessment as regards potential leachables from the single-use equipment, and the associated risk can be considered as negligible. Also, a summary of all deviations observed in the course of process validation studies has been provided and the respective handling appears appropriate.

Sterile filter validation was performed. The Applicant presented data on media fills which gave satisfactory results. Based on the results obtained, the maximum aseptic process time is considered sufficiently validated.

Transport/shipping has been adequately validated, and a respective summary has been included in the dossier.

Product specification

The specifications proposed for release and stability testing of MB02 finished product comply with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008 GL. The specifications include tests for appearance, general tests, tests for identity, tests for purity/product-related impurities, biological activity (competitive binding ELISA, HUVEC bioassay), quantity, tests for contaminants, and container closure integrity.

The proposed acceptance criteria have been justified and are considered acceptable. Justifications included overall knowledge based on release and stability data for MB02 batches, clinical qualification by means of batches used in clinical trials, as well as data on the reference product Avastin.

In line with the active substance section, the Applicant committed to re-evaluate several limits after at least 30 batches of commercial material have been manufactured (See "Recommendations for future quality development").

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities as part of the ongoing leachables study. Based on the risk assessment and ICP-MS data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory. As the leachables study is still ongoing the Applicant committed to also present these data when the study is finalized (See "Recommendations for future quality development").

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report-Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical procedures

With the exception of the finished product specific general tests, all analytical methods are common for MB02 active substance and MB02 finished product. These common methods are described and discussed in the respective active substance section. The finished product specific general tests are performed according to Ph. Eur. and USP.

Batch analyses

Batch analyses data are presented for both presentations (i.e. 100 mg / 4 mL and 400 mg / 16 mL). The respective results comply with the specifications valid at time of release testing and indicate a consistent manufacturing process.

Stability of the product

The Applicant is proposing a shelf-life of 30 months when stored at the intended long-term condition (i.e. 2-8°C, protected from light). Data up to 30 months are available for GMP batches of MB02 finished product in 4 mL vials and GMP batches of MB02 finished product in 16 mL vials. Additional stability data are available for additional clinical batches, and for PPQ batches. Stability data at accelerated conditions (25ºC ± 2ºC/60% ± 5% RH) are available for most batches.

Degradation pathways have been evaluated in forced degradation studies.

Photostability testing was conducted in line with ICH Q1B. Based on the study results, it can be concluded that MB02 should be stored protected from light and this is appropriately reflected in the SmPC.

Furthermore, stress stability of the finished product was studied in the secondary packing to reflect real-life conditions. The provided data indicate that MB02 finished product is stable upon short term excursion at high temperature or low temperature (40ºC / 60% RH or -20ºC for 3 days), upon agitation (300 rpm), freeze and thaw and exposure to ambient and UV light while enclosed in the secondary package.

Chemical and physical in-use stability has been demonstrated for 30 days at 2ºC to 8ºC plus an additional 48 hours at temperature not exceeding 30°C in sodium chloride 9 mg/mL (0.9%) solution for injection.

Taken together, the presented data sufficiently support the proposed shelf-life of 30 months when stored at the intended storage conditions (i.e. 2-8°C, protected from light).

Biosimilarity

Analytical similarity of MB02 was assessed in a comprehensive similarity exercise using EU-sourced Avastin as reference medicinal product. The approach and methodology of the analytical similarity assessment is sufficiently described and overall acceptable.

Several MB02 finished product lots of the 100 mg/4 mL and 400 mg/16 mL presentations) were included in the analytical similarity exercise. The active substance batches were manufactured according to the intended commercial process at the intended commercial site GH Genhelix S.A., the corresponding finished product lots have been manufactured at the intended commercial site. The MB02 batches/lots have been used in the pivotal PK study and the comparative NSCLC study and for active substance/finished product process validation and stability studies. The lot-to-lot variability is considered to be sufficiently reflected.

The reference product EU-Avastin was procured over an extended period. Several lots (100 mg/4 mL and 400 mg/16 mL presentations) including most of the lots used in the comparative clinical studies

were analysed. The number of lots is expected to sufficiently reflect variability and appears adequate for evaluation of similarity. In addition to EU-sourced Avastin, US-sourced Avastin (100 mg/4 mL and 400 mg/16 mL presentations) have been included – these data are provided for information only as the pivotal clinical studies have been performed with EU-Avastin.

A broad range of lot ages is covered for the proposed biosimilar and the reference product with sufficient overlap between both products.

The Applicant followed a tiered approach to demonstrate analytical similarity. Based on their criticality, quality attributes/corresponding analytical methods were assigned to three tiers with assessment criteria of different stringency. Tier 1 included QAs with highest risk ranking directly related to the mechanism of action (i.e. binding to VEGF), quantitative attributes not directly related to the mechanism of action were assigned to Tier 2, and Tier 3 comprised QAs with lowest risk ranking and QAs not amendable to quantitation. The comparability ranges were based on analytical characterisation of EU-Avastin and set to mean ± 2 SD (Tier 1) and mean ± 3 SD (Tier 2; for highly variable Tier 2 methods: mean ± 2 SD), respectively; for several Tier 2 parameters a pre-defined limit derived from method capability was used (e.g. mass spectrometry). For Tier 3 attributes, data were visually compared. In principle, the Applicant´s approach to set the comparability ranges based on ± x SD is acceptable if data are normally distributed and are not impacted by few extreme results (for most attributes this seems to be the case). It is noted that the justification for the statistical approach is limited. However, the Applicant provided graphical and tabular presentations of individual analytical results as well as descriptive statistics, which enable also an assessment independent of the defined quality ranges.

The selected comprehensive set of orthogonal state-of-the–art analytical methods, which covers primary and higher order structure, post-translational modifications, size and charge variants, larger aggregates, general attributes, as well as Fab- or Fc-mediated biological functions, appears adequate to address the relevant quality attributes of bevacizumab. The Fab-mediated mechanism of action was evaluated by a range of biological assays at different levels (binding to various VEGF isoforms, HUVEC anti-proliferation assay, VEGF blocker reporter gene assay, receptor dimerization assay). Biological characteristics were further compared with regard to Fc receptor and mannose receptor binding, C1q binding, and CDC and ADCC activity. Adequate descriptions and qualification data have been provided for the analytical methods used for the analytical comparability exercise.

For many quality attributes, MB02 was demonstrated to be analytically highly similar to Avastin EU. The primary structure attributes molecular mass, amino acid sequence (low level metabolic amino acid substitutions were detected for MB02 – see below), post translational modifications (oxidation, isomerisation, deamidation, O-glycosylation), extinction coefficient, protein concentration as well as the higher order structure (disulphide structure, CD, Fluorescence, HDX, µDSC, DLS) were shown to be highly similar. Concerning biological activity, similarity was demonstrated for the mechanism of action (VEGF binding including the relevant isoforms, VEGF neutralisation, anti-proliferation) as well as for binding to FcγRIIa, FcγRIIb, FcγRIIIa V/F (by SPR), FcRn, mannose receptors and C1q. Lack of CDC and ADCC activity was confirmed for both MB02 and Avastin.

Results from several analytical methods show differences between MB02 and the reference product EU-Avastin:

Compared to EU-Avastin slightly lower glycation levels were observed for MB02. Biological activity is not impacted by the different glycation levels.

Minor differences are observed between MB02 and EU-Avastin regarding N- and C-terminal integrity. No effect on clinical performance is expected.

A somewhat higher level of free thiols is present in MB02 compared to EU-Avastin which was initially explained by metabolic amino acid substitutions present in MB02. However, further analysis revealed that the higher level of free thiols cannot only be attributed to the amino acid substitution. No impact on VEGF binding was observed for fractions enriched for HHL and biological activity of MB02 and EU-Avastin is similar. A potential effect on immunogenicity cannot be excluded but the clinical data do not indicate an issue with immunogenicity. Absolute quantitation of the amino acid substitution revealed a low substitution level. Overall, it is concluded that the substitution does not preclude biosimilarity.

Minor differences in distribution of charge variants are evident between MB02 and EU-Avastin. Overall, the differences are small, and characterisation of the individual peaks did not corroborate any significant differences between MB02 and EU-Avastin. An impact on clinical performance is unlikely.

The distribution of the glycoforms (HILIC-UHPLC-FLR analyses) differs between MB02 and EU-Avastin. It is unlikely that these differences have an impact on immunogenicity. Considering the mechanism of action of bevacizumab and that MB02 and EU-Avastin show similar Fab- and Fc-related biological activities including mannose receptor binding, these differences are not expected to impact clinical performance and hence, do not preclude similarity. The clinical PK, efficacy and safety data from the pivotal studies support these conclusions.

Compared to EU-Avastin no new size variants are observed for MB02 by the different techniques applied. SEC-HPLC shows a higher purity of MB02 and a lower aggregate content. Reduced CE-SDS reveals a slightly higher content of HC+LC for MB02 associated with lower levels of NGHC. On the contrary, under non-reducing conditions CE-SDS for MB02 a lower IgG content and higher levels of a HHL fragment are detected. In addition, the content of LC and LMW variants is slightly increased for MB02 when analysed by non-reducing CE-SDS. Analytical ultracentrifugation also reveals a slightly higher monomer content for MB02. No obvious differences between MB02 and EU-Avastin were noted by SDS-PAGE (reduced, non-reduced) and DLS. A higher purity (lower level of aggregates, higher monomer/HC+LC content) as observed by SE-HPLC, CE-SDS reduced, and svAUC does not preclude similarity. As discussed above, the higher level of the HHL fragment is not expected to impact efficacy. Overall, MB02 and EU-Avastin are considered similar with regard to size variants/purity.

A broader range of activity is observed for MB02 in the cell-based reporter gene assay. However, it should be noted that the Applicant identified one out-of-trend result for EU-Avastin that was excluded from the analysis. In addition, comparable activity of MB02 and EU-Avastin was demonstrated in the other VEGF binding and bioassays.

Compared to EU-Avastin, MB02 shows a slightly higher relative binding affinity to FcγRI. However, the difference is small and the KD is highly comparable for MB02 and EU-Avastin.

When analysed by AlphaLISA, relative binding to both FcγRIII V and F variant differed between MB02 and EU-Avastin. The difference in binding could be correlated to the different levels of G0 present in MB02 and EU-Avastin. A noticeable difference in binding or affinity between MB02 and the reference product was not detected with an orthogonal method (i.e. SPR). Taking into account that ADCC is not a mechanism of action for bevacizumab and absence of ADCC activity has been demonstrated for MB02 and Avastin it is agreed that these differences are not clinically relevant.

Comparative forced degradation studies were conducted to further demonstrate similarity of MB02 and EU-Avastin (one lot each of MB02, EU-Avastin, and US-Avastin were included). Using a set of stability indicating analytical methods including additional characterisation methods, similar degradation profiles and kinetics were observed for MB02 and the reference product under thermal, mechanical, low/high pH, and light stress. Overall, the presented stress stability data support the conclusion of similarity.

In summary, the presented analytical data support the claim for biosimilarity between the proposed biosimilar MB02 and the reference product EU-Avastin. Minor analytical differences have been

appropriately assessed and justified by the Applicant with regard to their potential impact on clinical performance of the product. The results are summarised in the following table.

Table 1: Summary of analytical similarity assessment between MB02 and EU-Avastin

Molecular parameter	Attribute	Methods for control and characterization	Key findings
General test	Extinction coefficient	Amino acid analysis	Similar extinction coefficients
	Protein content	UV	Similar protein concentration in MB02
Primary structure	Intact mass	RPLC-UV/MS	Comparable mass profile
	Reduced and de-N-glycosylated (LC and HC)	RPLC-UV/MS	Comparable mass profile
	Glycation (HC and LC)	RPLC-UV/MS	Slightly lower levels for MB02; not clinically meaningful
	Primary structure confirmation by reduced peptide mapping with multiple enzymatic digestions	Reducing peptide mapping by RPLC-ESI-TOF MS/MS	100% sequence coverage, identical
	Primary structure confirmation by reduced tryptic peptide mapping	Reducing peptide mapping by RPLC-UV-MS	100% sequence coverage, identical
	N- and C-terminal integrity	Tryptic peptide mapping by RPLC-UV-MS	Marginal differences; not clinically meaningful
Higher order structure	Disulphide bridges	Non Reduced Peptide mapping	Comparable mapping profile
	Free Thiols	Ellmans test	Slightly higher levels; not clinically meaningful
	Secondary Structure	CD	Similar content in structural components and Similar CD spectra
	Tertiary Structure	Fluorescence	Similar fluorescence spectra
	Higher Order Structure	HDX-MS at peptide and intact level	Same higher order structure
	Epitope mapping	HDX-MS	Same amino acids compose the epitope binding site
	Colloidal stability	DLS	Similar colloidal stability

Molecular parameter	Attribute	Methods for control and characterization	Key findings
	Structural stability	µDSC	Similar thermal stability (Tm)
Post-translational modifications	Charge variants	CEX HPLC chromatogram profile and data	Slight difference in one MB02 basic peak and minor difference in distribution of charge variants (age dependent); not clinically meaningful
	Charge variants	cIEF electropherogram profile and data	Similar profile and similar isoelectric point
	Oxidation/Deamidation/Aspartate isomerisation	Peptide mapping (LC-ESI MS/MS)	Similar levels of deamidation, oxidation and aspartate isomerisation
	O-glycosylation	Peptide mapping	No O-glycosylation for either Avastin or MB02
	Site of N-glycosylation	Peptide mapping	Identical site of N-glycosylation on N303
	Monosaccharides content	GC-MS	Level of galactose is higher; no impact on clinical performance expected
	Sialic Acids content	UHPLC-FLR	Slightly higher sialic acids content for MB02; levels are very low; difference is not significant from clinical perspective
	Glycosylation assessment	HILIC-UHPLC-FLR Overall N-glycosylation HILIC profile	Similar N-glycans identity and distribution; differences are not clinically meaningful, similar biological activity demonstrated
	Glycosylation assessment	LC-MS	Comparable masses of G0F and G1F
Purity	Size heterogeneity	SE HPLC chromatogram profile and data	Similar profile, slightly lower HMW species (higher purity); minor differences not clinically meaningful

Molecular parameter	Attribute	Methods for control and characterization	Key findings
	Size heterogeneity	CE SDS R and NR electropherogram profile and data	Similar profiles, slightly higher levels of HC+LC and lower levels of NGHC (R), slightly lower levels of IgG and higher levels of HHL peak (forms under denaturing conditions) (NR); minor differences not clinically meaningful
	Size heterogeneity	SDS-PAGE R and NR	Similar band profiles
	Aggregate assessment	sv-AUC	Similar monomer content (slightly higher for MB02)
	Aggregate assessment	Isothermal DLS	Similar hydrodynamic size of predominant peak
Biological activity (Fab region)	Binding to VEGF-A_{165}	Competitive binding ELISA	Highly similar relative binding
	Binding to VEGF-A_{165}	SPR	Highly similar relative affinity and KD
	Binding to VEGF-A_{121}, -A_{189}, and -A_{206}	ELISA	Highly similar relative binding
	VEGF B, C and D variants and PlGF	BLI	Absence of binding for both MB02 and Avastin
	Antiproliferation bioassay	HUVEC assay	Similar relative potency
	VEGF neutralization	VEGF blocker reporter assay	Similar relative potency
	Blockade of KDR signalization pathway	KDR/KDR dimerization bioassay	Similar relative potency
Biological activity (Fc region)	ADCC and CDC activity	ADCC and CDC bioassays	No ADCC and CDC activity
	Binding to C1q	ELISA	Highly similar relative binding
	Binding to FcγRI	SPR	Slightly higher relative affinity, similar KD; minor

Molecular parameter	Attribute	Methods for control and characterization	Key findings
			difference not clinically meaningful
	Binding to FcγRIIa	SPR	Highly similar relative affinity and KD
	Binding to FcγRIIb	SPR	Highly similar relative affinity and KD
	Binding to FcγRIIIa V variant	SPR	Highly similar relative affinity and KD
	Binding to FcγRIIIa V variant	AlphaLISA	Differences in relative binding; minor differences not clinically meaningful
	Binding to FcγRIIIa F variant	SPR	Highly similar relative affinity and KD
	Binding to FcγRIIIa F variant	AlphaLISA	Differences in relative binding; minor differences not clinically meaningful
	Binding to macrophage mannose receptor	BLI	Similar KD in the 10^{-8} M range
	Binding to FcRn	SPR	Highly similar relative affinity and KD
	Binding to FcRn	ELISA	Similar relative binding

Post approval change management protocol(s)

A PACMP covering an intended change of the active substance manufacturing process has been submitted and is considered acceptable (see also characterisation section above).

Adventitious agents

Overall, the risk of contamination of MB02 with adventitious agents is considered low. The Applicant implemented multiple complementing measures to ensure product safety with regard to non-viral and viral adventitious agents. The measures include selection of materials, testing of cell banks and process intermediates, testing of microbial attributes at release, and implementation and validation of dedicated virus clearance steps and steps contributing to virus reduction:

- MB02 is manufactured from a CHO cell line without materials of direct animal or human origin. Based on the information provided the risk with regard to TSE or viral contamination is low.
- The production cell line, the MCB, as well as the WCB have been manufactured without using materials of direct animal or human origin. The cell banks have been tested for the absence of adventitious viruses and microbial contamination.

- Each unprocessed harvest is routinely tested for the absence of adventitious viruses and mycoplasma.
- Endotoxin levels and bioburden/sterility are adequately controlled throughout the manufacturing process and at active substance and finished product release.
- Robust and effective overall virus clearance by five orthogonal manufacturing process steps has been demonstrated using validated down-scaled models. The manufacturing process includes two dedicated virus clearance steps that are effective against enveloped and non-enveloped viruses**.**

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The dossier includes a PACMP to support a future change of the fed batch step of the active substance manufacturing process, which is considered acceptable.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the below aspects and are put forward and agreed as recommendations for future quality development.

- To re-evaluate a number of active substance and finished product specification limits based on at least 30 commercial batches.
- To implement a process specific HCP ELISA method.
- To present the final study report on leachables/elemental impurities testing when the respective study is finalized.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The active substance and finished product specification limits should be re-evaluated after at least 30 batches of commercial batches have been manufactured.
2. The process specific HCP ELISA should be implemented.
3. The final results of the ongoing leachables/elemental impurities study should be provided.

2.3. Non-clinical aspects

2.3.1. Introduction

Bevacizumab is a recombinant humanised monoclonal antibody that binds specifically to all soluble forms of human VEGF, neutralising its biological activity and acting as an anti-neoplastic agent (ATC code L01XC07).

2.3.2. Pharmacology

Primary pharmacodynamic studies

The Applicant conducted an extensive *in vitro* programme to test biosimilarity between MB02 DP and the EU reference medicinal product Avastin. These studies were submitted in Module 3 of this MAA; hence, the corresponding assessment can be found in the quality assessment report and in section 2.2.4. No non-clinical *in vivo* pharmacology studies were conducted, which is acceptable.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been conducted.

Safety pharmacology programme

No safety pharmacology studies have been conducted.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted.

2.3.3. Pharmacokinetics

No stand-alone pharmacokinetics studies were submitted. However, toxicokinetics endpoints were included in the conducted cynomolgus monkey repeated dose toxicity study (BEVZ92-NC-01).

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity study was submitted.

Repeat dose toxicity

The Applicant conducted a 28-day repeated dose toxicity study in cynomolgus monkeys (study BEVZ92-NC-01).

The Applicant studied the toxicity of the investigational product in comparison to the comparator EU-Avastin and a NaCl vehicle group. Per treatment, male and female cynomolgus monkeys were used at

group sizes of only three animals each. The experimental setup of this study is illustrated in the Table below:

Group Number	Description	Dose level (mg/kg/twice per week)	Number of animals in group	
			Male	Female
1	Control	0	3	3
2	BEVZ92 (Biosimilar)	50	3	3
3	Avastin®	50	3	3

An earlier version of Alymsys was used for this study, namely BEVZ92. This study is presented as a supportive study in the MB02 marketing authorization application.

No relevant differences between BEVZ92 and EU Avastin were observed in mortality, clinical signs, body weights, ophthalmology, electrocardiography, haematology, clinical chemistry, urine analysis, organ weights, macroscopic and microscopic findings. However, no statistical analyses were applied to compare the means of the assessed parameters.

The toxicokinetic investigations that were included in study BEVZ92-NC-01 ($AUC_{0\text{-}72h}$, C_{max}, T_{max}, RA_{AUC}, RA_{Cmax} and F_{rel}) generally indicate that BEVZ92 and EU Avastin had a comparable toxicokinetic profile. This was especially demonstrated for e.g. AUC and C_{max}, whereas T_{max} values were compromised by high inter-individual variability so that statements on biosimilarity are not possible for this endpoint.

No other toxicology studies were conducted, which is acceptable.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Alymsys is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

One *in vivo* BEVZ92-NC-01 study was submitted in Module 4 of this MAA. All bio-comparability *in vitro* assays were submitted in Module 3; hence, their assessment can be found in the quality assessment section 2.2.4.

No dedicated pharmacokinetic studies have been conducted, which is acceptable according to the EMA/CHMP guidelines on biosimilar products (EMEA/CHMP/BMWP/42832/2005 Rev1, EMA/CHMP/BMWP/403543/2010).

The submitted 28 day repeated dose toxicity study in cynomolgus monkeys (study BEVZ92-NC-01) showed no relevant differences between BEVZ92 and EU Avastin in mortality, clinical signs, body weights, ophthalmology, electrocardiography, haematology, clinical chemistry, urine analysis, organ weights, macroscopic and microscopic findings. Consequently, the study suggests biosimilarity of BEVZ92 and EU Avastin. In addition, the small group size and occasionally high inter-individual variability make the study unreliable in terms of demonstrating biosimilarity. Therefore, the results of this study should only be regarded as supplementary data, but not as pivotal approach to test biosimilarity between both bevacizumab substances.

No other toxicology studies were conducted, which is acceptable and in line with relevant EMA guidelines (e.g. EMEA/CHMP/BMWP/42832/2005 Rev1).

In accordance with the EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" EMEA/CHMP/BMWP/42832/2005 Rev1, specific studies on genotoxicity, carcinogenicity, reproductive and developmental toxicity, and local tolerance have not been submitted.

2.3.7. Conclusion on non-clinical aspects

The *in vitro* studies are presented in Module 3 and thus, the non-clinical assessment focusses on one *in vivo* study conducted to fulfil regulatory requirements for non-EU regions. The results of the cynomolgus monkey repeated dose toxicity study (BEVZ92-NC-01) appear to demonstrate biosimilarity between BEVZ92 (an earlier version of MB02) and EU Avastin. No concerns are raised on this study since it is only considered supportive.

The submitted non-clinical data are considered adequate to support biosimilarity of MB02 and the reference product.

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

Overview of the Clinical Development Plan for Evaluation of Pharmacokinetic Similarity/ Comparability

Study ID (Country)	**Study Objectives**	**Subjects**	**Study Design/Duration**	**Treatments**	**Primary endpoints**
MB02-A-02-17 (United Kingdom)	Primary objective: To investigate and compare the PK profiles of MB02, US- and EU-Avastin to establish bioequivalence Secondary objectives: To compare other PK parameters and safety profiles and immunogenicity	114 healthy male subjects: (n=38 per treatment arm)	A randomized, double-blind, three-arm, parallel group, single-dose study. A maximum of 19 weeks (screening to final visit)	Single-dose IV infusion for 90 minutes: 3 mg/kg of either MB02, EU Avastin or US Avastin	AUC(0-inf) Cmax

Study ID (Country)	Study Objectives	Subjects	Study Design/Duration	Treatments	Primary endpoints
MB02-C-02-17 (Bulgaria, Brazil, Chile, Georgia, Greece, Hungary, India, Lebanon, Malaysia, Mexico, Philippines, Russian Federation, Serbia, Thailand, Turkey, Ukraine)	Primary objective: To compare objective response rates of MB02 and EU-Avastin Secondary objectives: To compare safety profiles, immunogenicity and other efficacy parameters of MB02 compared to EU-Avastin	Patients with Stage IIIB/IV non-squamous non- small cell lung cancer (NSCLC) N=627 subjects randomised (MB02 n=315; EU- Avastin n=312)	A randomized, double-blind, parallel-group, multicenter study. Treatment was administered until disease progression, unacceptable toxicity or withdrawal of consent – 52 weeks maximum duration	15 mg/kg of MB02 or EU-Avastin by IV infusion every 3 weeks (cycle 1-6) with paclitaxel/ carboplatin chemotherapy (from cycle 7 onwards) MB02 or EU-Avastin administered as monotherapy	Objective response rate (ORR) at study week 18
BEVZ92-A-01-13 (Argentina, Brazil, India, Spain, Ukraine) MB02 DP used in this study (BEVZ92) was manufactured at a different site to that used in all other clinical studies	Primary objective: To compare the PK profile of BEVZ92 and EU-Avastin Secondary objectives: To evaluate and compare additional PK parameters; to compare the safety profile and immunogenicity, and ORR and PFS of BEVZ92 and EU-Avastin.	N=142 patients with metastatic colorectal cancer (n=71 per treatment arm)	Open label, randomised, parallel arm study Maximum duration was 122 weeks	5 mg/kg BEVZ92 or EU-Avastin administered in combination with FOLFOX or FOLFIRI by IV infusion once every two weeks	AUC0-336h AUCSS
MB02-A-05-18 (Germany)	Primary objective: To investigate and compare the PK profiles of MB02 and US- and EU-Avastin Secondary objectives: To compare other PK parameters and the safety profiles and immunogenicity	114 healthy male volunteers (n=38 per treatment arm)	Double blind, randomised, parallel arm Maximum duration was 19 weeks	Single dose of 3 mg/kg MB02, or US- or EU-Avastin administered by IV infusion	AUC(0-inf) Cmax
MB02-A-04-18 (Japan)	Primary objective: To investigate and compare the PK profiles of MB02 and EU-Avastin Secondary objectives: To compare other PK parameters and the safety profiles and immunogenicity	48 healthy male volunteers (n=24 per treatment arm)	Double blind, randomised, parallel arm Minimum duration was 14 weeks	Single dose of 3 mg/kg MB02, or EU-Avastin administered by IV infusion	AUC(0-inf)

2.4.2. Pharmacokinetics

The PK was characterized in healthy subjects in three clinical studies. The pivotal study ***MB02-A-02-17*** was a randomised, double-blind, three-arm, single 3 mg/kg dose, parallel study comparing the pharmacokinetics, safety and immunogenicity of MB02, US-licensed Avastin and EU-approved Avastin in healthy male volunteers, conducted at two sites in the United Kingdom.

PK evaluation is further supplemented with data from two single-dose PK/ immunogenicity studies in healthy volunteers (MB02-A-04-18 and MB02-A-05-18).

- A phase I, single-dose pharmacokinetics study conducted in Germany with 114 healthy volunteers, comparing MB02 to EU Avastin and US Avastin (***MB02-A-05-18***) with a study design similar to the study MB02-A-02-17 to support FDA filing.
- A phase I, single-dose comparative pharmacokinetics study was conducted in Japan with 48 healthy volunteers comparing MB02 to EU Avastin (***MB02-A-04-18***) to support PMDA filing.

Note: A phase I comparative pharmacokinetics study in patients with metastatic colorectal cancer (***BEVZ92-A-01-13***) was performed as part of the clinical development program oMB02. Only safety results from this study are described in the dossier since a drug product different from the to-be-marketed product was used.

Study MB02-A-02-17 - Pivotal Pharmacokinetics

A total of 114 subjects were randomized to one of three treatment arms in a 1:1:1 ratio to receive a single 3 mg/kg dose of either MB02, US-licensed Avastin and EU-approved Avastin, and 113 subjects completed the study. The study was performed between 15 November 2017 (date of first informed consent) and 29 May 2019 (date of final poststudy observation) at two sites in the UK.

The population consisted of healthy male subjects aged between 18 and 55 years, inclusive, with a body mass index between 18.5 and 29.9 kg/m^2, inclusive. 51.8% of subjects had a body weight ≥60.0 to <77.5 kg and 47.4% had a body weight ≥77.5 to <95.0 kg. The majority of subjects were White/Caucasian (95; 83.3%).

Data of all subjects who entered the study were included in the PK, safety and immunogenicity analyses. The PK population comprised all 114 subjects. PK parameters (other than Cmax and tmax) from 1 subject (administered US Avastin) were not included in the summary and inferential statistics due to the subject having an incomplete, and thus unrepresentative, PK profile.

Doses of 3 mg/kg MB02 (Batch #17A043), US Avastin (Batch #3155155 and #3240772) and EU Avastin (Batch B8027H01 and B8034H02) were administered as a slow intravenous (IV) infusion, (over approximately 90 minutes). The total duration of trial participation for each subject (from screening through to the final visit) was max. 19 weeks.

Blood sampling for PK was performed pre-dose, and at hour 1.5, 2, 3, 4, 5, 6, 8, 12, 24, day 3, 4, 5, 6, 7, 8, 10, 14, 21, 28, 42, 56, 78 and day 100 post-dose.

Immunogenicity samples were collected at pre-dose (D-1) and days 14, 28, 56 and 78.

The **primary PK parameter endpoints** were maximum observed serum concentration (**Cmax**) and area under the serum concentration-time curve (AUC) from time zero extrapolated to infinity [**AUC(0-∞)**] for bevacizumab.

The **secondary PK endpoints** included area under the concentration-time curve from time 0 to the time of last quantifiable concentration (**AUC(0-t)**), time of observed maximum serum concentration

(**tmax**), apparent serum terminal elimination half-life (**t1/2**), and total body clearance of drug after IV administration (**CL**).

PK parameters were derived by using standard non-compartmental methods.

Statistical methods:

MB02 was considered to be bioequivalent to US Avastin and EU Avastin if the 90% confidence intervals (CIs) for the ratios of MB02 relative to US Avastin and EU Avastin were completely contained within the interval 0.80 to 1.25 for AUC(0-∞) and Cmax. The PK parameters (AUC[0-∞], AUC[0-t], and Cmax) were log transformed (base e) prior to analysis and were analysed using an ANCOVA model. The model included treatment as a fixed effect and body weight as a covariate.

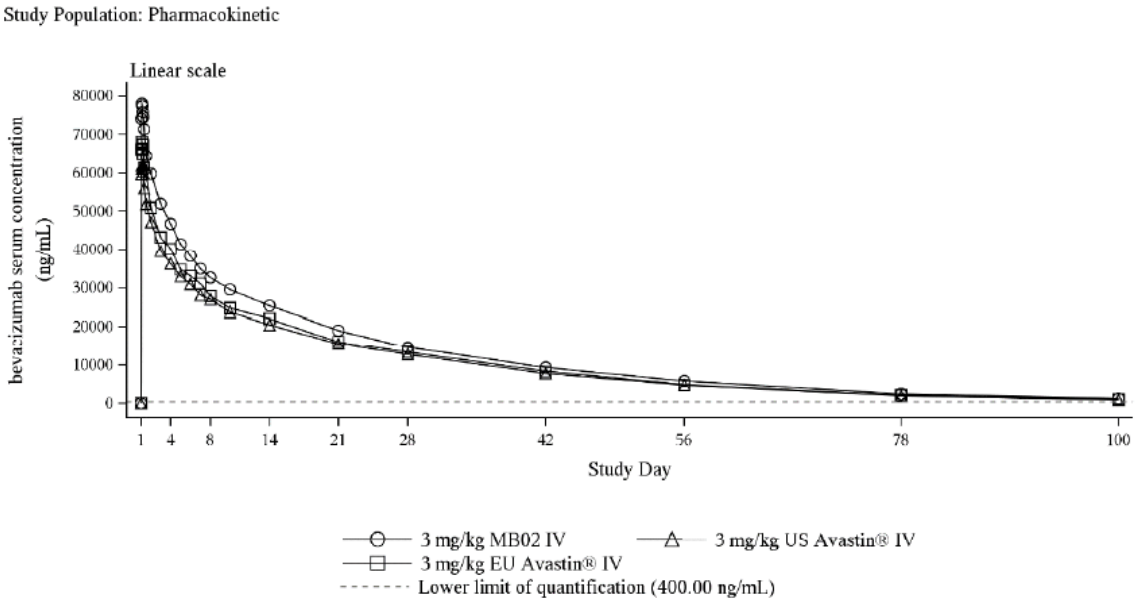
An additional sensitivity analysis was also performed using the same methodology as the primary analysis but using the protein-adjusted PK parameters as the response variables to assess the impact of the actual protein content on the study results.

The protein-adjusted analyses were derived by dividing each parameter, AUC(0-∞), AUC(0-t) measured in (h*ng/mL), and Cmax measured in (ng/mL), by the actual protein content of the product batch in (mg/mL). This kind of analysis delivers AUC(0-∞) in (h*ng/mL)/(mg/mL), AUC(0-t) in (h*ng/mL)/(mg/mL) and Cmax in (ng/mL)/(mg/mL) which are not the actual area under the plasma drug concentration-time curve or peak concentration, but a new outcome variable formed by the division.

Results:

- Primary PK Parameters:

The mean serum concentration profiles across all days on a linear scale for the PK population are presented for MB02 and EU-approved Avastin in Figure 1. Statistical comparison of PK parameters of MB02 and EU-approved Avastin for the PK population are presented in the Table 2.



Reference: Table/Listing 14.2.1-3a/16.2.6-1a

Figure 1: Arithmetic Mean Serum Concentration Profiles of Becacizumab Across All Days-Pharmacokinetic Population

Table 2: Statistical Comparison of PK Parameters for MB02 and EU Avastin Pharmacokinetic Population

Parameter	Treatment	n	GLSM	Ratio of GLSMs MB02:EU Avastin® (90% CI)
$AUC_{(0-t)}$ (h*ng/mL)	3 mg/kg MB02 IV (N=38)	38	27441093	1.16 (1.10, 1.22)
	3 mg/kg EU Avastin IV (N=38)	38	23650351	
$AUC_{(0-\infty)}$ (h*ng/mL)	3 mg/kg MB02 IV (N=38)	38	28241106	1.16 (1.09, 1.22)
	3 mg/kg EU Avastin IV (N=38)	38	24427884	
C_{max} (ng/mL)	3 mg/kg MB02 IV (N=38)	38	83220	1.12 (1.03, 1.22)
	3 mg/kg EU Avastin IV (N=38)	38	74225	

Source: Table 14.2.1-1.1a
Abbreviations: $AUC_{(0-t)}$ = area under the concentration-time curve from time 0 to the time of last quantifiable concentration; $AUC_{(0-\infty)}$ = area under the concentration-time curve from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum serum concentration observed; GLSM = geometric least squares mean; N = number of subjects in the Pharmacokinetic population per treatment; n = number of subjects with data available.

Parameter	Treatment	n	GLSM	Ratio of GLSMs MB02:US Avastin® (90% CI)
$AUC_{(0-t)}$ (h*ng/mL)	3 mg/kg MB02 IV (N=38)	38	27441929	1.23 (1.16, 1.31)
	3 mg/kg US Avastin IV (N=38)	37	22290090	
$AUC_{(0-\infty)}$ (h*ng/mL)	3 mg/kg MB02 IV (N=38)	38	28243284	1.23 (1.16, 1.31)
	3 mg/kg US Avastin IV (N=38)	37	22897787	
C_{max} (ng/mL)	3 mg/kg MB02 IV (N=38)	38	83207	1.28 (1.18, 1.39)
	3 mg/kg US Avastin IV (N=38)	38	65070	

Source: Table 14.2.1-1.1a
Abbreviations: $AUC_{(0-t)}$ = area under the concentration-time curve from time 0 to the time of last quantifiable concentration; $AUC_{(0-\infty)}$ = area under the concentration-time curve from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum serum concentration observed; GLSM = geometric least squares mean; N = number of subjects in the Pharmacokinetic population per treatment; n = number of subjects with data available.

Parameter	Treatment	n	GLSM	Ratio of GLSMs EU Avastin®:US Avastin® (90% CI)
$AUC_{(0-t)}$ (h*ng/mL)	3 mg/kg US Avastin IV (N=38)	37	22335142	
	3 mg/kg EU Avastin IV (N=38)	38	23698812	1.06 (1.00, 1.12)
$AUC_{(0-\infty)}$ (h*ng/mL)	3 mg/kg US Avastin IV (N=38)	37	22943305	
	3 mg/kg EU Avastin IV (N=38)	38	24475912	1.07 (1.00, 1.13)
C_{max} (ng/mL)	3 mg/kg US Avastin IV (N=38)	38	65185	
	3 mg/kg EU Avastin IV (N=38)	38	74397	1.14 (1.05, 1.24)

Source: Table 14.2.1-1.1a
Abbreviations: $AUC_{(0-t)}$ = area under the concentration-time curve from time 0 to the time of last quantifiable concentration; $AUC_{(0-\infty)}$ = area under the concentration-time curve from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum serum concentration observed; GLSM = geometric least squares mean; N = number of subjects in the Pharmacokinetic population per treatment; n = number of subjects with data available.

The 90% CI for the geometric mean ratio for the primary parameters AUC(0-∞), and Cmax, as well as for AUC(0-t), were fully contained within the predefined equivalence limits of 0.80 to 1.25, and therefore demonstrated similarity between MB02 and EU Avastin, and EU and US Avastin for all parameters.

For one subject in the MB02- and EU Avastin treatment arm each, bevacizumab pre-dose concentrations were detected. Nevertheless, values were only slightly above LLOQ, below 5% of Cmax, and were included in descriptive statistics and PK analysis.

In general, as assessed by the geometric CV%, low between-subject variability was observed for AUC(0-t) and AUC(0-∞), and moderate between-subject variability for Cmax was noted for all treatment arms, with values ranging from 14.2% to 16.9%, 15.2% to 17.8% and 21.9 to 25.3%, respectively.

- Secondary Pharmacokinetic Parameters:

Table 3: Summary of Pharmacokinetic Parameters for Bevacizumab-Pharmacokinetic Population

Parameter	3 mg/kg MB02 IV (N=38)	3 mg/kg US Avastin® IV (N=38)	3 mg/kg EU Avastin® IV (N=38)
$AUC_{(0-t)}$ (h*ng/mL)	27400000 (15.5)	22300000 (16.9)[b]	23700000 (14.2)
$AUC_{(0-\infty)}$ (h*ng/mL)	28200000 (16.3)	22900000 (17.8)[b]	24500000 (15.2)
C_{max} (ng/mL)	83000 (22.4)	65200 (21.9)	74400 (25.3)
t_{max} (h)[a]	2.51 (1.62-71.98)	4.00 (1.62-11.98)	3.00 (1.57-12.00)
$t_{1/2}$ (h)	451 (14.4)	437 (15.5)[b]	449 (19.3)
k_{el} (h^{-1})	0.00154 (14.4)	0.00158 (15.5)[b]	0.00155 (19.3)
CL (L/h)	0.00814 (16.5)	0.0101 (17.9)[b]	0.00947 (15.4)
V_z (L)	5.30 (12.8)	6.37 (14.2)[b]	6.13 (14.8)

Source: Table 14.2.1-2a
Abbreviations: $AUC_{(0-t)}$ = area under the serum concentration-time curve from time zero to the time of the last observable concentration; $AUC_{0-\infty}$ = area under the serum concentration-time curve from time zero to infinity; CL = total body clearance of drug after intravenous administration; C_{max} = maximum observed serum concentration; CV = coefficient of variation; k_{el} = elimination rate constant of the terminal phase; N = number of subjects; $t_{1/2}$ = apparent serum terminal elimination half-life; t_{max} = time of maximum observed serum concentration; V_z = volume of distribution during terminal phase after intravenous administration.
Note: Geometric mean (CV%) data are presented
[a] Median (min-max)
[b] N = 37

In addition, the secondary endpoints were in support of PK similarity. The median Tmax was slightly longer with EU-Avastin compared to MB02: 3h (arithmetic mean: 3.70h) vs. 2.51h (arithmetic mean: 5.27 h), respectively. For US Avastin the median Tmax was at 4 hours after start of infusion. The majority of subjects experienced Cmax within 6 hours after the start of infusion.
A prolonged Tmax of up to 12 hours was reported in several subjects receiving MB02 and EU-Avastin (7 subjects and 8 subjects, respectively), with one subject in the MB02 arm of the study not reaching Cmax until approximately 72 hours post-infusion.

After reaching Cmax, observed serum concentrations declined in a biphasic manner with a slow terminal elimination phase. Similar geometric mean (%CV) elimination half-lives (t1/2) of 451 (14.4%), 437 (15.5%) and 449 (19.3%) hours were determined for MB02, US and EU Avastin respectively. The elimination rate constants were similar.

Sensitivity analysis:
Due to variability in the actual protein content between the study drugs and study drug batches, which had the potential to influence the study results, protein-adjusted sensitivity analyses for AUC(0-∞), AUC(0-t), and Cmax were also conducted.

Table 4: Statistical Comparison of Protein-adjusted PK Parameters for MB02 and EU Avastin-Pharmacokinetic Population

Comparison (Test versus Reference): MB02 versus EU Avastin®

Parameter	Treatment	n	GLSM	Ratio of GLSMs MB02:EU Avastin® (90% CI)
$AUC_{(0-t)}$ (h*ng/mL) /(mg/mL)	3 mg/kg MB02 IV (N=38)	38	1008887	1.02 (0.969, 1.07)
	3 mg/kg EU Avastin IV (N=38)	38	989107	
$AUC_{(0-\infty)}$ (h*ng/mL) /(mg/mL)	3 mg/kg MB02 IV (N=38)	38	1038298	1.02 (0.962, 1.07)
	3 mg/kg EU Avastin IV (N=38)	38	1021627	
C_{max} (ng/mL) /(mg/mL)	3 mg/kg MB02 IV (N=38)	38	3060	0.986 (0.903, 1.08)
	3 mg/kg EU Avastin IV (N=38)	38	3104	

Source: Table 14.2.1-1.2a

Abbreviations: $AUC_{(0-t)}$ = area under the concentration-time curve from time 0 to the time of last quantifiable concentration; $AUC_{(0-\infty)}$ = area under the concentration-time curve from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = maximum serum concentration observed; GLSM = geometric least squares mean; N = number of subjects in the Pharmacokinetic population per treatment; n = number of subjects with data available.

The additionally performed sensitivity analysis correcting for actual protein content confirmed pharmacokinetic similarity, showing no statistically significant difference, with point estimates close to "1".

Upon request, bioequivalence assessment on protein-unadjusted PK parameters was performed, including the actual protein in the model as a nested parameter of treatment. The ratios of the geometric means and CIs for MB02 vs EU-Avastin support bioequivalence, with values of 0.892 (90%CI 0.837 to 0.950), 0.885 (90%CI 0.829 to 0.946) and 0.897 (90%CI 0.818 to 0.984) for AUC0-inf, AUC0-t and Cmax, respectively.

In general, as assessed from the geometric CV%, between-subject variability remained similar following protein adjustment compared to the unadjusted AUCs and Cmax.

The sensitivity analyses performed of MB02 vs US-Avastin as well as the comparison of EU- vs. US-Avastin demonstrated biosimilarity in the primary endpoints AUC and Cmax as well. Nevertheless, even in the protein corrected analysis, Cmax was statistically significantly different, and the upper 90% CI close to the acceptance limit: 1.12 (1.02, 1.22).

Study MB02-A-05-18:

The design, conduct and analysis of study **MB02-A-05-18** was identical to that of study MB02-A-02-17, except that is was conducted in Germany. The applicant has clarified that during the execution of Study MB02-A-02-17, a difference in the protein concentration of the vials used was identified. Considering the possible impact of these differences to achieve bioequivalence between the three products MB02, EU-approved Avastin and US-licensed Avastin, a new clinical study with the same design was initiated in order to avoid any delay in the regulatory strategy planned for registration of MB02 in the EU and the US.

The study was performed between 17 September 2019 and 17 March 2020 in Germany. The analysis of bevacizumab concentrations was performed in the UK.

A total of 114 subjects were randomized to one of 3 treatment arms in a 1:1:1 ratio, and 113 subjects completed the study. The population consisted of healthy male subjects aged between 18 and 55 years, inclusive, with a body mass index between 18.5 and 29.9 kg/m^2. In each treatment arm, 42.1% of subjects had a body weight ≥60.0 to <77.5 kg and 57.9% had a body weight ≥77.5 to <95.0 kg. The majority of subjects were White (108; 94.7%).

Data of all subjects who entered the study were included in the PK, safety and immunogenicity analyses. The PK population comprised all 114 subjects.

Doses of 3 mg/kg MB02 (Batch #19A010), US Avastin (Batch # 3301269) and EU Avastin (Batch N7261H05) were administered as a 90-minute i.v. infusion. The total duration of trial participation for each subject (from Screening through to the final visit) was max. 19 weeks.

Study methods were identical to that of study MB02-A-02-17.

Results:

- Primary PK Parameters:

Table 5: Statistical Analysis of the Primary Pharmacokinetic Parameters of Bevacizumab: MB02 versus EU Avastin (Pharmacokinetic Population)

Parameter	Treatment	n	Geometric Least Square Means	Ratio of Geometric Least Square Means (MB02:EU Avastin)	90% CI for the Ratio (Test:Reference) Lower	Upper	Between-Subject CV%
$AUC_{(0-\infty)}$ (h*ng/mL)	3 mg/kg MB02 IV (N = 38)	38	30700000	-	-	-	15.9
	3 mg/kg EU Avastin® IV (N = 38)	38	28800000	1.07	1.00	1.14	16.2
C_{max} (ng/mL)	3 mg/kg MB02 IV (N = 38)	38	86100	-	-	-	24.8
	3 mg/kg EU Avastin® IV (N = 38)	38	81100	1.06	0.976	1.16	20.2

ANCOVA = analysis of covariance; AUC = area under the serum concentration-time curve; $AUC_{(0-\infty)}$ = AUC from time 0 to infinity; CI = confidence limit; C_{max} = maximum observed serum concentration; CV = coefficient of variation; LS = least square; N = number of subjects in the PK population per treatment; n = number of subjects with data available; PK = pharmacokinetic
The PK parameters were log transformed (base e) before analysis and analysed using an ANCOVA model. The model included treatment as a fixed effect and body weight as a covariate.
The ratio and corresponding CIs were back-transformed from the difference and CIs calculated on the $\log_e$ scale.
Data source: Table 14.2.1-1.1

The ratio of geometric LS mean (MB02: EU Avastin) for AUC(0-∞) was 1.07 (90% CI: [1.00, 1.14]) and for Cmax was 1.06 (90% CI: [0.976, 1.16]).The 90% CIs were fully contained within the predefined equivalence limits of 0.80 to 1.25. The resulting 90% CI for AUC(0-∞), where the lower limit covers exactly "1", even indicates a slight overexposure of MB02.
The statistical comparison of MB02 vs. US Avastin and EU Avastin vs. US Avastin could also demonstrate bioequivalence in terms of AUCs and Cmax.

Table 6: Statistical Analysis of the Primary Pharmacokinetic Parameters of Bevacizumab: MB02 versus US Avastin (Pharmacokinetic Population)

Parameter	Treatment	n	Geometric Least Square Means	Ratio of Geometric Least Square Means (MB02:US Avastin)	90% CI for the Ratio (Test:Reference) Lower	Upper	Between-Subject CV%
$AUC_{(0-\infty)}$ (h*ng/mL)	3 mg/kg MB02 IV (N = 38)	38	30700000	-	-	-	15.9
	3 mg/kg US Avastin® IV (N = 38)	38	30800000	0.998	0.944	1.05	12.8
C_{max} (ng/mL)	3 mg/kg MB02 IV (N = 38)	38	86100	-	-	-	24.8
	3 mg/kg US Avastin® IV (N = 38)	38	87500	0.983	0.897	1.08	24.1

Table 7: Statistical Analysis of the Primary Pharmacokinetic Parameters of Bevacizumab: EU Avastin versus US Avastin (Pharmacokinetic Population)

Parameter	Treatment	n	Geometric Least Square Means	Ratio of Geometric Least Square Means (EU Avastin:US Avastin)	90% CI for the ratio (Test : Reference) Lower	Upper	Between-Subject CV%
$AUC_{(0-\infty)}$ (h*ng/mL)	3 mg/kg EU Avastin® IV (N = 38)	38	28700000	-	-	-	16.2
	3 mg/kg US Avastin® IV (N = 38)	38	30800000	0.934	0.884	0.988	12.8
C_{max} (ng/mL)	3 mg/kg EU Avastin® IV (N = 38)	38	81000	-	-	-	20.4
	3 mg/kg US Avastin® IV (N = 38)	38	87500	0.926	0.851	1.01	24.4

- In general, between-subject variability was low (< 25%) for MB02, US Avastin and EU Avastin treatments with geometric CV% values for AUC(0-∞) and Cmax, ranging from 12.8 to 24.8%.Secondary PK parameters:

Table 8: Summary Pharmacokinetic Parameters of Bevacizumab (Pharmacokinetic Population)

Parameter	3 mg/kg MB02 IV (N = 38)	3 mg/kg US Avastin IV (N = 38)	3 mg/kg EU Avastin IV (N = 38)
$AUC_{(0-t)}$ (h*ng/mL)	29900000 (15.6)	29900000 (12.5)	27900000 (16.0)*
$AUC_{(0-\infty)}$ (h*ng/mL)	30700000 (16.2)	30700000 (12.9)	28800000 (16.4)
$\%AUC_{extrap}$ (%)	2.6 (1.45)	2.8 (1.5)	3.3 (4.6)
C_{max} (ng/mL)	86100 (24.8)	87500 (24.9)	81100 (20.0)
t_{max} (h)	4.0 (1.5, 8.0)	4.0 (1.5, 12.0)	4.0 (1.5, 11.9)
$t_{1/2}$ (h)	443 (16.9)	458 (16.1)	444 (14.5)
k_{el} (1/h)	0.00157 (16.9)	0.00151 (16.1)	0.00156 (14.5)
CL (L/h)	0.00770 (18.1)	0.00766 (16.2)	0.00823 (18.5)
V_z (L)	4.92 (15.6)	5.07 (16.7)	5.28 (18.2)
V_{ss} (L)	4.76 (15.8)	4.87 (16.0)	5.11 (17.9)

AUC = area under the serum concentration-time curve; $AUC_{(0-t)}$ = AUC from time zero to the time of last quantifiable concentration; $AUC_{(0-\infty)}$ = AUC from time zero extrapolated to infinity; CL = total body clearance of drug after intravenous administration; C_{max} = maximum observed serum concentration; CV = coefficient of variation; IV = intravenous; k_{el} = elimination rate constant of the terminal phase; mg = milligram; N = number of subjects; t½ = apparent serum terminal elimination half-life; tmax = time of maximum observed serum concentration; V_{ss} = volume of distribution at steady state after intravenous administration; V_z = volume of distribution during the terminal elimination phase after intravenous administration; $\%AUC_{extrap}$ = percentage of AUC that is due to extrapolation from the last quantifiable concentration to infinity
* n = 37
Note: Geometric mean (geometric CV%) results are presented unless otherwise indicated.
Arithmetic mean (SD) is presented for $\%AUC_{extrap}$.
Median (minimum, maximum) is presented for t_{max}.
Data source: Table 14.2.1-2

The geometric mean terminal elimination half-life (t1/2) of bevacizumab was similar for MB02 treatment compared to US Avastin and EU Avastin treatments, with values of 443 hours (18.46 days), 458 hours (19.08 days) and 444 hours (18.5 days), respectively. The secondary endpoints were in support of PK similarity.

Overall, the PK was comparable between MB02 and EU Avastin.

Note: The statistical comparison of MB02 vs. US Avastin and EU Avastin vs. US Avastin could also demonstrate bioequivalence.

Study MB02-A-04-18:

With the exception of the lack of an US-Avastin treatment arm, the design, conduct and analysis for this study is similar to that described for the pivotal study MB02-A-02-17 with some differences: there was only one primary endpoint (AUC0-inf) and the duration of safety follow up was shorter (70 days compared to 100 days).

A total of 48 subjects were randomized following 1:1 ratio and stratified into 2 groups based on body weight (⩾50 to <67 kg, and ⩾67 to <100 kg respectively). The study was double-blinded.

The study population consisted of Japanese healthy male subjects between 20 and 55 years of age, inclusive, with a BMI ⩾18.5 to ⩽28 kg/m2, inclusive, and a BW between ⩾50 and ⩽100 kg, inclusive. 24 subjects (50%) were included in the MB02- and 24 subjects (50%) included in EU Avastin treatment arm. The mean age and BMI were 28.3 years and 22.54 kg/m2 and 28.5 years and 23.33 kg/m2 for MB02 and EU Avastin treatment arms, respectively. The mean demographic parameters were comparable between treatment arms.

The study was performed between 31 August 2019 (first subject visit) and 27 December 2019 (last subject completed) at one study center in Japan. Bioanalytical analysis was performed in the UK.

49 subjects were enrolled and randomized and 48 subjects were assigned to a treatment sequence and dosed. One subject was enrolled and randomized in the study to EU Avastin but not dosed as the subject was withdrawn himself prior to dosing. All dosed subjects completed the study.

Doses of 3 mg/kg MB02 (Batch #19A010) and Avastin sourced from the EU (Batch #N7261H05) were administered as a slow 90-minute i.v. infusion.

Results:

- Primary PK Parameter:

Table 9: Statistical Bioequivalence Analysis of Bevacizumab Following Single IV Doses of MB02 and Avastin to Japanese Healthy Male Subjects

Study Population: Pharmacokinetic
Comparison: MB02 versus EU Avastin®

Parameter	Treatment	n	Geometric least squares means	Ratio of geometric least squares means (MB02 : EU Avastin®)	90% CI for the ratio (Test : Reference) Lower	Upper	Between-subject CV%
$AUC_{(0-\infty)}$ (h*ng/mL)	3 mg/kg MB02 IV (N = 24)	24	30200000				14.7
	3 mg/kg EU Avastin® IV (N = 24)	24	29000000	1.04	0.981	1.11	10.8

N = number of subjects in the Pharmacokinetic population per treatment, n = number of subjects with data available
The PK parameters are log transformed (base e) prior to analysis and analyzed using an ANCOVA model. The model includes treatment as a fixed effect and body weight as a covariate.
The ratio and corresponding confidence limits are back-transformed from the difference and confidence limits calculated on the $\log_e$ scale.

Data source: Table 14.2.1-1.1

The ratio of geometric LS means for AUC(0-∞) was 1.04. The 90% CI for the geometric means ratio for primary PK endpoint of AUC(0-∞) (0.981, 1.11) was fully contained within the predefined equivalence limits of 0.80 to 1.25.

- Secondary PK Parameters:

Table 10: Statistical Bioequivalence Analysis of Bevacizumab Following Single IV Doses of MB02 and Avastin to Japanese Healthy Male Subjects

Study Population: Pharmacokinetic
Comparison: MB02 versus EU Avastin®

Parameter	Treatment	n	Geometric least squares means	Ratio of geometric least squares means (MB02 : EU Avastin®)	90% CI for the ratio (Test : Reference) Lower	Upper	Between-subject CV%
$AUC_{(0-t)}$ (h*ng/mL)	3 mg/kg MB02 IV (N = 24)	24	28200000				12.3
	3 mg/kg EU Avastin® IV (N = 24)	24	26800000	1.05	0.997	1.11	9.18
C_{max} (ng/mL)	3 mg/kg MB02 IV (N = 24)	24	92900				22.1
	3 mg/kg EU Avastin® IV (N = 24)	24	82300	1.13	1.03	1.24	16.9

N = number of subjects in the Pharmacokinetic population per treatment, n = number of subjects with data available
The PK parameters are log transformed (base e) prior to analysis and analysed using an ANCOVA model. The model includes treatment as a fixed effect and body weight as a covariate.
The ratio and corresponding confidence limits are back-transformed from the difference and confidence limits calculated on the $\log_e$ scale.
Data source: Table 14.2.1-1.1

The ratios of geometric LS means for AUC(0-t) and Cmax were 1.05 and 1.13, respectively. The 90% CI for the geometric means ratios for AUC(0-t) and Cmax (0.997, 1.11 and 1.03, 1.24, respectively) were fully contained within the predefined equivalence limits of 0.80 to 1.25.

Between-subject variability was low for MB02 and EU Avastin with geometric CV% of AUC and Cmax values ranging from 9.6 to 24.1%.

Descriptive statistics were described for the following parameters:

Table 11: Summary Serum Pharmacokinetic Parameters of Bevacizumab Following Single IV Doses of MB02 and EU-approved Avastin to Japanese Healthy Male Subjects

Parameter	MB02 (Biosimilar) (N=24)	EU Avastin® (Reference) (N=24)
$AUC_{(0-t)}$ (h*ng/mL)	28100000 (12.7)	26900000 (9.55)
$AUC_{(0-\infty)}$ (h*ng/mL)	30200000 (14.9)	29000000 (11.1)
$\%AUC_{extrap}$ (%)	6.77 (2.93)	7.38 (2.58)
C_{max} (ng/mL)	92400 (24.1)	82800 (17.4)
t_{max} (h)	4.50 (1.52, 24.00)	4.00 (1.52, 12.00)
$t_{1/2}$ (h)	430 (16.4)	450 (12.9)
k_{el} (1/h)	0.00161 (16.4)	0.00154 (12.9)
CL (L/h)	0.00660 (18.3)	0.00702 (14.4)
V_z (L)	4.10 (13.2)	4.56 (12.5)
V_{ss} (L)	3.88 (11.7)	4.28 (13.3)

Source: Table 14.2.1-2
Note: Geometric mean (geometric CV%) results are presented unless otherwise indicated.
Arithmetic mean (SD) is presented for $\%AUC_{extrap}$.
Median (minimum, maximum) is presented for t_{max}.
Abbreviations: $AUC_{(0-t)}$ = area under the concentration-time curve from time zero to the time of last quantifiable concentration; %AUCextrap = percentage of AUC that is due to extrapolation from the last quantifiable concentration to infinity; $AUC_{(0-\infty)}$ = area under the concentration-time curve from time zero extrapolated to infinity; CL = total body clearance of drug after IV administration; C_{max} = maximum observed serum concentration; CV% = coefficient of variation; N = number of subjects studied; $t_{1/2}$ = apparent serum terminal elimination half-life; k_{el} = elimination rate constant of the terminal phase; t_{max} = time of maximum observed serum concentration; V_z = volume of distribution during the terminal phase after IV administration; V_{ss} = volume of distribution at steady state after IV administration.

The serum bevacizumab concentration versus time profiles following IV infusion administration was similar for MB02 and EU Avastin treatments, which declined slowly in a biphasic manner with resultant geometric mean t1/2 values of 430 hours (18 days) and 450 hours (18.75 days), respectively.

Overall, the statistical analysis showed similarity regarding PK parameters between MB02 and EU Avastin in the Japanese population.

2.4.3. Pharmacodynamics

No clinical pharmacodynamic studies have been performed with MB02. No validated PD markers considered relevant to predicting efficacy of bevacizumab in patients exist. Therefore, no PD markers were included in the PK studies MB02-A-02-17, MB02-A-04-18, MB02-A-05-18.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic properties of MB02 were compared with both EU- and US-sourced bevacizumab (Avastin) in a pivotal phase I study in healthy male subjects (**MB02-A-02-17**), following a 3 mg/kg body weight single IV infusion. The study design is considered appropriate to sensitively detect potential PK differences between MB02 and Avastin.

In support of a global marketing authorisation, comparison with the US-licensed product (US Avastin) was also undertaken. The data generated using EU Avastin are used in support of the MAA while the data generated using US Avastin are presented as supportive data, only.

A parallel-group design was chosen due to the long half-life of bevacizumab of approximately 20 days, and the potential of ADA response, as recommended in respective EMA guidance. The selected sampling time points are able to reflect absorption, tmax and elimination period. The sampling

duration of 100 days covers about 5 half-lives of bevacizumab, which is acceptable. For none of the subjects, %AUCext was >20%, demonstrating that samples were taken for a sufficient time period. The selected 3 mg/kg dose is lower than approved doses of Avastin. Nevertheless, studies with Avastin showed that PK was linear at doses ranging from 1 to 20 mg/kg, and the lower dose level was selected based upon the dosages used in published studies of bevacizumab, which is acceptable, also taking into account ethical reasons and safety aspects of the healthy volunteers´ population.

No new pharmacodynamic data have been submitted in this MAA. Validated PD markers considered relevant for predicting efficacy of bevacizumab in patients do not exist. Thus, no PD markers were included in the PK study MB02-A-02-17 or supportive studies MB02-A-04-18 and MB02-A-05-18.

Similarity between MB02 and EU Avastin was demonstrated, as the 90% CI for the geometric LS means ratios of protein-unadjusted AUCs and Cmax parameters were fully contained within the predefined bioequivalence limits of 0.80 to 1.25. The point estimates for AUC and Cmax were 1.16 and 1.12, respectively, with an upper limit of the 90% CI of 1.22 for all three parameters, suggesting slight overexposure. In addition, the secondary endpoints were in support of PK similarity. The statistical comparison of MB02 vs. US Avastin did not demonstrate bioequivalence in terms of protein-unadjusted AUCs and Cmax ratios. The 90% CI of geometric least squares (LS) means ratios were not fully contained within the bioequivalence limits, with the upper bound of the CI exceeding the 1.25 limit for all 3 parameters, AUC 0-inf, AUC0-t and Cmax: The GLSM ratio of both, AUC0-inf and AUC0-t, was 1.23 (90% CI 1.16, 1.31), and of Cmax 1.28 (90% CI 1.18, 1.39); for the latter parameter, even the point estimate crossed the upper CI limit.
The statistical comparison of EU-Avastin vs. US-Avastin demonstrated biosimilarity, but a statistically significant difference was observed for Cmax (1.14 [1.18, 1.39]).Primary endpoint results showed a statistically significant difference, as "1" was not included in the GM ratio. In line with EMA guidance, a point estimate or substantive part of the confidence interval lying towards the extremes of the acceptance criteria requires further discussion. This includes instances where unity is excluded from the 90% CI. Specifically, results should be explained and justified in the context of evidence for similarity coming from other comparative studies/analyses in the development programme.

Although the protein content of each batch of MB02, US- and EU-Avastin was within the specified range, variability existed in the actual protein content between batches. Subjects in the US and EU Avastin arms thus received an approximately 12% - 14% lower bevacizumab dose than subjects in the MB02 arm.

The additional sensitivity analysis correcting for actual protein content confirmed pharmacokinetic similarity, showing no statistically significant differences, with point estimates close to "unity". Although the sensitivity analysis is seen with some caution, results regarding PK similarity seem reassuring. A bioequivalence assessment on protein-unadjusted PK parameters was also performed post-hoc including the actual protein in the model as a nested parameter of treatment. The point estimates for AUC0-inf, AUC0-t and Cmax were 0.892, 0.885 and 0.897, respectively, with an upper limit of the 90% CI excluding "1" for all three parameters. This suggests slight underexposure, which is explained by the unbalanced strata in the nested model (29 vs 9 subjects) and the magnitude of the differences, which could lead to an inability to estimate the model parameters due to a lack of variability in the protein content.

A list of the clinical and bioanalytical facilities involved in the MB02-A-02-17 study, which have been inspected by an EU inspectorate, the WHO or another competent authority, was submitted with the D120 responses. The results in both Phase I units, Covance Clinical Research Unit Ltd, Leeds, UK, and PAREXEL International, Harrow, UK, were without critical GCP findings.

PK sampling in the target population is generally encouraged as providing supportive evidence (see Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies –Non-clinical and

Clinical Issues; EMA/CHMP/BMWP/403543/2010). The applicant did not perform any comparative PK evaluation in the efficacy/safety study MB02-C-02-17 in NSCLC patients.

However, the Applicant has satisfactorily justified the lack of comparative PK data in patients as the PK similarity was conducted in the most homogeneous and sensitive population to detect any possible differences between the biosimilar and the RMPs, and comprised three clinical trials involving 276 healthy male subjects. The inter-subject variability was generally low (<25%). The role of target-mediated clearance was also discussed, with the applicant providing supporting literature data. In the absence of target mediated clearance, elimination by intracellular catabolism after fluid phase endocytosis is the major pathway for mAb clearance and FcRn-mediated recycling underlies the prolonged elimination half-lives (approximately 25 days) and linear pharmacokinetics of such antibodies (Tabrizi et al., 2006; Wang et al., 2008). According to the most recent population PK model for bevacizumab in cancer patients, clearance is affected by body weight, serum albumin levels and baseline alkaline phosphatase but not tumour burden (Han et al., 2016a). The data generated from the PK studies conducted in healthy male volunteers as part of the comparability exercise support the notion that MB02 and EU-Avastin are eliminated at similar rates and are thus likely to be cleared via similar routes. It is agreed that there is no evidence for target-mediated clearance of bevacizumab.

A repeated dose bioequivalence study compared PK, safety, efficacy and immunogenicity of the biosimilar candidate and Avastin in patients with metastatic colorectal cancer.

Two further PK studies for US FDA and Japan approval were presented. In the single-dose study **MB02-A-05-18**, MB02 is compared to EU- and US Avastin in 114 subjects. In study MB02-A-04-18, MB02 is compared with EU Avastin in 48 healthy Japanese subjects. Similarity between MB02 and EU Avastin was demonstrated in study **MB02-A-05-18**. The ratio of geometric least squares mean for AUC0-inf was 1.07 (90% CI: [1.00, 1.14]) and for Cmax was 1.06 (90% CI: [0.976, 1.16]). The 90% CIs were fully contained within the predefined equivalence limits of 0.80 to 1.25. The secondary endpoints were in support of PK similarity. Results from study **MB02-A-04-18** showed equivalence between MB02 and EU Avastin following a single 3 mg/kg dose administered as a 90-minute IV infusion in healthy Japanese male subjects. The 90% CIs ratios were fully contained within the pre-defined equivalence limits of 0.80 to 1.25 for the primary endpoint AUC(0-∞) and the secondary endpoints Cmax and AUC(0-t).

2.4.5. Conclusions on clinical pharmacology

The pivotal PK study MB02-A-02-17 in healthy volunteers and the two supportive studies MB02-A-04-18 and MB02-A-05-18 demonstrated similarity of the pharmacokinetics of MB02 and EU Avastin, based on the primary PK parameters. The protein-corrected sensitivity analysis performed post-hoc supports the primary results as is the requested re-analysis for protein correction (including a term for the actual protein content of the product batch in the ANOVA model), therefore, biosimilarity on the PK level can be concluded.

2.5. Clinical efficacy

2.5.1. Dose-response studies and main clinical studies

No dose response study was conducted (see discussion on clinical efficacy).

2.5.2. Main study

MB02-C-02-17

This was a multicentre, double-blind, 1:1 randomized, parallel-group, equivalence study to compare the efficacy and safety of MB02 plus chemotherapy (carboplatin and paclitaxel) versus EU-licensed Avastin plus chemotherapy (carboplatin and paclitaxel) in subjects with Stage IIIB/IV non-squamous NSCLC. The study was conducted at 93 study sites located in 16 countries.

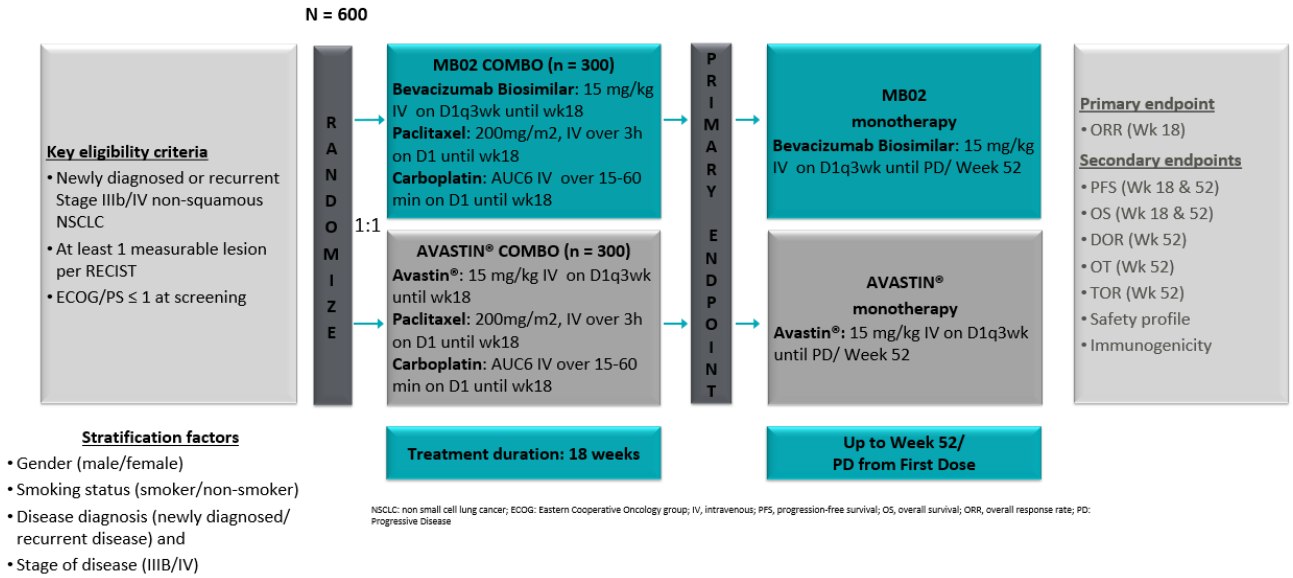


Figure 2: Study Design

Methods

627 subjects with newly diagnosed or recurrent stage IIIb/IV non squamous-NSCLC were randomized to receive either MB02 (n=315) or EU-Avastin (n=312).

Study Participants

Main inclusion criteria

- Aged ≥18 years to ≤80 years.
- Signed informed consent.
- Newly diagnosed or recurrent Stage IIIB/IV non-squamous NSCLC not amenable to curative intent surgery, and were not to have received any systemic therapy for advanced disease.
- Previous radiation therapy if completed >4 weeks before randomization. Palliative radiotherapy to bone lesions was allowed if completed >2 weeks prior to randomization.
- At least 1 unidimensional measurable lesion per RECIST version 1.1 (assessed locally).
- ECOG PS ≤1.
- Adequate hepatic, renal and hematologic functions.
- Systolic blood pressure of ≤140 mm Hg, diastolic blood pressure of ≤90 mm Hg at Screening.
- Women of childbearing potential, and their partners, must have agreed to adhere to pregnancy prevention methods throughout the duration of the study (non-fertile women with hysterectomy, bilateral oophorectomy (ovariectomy), bilateral tubal ligation, or postmenopausal women could have been included).

Main exclusion criteria

- Inability to comply with protocol procedures.
- Participation in another clinical trial or treatment with another investigational agent within 4 weeks or 5 half-lives of investigational agent before randomization, whichever was longer.
- Previously treated with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors.
- Previously treated with chemotherapy, immunotherapy, targeted therapy, or biological therapy for their lung cancer.
- Known malignant central nervous system disease, with the exception of treated brain metastases who had completed treatment (radiation, surgery or stereotactic surgery) and had not received steroids for at least 4 weeks before randomization.
- Current or recent (within 10 days of the first dose of study treatment) use of aspirin (at least 325 mg/day) or other nonsteroidal anti-inflammatory drugs with antiplatelet activity or treatment with dipyridamole.
- Current or recent (within 5 days) use of therapeutic anticoagulation or use of thrombolytic agent. Prophylactic use of low molecular weight heparin was allowed.
- Small cell lung cancer or squamous cell lung cancer.
- Known activating epidermal growth factor receptor and anaplastic lymphoma receptor tyrosine kinase status (locally assessed).
- History of hypersensitivity to bevacizumab, carboplatin, and/or paclitaxel or any of the excipients.
- Known active viral infection, including hepatitis B, hepatitis C, or HIV.
- Pregnant or breastfeeding patients.
- Previous major surgery, open biopsy, open pleurodesis, or significant traumatic injury within 4 weeks before randomization or those anticipated to require major surgery during the study.
- Subjects who have had a core biopsy taken or have had another minor surgical procedure, excluding placement of vascular access device, closed pleurodesis, thoracentesis, and mediastinoscopy, within 1 week of randomization.
- History of abdominal fistula, GI perforation, intra-abdominal abscess within 6 months of randomization.
- Subjects with a non-healing wound, active ulcer, or untreated bone fracture.
- History of hypertensive crisis or hypertensive encephalopathy.
- New York Heart Association ≥ 2 congestive heart failure, or angina, myocardial infarction within 6 months before randomization; symptomatic arrhythmia or serious cardiac arrhythmia requiring medication; abnormal LVEF <50% assessed by ultrasound or multigated acquisition scan.
- Previous malignancy within 3 years of randomization (other than superficial basal cell and superficial squamous (skin) cell carcinoma, or carcinoma in situ of the uterine cervix, bladder, or prostate).
- History of a significant vascular event within 6 months before randomization (including, but not limited to myocardial infarction and stroke or transient ischemic attack).
- Known bleeding diathesis or significant coagulopathy defined as a bleeding event grade ≥2 within 3 months before randomization.
- History of grade ≥2 haemoptysis within 6 months before randomization (≥0.5 teaspoons of bright red blood per event).
- Tumor(s) invading or compressing major blood vessels.

The inclusion/exclusion criteria were in accordance with the Avastin study in advanced NSCLC patients.

Treatments

The study treatment consisted of an initial administration of paclitaxel 200 mg/m2 IV over 3 hours, followed by carboplatin AUC6 IV over 15 to 60 minutes and then, immediately afterwards, either MB02 or EU-Avastin was to be administered 15 mg/kg on Day 1 of each 21 cycle (-1/+3 days) until objective disease progression (DP) or other criteria for treatment discontinuation were met.

MB02/Avastin plus chemotherapy was repeated every 3 weeks for 6 cycles unless there was evidence of disease progression or intolerance of the study treatment. After 6 cycles (i.e., at the start of Cycle 7), subjects could have continued to receive MB02/Avastin monotherapy treatment every 3 weeks until evidence of DP or until unacceptable toxic effects developed. The study duration was 52 weeks. After Week 52, all subjects (including those randomized to Avastin during the study) were offered the opportunity to continue receiving biosimilar MB02 monotherapy until DP, unacceptable toxicity, lost to follow-up, withdrawal of consent, initiation of any new treatment, or death.

The treatment doses and schedules are according to the labelling for Avastin, Paclitaxel and Carboplatin. Dose modifications for both the MB02/Avastin and chemotherapy were not allowed until the Week 18 assessment.

If a subject discontinued MB02/Avastin treatment before completing 6 cycles of therapy and before the primary endpoint at Week 18, the subject was discontinued from study treatment and proceeded to End-of-Treatment Visit.

Tumour Assessments

Tumor assessments were performed using CT and/or MRI of the chest, upper abdomen, and any other involved regions; the same method of assessment used at Screening was used at all subsequent time points.

Tumour response was assessed by the IRC using the RECIST version 1.1 criteria to evaluate ORR. Disease status, PFS, and OS was evaluated by investigators.

Schedule for Tumour Assessment

Baseline assessment was performed up to 28 days before the start of study treatment and ideally as closely as possible to the start of study treatment; it was to include all areas known for possible metastases. Tumour assessments were performed at intervals of 6 weeks, from Cycle 1 Day 1 until the end of Cycle 6 (i.e., 18 weeks after first study drug administration); after Cycle 6, tumour assessments will be performed at intervals of 9 weeks until evidence of disease progression and/or the start of new antitumour treatment, death, or Week 52 (End-of-Study Visit), whichever occurs first. Additional tumour assessments were made at any time if the investigator considered this to be clinically indicated. Tumour measurements will also be performed during the Week 52 End-of-Study Visit if not done within the previous 4 weeks.

Objectives

The primary objective of the study was to demonstrate equivalent efficacy of MB02 and EU-Avastin when used in combination with paclitaxel/carboplatin as measured by the objective response rate (ORR) as assessed according to Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1).

The secondary objectives of the study were as follows:

• To assess progression free survival (PFS) and overall survival (OS) at Week 52 compared with those of Avastin. Duration of overall response (DOR) time to overall response (Time to OR) and observation time (OT) will also be analysed at Week 52 of the study.

• To evaluate the safety profile of MB02 compared with Avastin as per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.03).

• To compare the potential immunogenicity of MB02 and Avastin assessed through determination of ADAs.

The comparison of the safety profile and immunogenicity of MB02 and EU-Avastin are discussed in section 2.6. Clinical safety.

Outcomes/endpoints

Primary endpoint

- **Objective response rate (ORR)** was assigned for a subject if the subject displayed either complete response (CR) or partial response (PR) per RECIST version 1.1 at Week 18.

Secondary efficacy endpoints

- **Progression free survival (PFS)** defined as the time from randomization to subsequent confirmed progression per RECIST version 1.1, or death (whichever occurs first).
- **Overall survival (OS)** defined as the time from randomization to subsequent death.
- **Duration of overall response (DOR)** is the time from date of the first documentation of objective tumour response (CR or PR) to the first documentation of PD, or to death due to any cause in the absence of documented PD.
- Duration of **observation time (OT)** on the study is the time from date of randomization until final follow-up or death.
- **Time to overall response (Time to OR)** is the time from date of randomization until the date of the first documentation of objective tumour response (CR or PR).

Randomisation

Subjects (i.e., the unique subject ID consisting of centre ID and subject ID) were randomly allocated (1:1 ratio) to treatment according to a pre-specified blocked randomization scheme. Randomization was stratified by sex (male/female), smoking status (smoker/non-smoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (Stage IIIB/Stage IV).

Blinding (masking)

The pharmacist at each study site and a specific clinical team from the Clinical Research Organization and the Sponsor was unblinded to treatment assigned. Subjects as well as investigators, all other study staff, laboratories and the rest of the Clinical Research Organization and Sponsor team will remain blinded to treatment assignment up to Week 52. The blind for a specific subject was broken by the investigator (emergency code breaking) only if the investigator considered the information indispensable to the safety of the subject.

All subjects whose treatment was unblinded by the investigator (break blind option, emergency code breaking) while on the study was withdrawn at the moment of unblinding, with the reason for unblinding given as the reason for discontinuation from the study.

The main analysis at Week 18 was carried out by an unblinded study team independent from the blinded study team. Upon and after the analysis and reporting of the Week 18 unblinded data, the blinded study team continued to remain blinded.

Statistical methods

Primary endpoint

Objective response rate (ORR): OR will be assigned for subjects if they experience either CR or PR per RECIST v1.1 at Week 18, as assessed by independent review. This assessment will be carried out by an independent radiology review committee (IRC).

Analysis sets

- The intention to treat (ITT) analysis set consists of all randomized subjects and subjects are analysed according to the randomized treatment.
- The modified intention to treat (mITT) analysis set consists of all randomized subjects who were treated with investigational medicinal product (IMP) and had measurable disease at screening as determined by central radiological review.
- The per protocol set (PPS) consists of all subjects in the mITT set who completed at least the first 6 cycles of IMP and chemotherapy, or who discontinued IMP or chemotherapy after completing at least 4 cycles of IMP and chemotherapy due to reasons allowed per protocol; and for whom no major protocol deviations affecting efficacy occurred up to and including Week 18. Subjects from the PPS will be analysed according to the actual treatment received.

The determination of equivalence is based on the Intention to Treat (ITT) set. Per protocol set (PPS) is used as a supportive set for evaluating sensitivity of the main analysis. Nevertheless, in the equivalence setting, the ITT and the PPS have equal importance and for a robust interpretation have to lead to similar results (Points to consider on switching between superiority and non-inferiority CHMP/EWP/482/99).

Analysis methods

The ORR at Week 18 is calculated as the proportion of subjects with OR, and both the Risk Ratio (RR) of the ORRs (MB02/Avastin) and Risk Difference (RD) of the ORRs (MB02 minus Avastin) is analysed using the ITT, mITT and PP populations. As equivalence criterion on the primary endpoint a 2-sided 90% CI for the respective summary measure were pre-planned to be compared to pre-defined equivalence margins and the broader 2-sided 95% CI are only provided in addition. Taking a 90% CI as primary instead of a 95% CI would increase the type I error rate to 10% and correspond to a two-sided test at a significance level of 10%. Therefore, the 95% CI should be considered primary and the 90% CI only supportive. Any subjects who discontinue study treatment before Week 18 were classed as non-responders in the final analysis of the primary efficacy endpoint (both for RR and RD analysis).

<u>Primary efficacy analysis</u>

For the EMA submission the difference in ORRs is used as the primary efficacy analysis. The statistical hypotheses associated with the primary analysis of ORR at Week 18 using risk difference are:

- H0: (ORRMB02 - ORRAvastin $\leq$ -12%) or (ORRMB02 - ORRAvastin $\geq$ +12%)
- H1: -12% < (ORRMB02 - ORRAvastin) < +12%,

where ORRMB02 and ORRAvastin are the ORRs for MB02 and Avastin, respectively.

The ORR estimate is adjusted for the randomization strata sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (Stage IIIB/Stage IV) using the Cochran-Mantel-Haenszel estimate of the RD and corresponding 2-sided CIs. The Newcombe method is used for estimating the CIs.

A sample size of 300 subjects in each treatment group would show that the two-sided 95% CI of the ORR difference between Avastin and MB02 lies within [-12%, 12%] with 82% power under the alternative that there is no difference in response rate assuming a response rate of 0.429 in both treatment arms.

Supportive analyses of the primary endpoint

1. An equivalence analysis based on the RR with the equivalence margin [0.73, 1.36] is used to ascertain clinical equivalence of the primary efficacy endpoint.
2. In addition to ORR being assessed via an independent radiology review committee (IRC), ORR are assessed based on the investigator's tumour assessment at week 18.

Secondary efficacy analyses

- Overall survival (OS) and progression free survival (PFS).

  Analyses will occur at Week 18 and Week 52; at each analysis, all subject data accrued during the study up to this point will be included to inform survival. The analysis is conducted in the ITT and PP populations for PFS and in the ITT population for OS.

  The Cox proportional hazards model is used to estimate the Hazard Ratio and its 90% CI of MB02 compared with Avastin. The main Cox proportional hazards model includes treatment group (reference: Avastin), with sex, smoking status, disease diagnosis, and disease stage as covariates.

- DOR, OT and Time to OR analyses will occur at Week 52, this analysis will be conducted on the ITT.

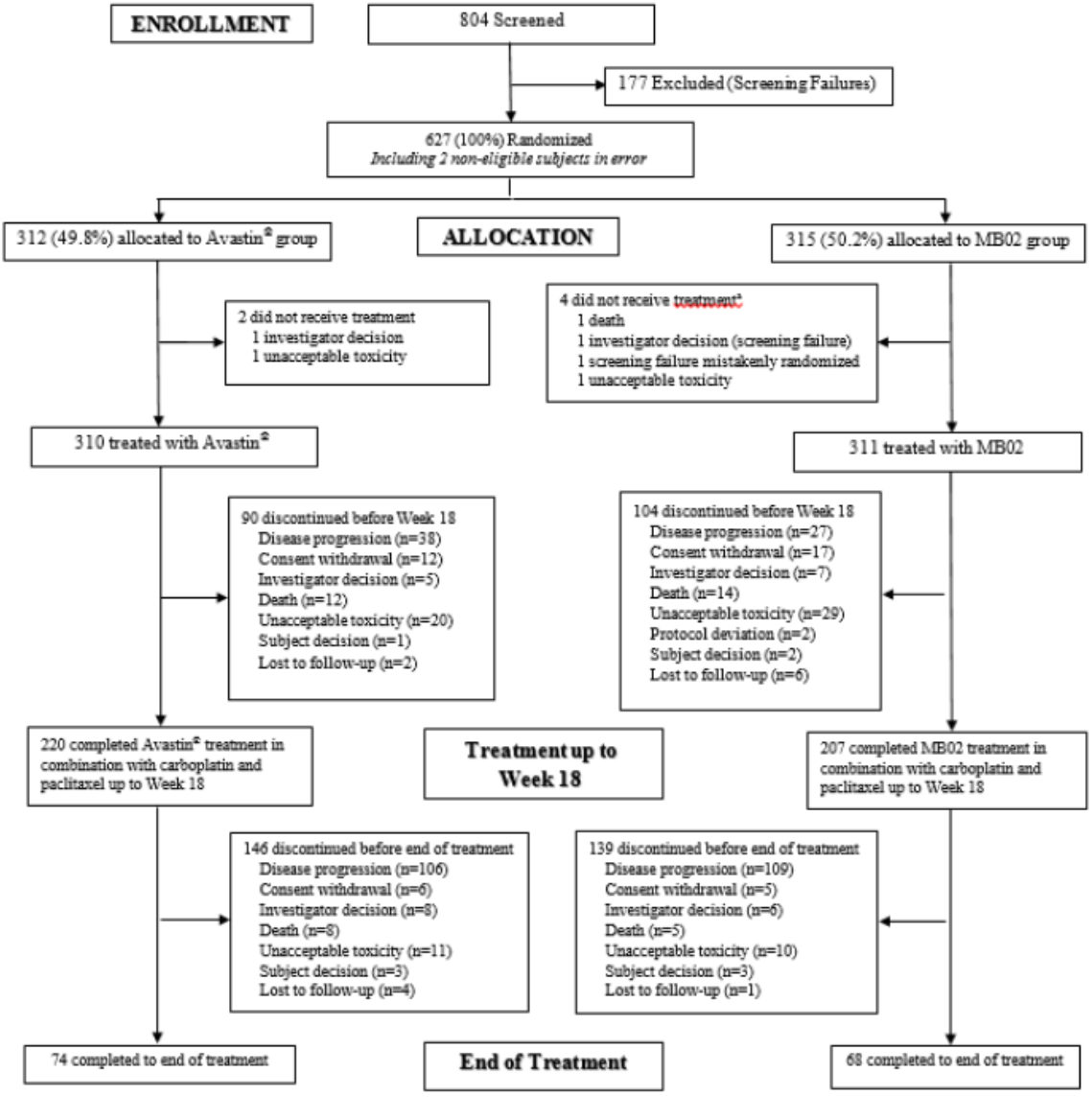
Subgroup analyses

Subgroup analyses are performed using the stratification covariates of sex (male/female), smoking status (smoker/non-smoker, disease diagnosis (newly diagnosed/recurrent disease) and disease stage (IIIB/IV).

RR and RD estimate and the two-sided 90% CIs of ORR is restricted within each stratification factor on the ITT set (i.e. 16 analyses in total) and summarized within forest plots.

Results

Participant flow



[a]Two subjects in the MB02 group failed screening but were randomized in error; these subjects did not receive treatment.
Note: Numbers may differ from those in Table 14.1.1.1, which were calculated across screened subjects and include subjects who were randomized but did not receive treatment in each step of discontinuation.

Figure 3: Subject Disposition

Baseline data

Table 12: Demographics (Intention-to-Treat-Set)

	Avastin® N=312	MB02 N=315	Total N=627
Sex, n (%)			
Male	190 (60.9)	193 (61.3)	383 (61.1)
Female	122 (39.1)	122 (38.7)	244 (38.9)
Age (years)			
Mean (StD)	60.8 (9.23)	60.1 (9.56)	60.5 (9.40)
Median	61.0	61.0	61.0
Q1, Q3	56.0, 67.5	54.0, 67.0	55.0, 67.0
Race, n (%)			
Asian	54 (17.3)	71 (22.5)	125 (19.9)
White/Caucasian	241 (77.2)	228 (72.4)	469 (74.8)
Other, Brown	1 (0.3)	1 (0.3)	2 (0.3)
Other, Hispanic	4 (1.3)	1 (0.3)	5 (0.8)
Other, White	3 (1.0)	1 (0.3)	4 (0.6)
Other, White/Hispanic	8 (2.6)	12 (3.8)	20 (3.2)
Other, White/Latin	0	1 (0.3)	1 (0.2)
Not collected	1 (0.3)	0	1 (0.2)
ECOG PS at Baseline, n (%)[a, b]			
0	94 (30.3)	92 (29.6)	186 (30.0)
1	216 (69.7)	219 (70.4)	435 (70.0)
Height (cm) at Baseline			
Mean (StD)	166.37 (9.546)	166.17 (10.059)	166.27 (9.799)
Median	167.00	167.00	167.00
Q1, Q3	160.00, 173.00	160.00, 174.00	160.00, 174.00
Weight (kg) at Baseline			
Mean (StD)	69.501 (15.4927)	68.343 (15.5610)	68.919 (15.5254)
Median	69.000	67.500	68.000
Q1, Q3	57.000, 80.000	57.400, 80.000	57.200, 80.000
BSA (m^2) at Baseline			
Mean (StD)	1.783 (0.2253)	1.768 (0.2380)	1.775 (0.2317)
Median	1.790	1.780	1.780
Q1, Q3	1.595, 1.940	1.600, 1.940	1.600, 1.940

Table 13: Non-Small Cell Lung Cancer History (Intention-To-Treat Set)

	Avastin® N=312		MB02 N=315		Total N=627	
Diagnosis type, n (%)						
Newly diagnosed	287 (92.0)		289 (91.7)		576 (91.9)	
Recurrent disease	25 (8.0)		26 (8.3)		51 (8.1)	
Smoking Status, n (%)						
Smoker	152 (48.7)		157 (49.8)		309 (49.3)	
Non-smoker	160 (51.3)		158 (50.2)		318 (50.7)	
NSCLC stage, Screening, n	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Stage II		2				**2**
Newly Diagnosed	-	***1***	-	-	-	***1***
Smoker	-	-	-	-	-	-
Non-smoker	-	1	-	-	-	1
Recurrent Disease	-	***1***	-	-	-	***1***
Smoker	-	1	-	-	-	1
Non-smoker	-	-	-	-	-	-
Stage IIIA	1		1		**2**	
Newly Diagnosed	***1***	-	***1***	-	***2***	-
Smoker	1	-	-	-	1	-
Non-smoker	-	-	1	-	1	-
Recurrent Disease	-	-	-	-	-	-
Smoker	-	-	-	-	-	-
Non-smoker	-	-	-	-	-	-
Stage IIIB	**26**	**11**	**21**	**10**	**47**	**21**
Newly Diagnosed	***24***	***10***	***21***	***9***	***45***	***19***
Smoker	16	4	13	4	29	8
Non-smoker	8	6	8	5	16	11
Recurrent Disease	***2***	***1***	-	***1***	***2***	***2***
Smoker	1	-	-	1	1	1
Non-smoker	1	1	-	-	1	1
Stage IV	**163**	**109**	**171**	**112**	**334**	**221**
Newly Diagnosed	***153***	***98***	***157***	***101***	***310***	***199***
Smoker	100	22	106	24	206	46
Non-smoker	53	76	51	77	104	153
Recurrent Disease	***10***	***11***	***14***	***11***	***24***	***22***
Smoker	6	1	8	1	14	2
Non-smoker	4	10	6	10	10	20

Abbreviations: N, number of subjects in intended set; n, number of subjects with data available; NSCLC, non-small cell lung cancer.
Note; Percentages were based on N.
Note: NSCLC time from first diagnosis is counted from the date of randomization.
Note: Non-smokers and former smokers were included in the "non-smokers" category, while current smokers were included in the "smokers" category.
Source: Table 14.1.2.3, Table 14.1.3.1.1, Table 14.1.3.2

According to exclusion criteria (exclusion criterion 10), the patients with NSCLC harbouring activating EGFR mutations or ALK translocations were not included. The status of epidermal growth factor receptor and anaplastic lymphoma receptor tyrosine kinase was assessed locally according to the study protocol.

The administration of prior systemic therapy (mostly adjuvant chemotherapy) and radiotherapy was balanced between the groups.

The proportion of reported protocol deviations was balanced between the two arms. There was no remarkable difference in the type of protocol deviations between arms that would affect the similarity assessment.

Numbers analysed

The ITT set consisted of 627 patients, the modified ITT set (mITT; all randomized subjects who were treated with IMP and had measurable disease at screening) consisted of 598 patients and a total of 511 patients met the criteria for PPS. The SAF consisted of 621 patients.

Table 14: Study Populations (Randomized Subjects)

	Avastin® N=312 n (%)	MB02 N=315 n (%)	Total N=627 n (%)
ITT set	312 (100)	315 (100)	627 (100.0)
mITT set	295 (94.6)	303 (96.2)	598 (95.4)
Did not have disease at Screening	15 (4.8)	8 (2.5)	23 (3.7)
Did not receive IMP	2 (0.6)	4 (1.3)	6 (1.0)
PPS[a]	255 (81.7)	256 (81.3)	511 (81.5)
Did not complete 6 cycles of IMP or 4 cycles of chemotherapy due to reasons other than disease progression, death, or AEs	20 (6.4)	34 (10.8)	54 (8.6)
Protocol deviation	20 (6.4)	15 (4.8)	35 (5.6)
Non-eligible	*9[b]*	*5*	*14*
With ORR at Week 18 outside of visit window (-7+14 days)	*10*	*10*	*20*
Non-compliance (<80% total administered dose)	*1*	*0*	*1*
SAF set	310 (99.4)	311 (98.7)	621 (99.0)
Did not receive IMP	2 (0.6)	4 (1.3)	6 (1.0)

Abbreviations: AE = adverse event; IMP = investigational medicinal product; ITT = intention-to-treat; mITT = modified intention-to-treat; N = number of subjects in the intended set; n = number of subjects with data available; ORR = objective response rate; PPS = per protocol set; SAF = safety.
N is number of subjects in intended set.
Percentages are based on N.
[a] For clarity, totals have been revised and relocated per Sponsor criteria.
[b] There was 1 additional subject who was non-eligible but also had non-measurable disease; this subject was already excluded from the mITT set.
Source: Table 14.1.2.3 (Totals have been revised and reassigned as per Sponsor criteria).

The primary analysis of efficacy (RD and RR of ORR at week 18) was conducted on the ITT population (all randomised subjects), to evaluate therapeutic equivalence between MB02 and Avastin. The applicant has stated that efficacy evaluation in the protocol population set (PPS) and modified ITT was used for further support for clinical similarity. Of importance from a regulatory perspective, is that consistency could be shown.

Outcomes and estimation

Primary outcome

ORR (by RECIST v1.1; assessed by an IRC) was conducted in the ITT population with supporting analyses on the PPS and mITT population.

During the preparation of the additional requested analyses for the pivotal MB02-C-02-17 study, the applicant identified an issue in the specification of the strata for the Week 18 primary analysis.

It was identified that the primary analysis modelling method implemented in SAS was incorrectly specified.

The primary analysis was a comparison of Objective Response Rate (ORR) between Bevacizumab biosimilar (MB02) and Avastin, based on Overall Response (OR) as assessed by Independent Radiological Committee (IRC).

The ORR estimate was planned to be adjusted for the randomization strata sex (male/female), smoking status (smoker/nonsmoker), disease diagnosis (newly diagnosed/recurrent disease) and - disease stage (Stage IIIB/Stage IV) using the Cochran-Mantel-Haenszel estimate of the RD and corresponding 2-sided 90% CI.

All Week 18 analyses have been re-run and the primary analyses of week 18 were replaced. The results of an independent review (Biostatistical Programming Independent Review Report) confirmed the reliability of the data, having identified no further issues of data reliability.

Therapeutic equivalence was demonstrated in the ITT set, with the risk difference (RD) of ORR of -4.02 and the 95% CI of the difference of the ORR between MB02 and Avastin (-11.76 to 3.71) falling within the equivalence margin of ±12%. In contrast to the ITT set, the primary endpoint was not met in the PPS population. The point estimate for the difference in the mITT population was -4.56 (95% CI: -12.52 to 3.40) and the point estimate for the difference in the PPS population was -4.27 (95% CI: -12.92 to 4.38). Both 95% CIs were outside of the proposed -12% lower bound of the margin for equivalence.

Table 15: Objective Response Rate – Per Independent Radiological Committee (Intention-To-Treat Population)

	Avastin® N=312	MB02 N=315	Total N=627
Overall Response – Week 18, n (%)			
CR	3 (1.0)	6 (1.9)	9 (1.4)
PR	136 (43.6)	121 (38.4)	257 (41.0)
SD	53 (17.0)	54 (17.1)	107 (17.1)
PD	23 (7.4)	19 (6.0)	42 (6.7)
Not evaluable	0	1 (0.3)	1 (0.2)
Early discontinuation[a]	97 (31.1)	114 (36.2)	211 (33.6)
Objective Response – Week 18[b,c]			
Responder, n (%)	139 (44.6)	127 (40.3)	266 (42.4)
95% CI	(39.0, 50.3)	(34.9, 46.0)	(38.5, 46.4)
Non-responder, n (%)	173 (55.4)	188 (59.7)	361 (57.6)
ORR Risk Ratio[d,e]		**0.910**	
90% CI		(0.780, 1.060)	
95% CI		(0.758, 1.092)	
ORR Risk Difference (%)[f,g]		**-4.02**	
90% CI		(-10.51, 2.47)	
95% CI		(-11.76, 3.71)	

Abbreviations: CI, confidence interval; CR, complete response; N, number of subjects in the intended set; n, number of subjects with data available; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Note: Percentages are based on N.

[a] Early discontinuation included subjects at Week 18 classified as "NonCR/NonPD" (8 subjects in MB02 group, 9 subjects in Avastin® group) and "missing" (106 subjects in MB02 group and 88 subjects in Avastin® group).

[b] In case of missing evaluation, i.e., in case the subject were withdrawn from study before Week 18, the subject was classified as a non-responder.

[c] Objective response was assigned if a subject displayed either CR or PR per RECIST version 1.1.

[d] The ORR estimate was adjusted for the actual randomization strata sex (male/female), smoking status (smoker/non-smoker), disease diagnosis (newly diagnosed/recurrent disease), and disease stage (Stage IIIB/Stage IV) using the Cochran-Mantel-Haenszel estimate of the risk ratio and corresponding 2-sided 90% CI.

[e] Equivalence is shown if the 90% CI was contained fully within [0.73; 1.36]. Confidence intervals calculated with the Mantel-Haenszel method.

[f] The ORR estimate was adjusted for the actual randomization strata sex (male/female), smoking status (smoker/non-smoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (Stage IIIB/Stage IV) using the Cochran- Mantel-Haenszel estimate of the risk difference and corresponding 2-sided 90% CI.

[g] Equivalence is shown if the 90% CI is contained fully within [-12.0%; 12.0%]. Wald asymptotic CIs are specified.

Source: Table 14.2.1.1.1

In the ITT set, the number of subjects achieving OR was comparable between treatment groups (127 subjects [40.3%; 95% CI: 34.9 to 46.0] in the MB02 group compared to 139 subjects [44.6%; 95% CI: 39.0 to 50.3] in the Avastin group) using non-responder imputation for missing values.

Upon request by EMA, the primary endpoint ORR RD at Week 18 was also analysed for the analysis set including only those patients (from the ITT set) who completed Week 18 and had overall response (OR/BOR of CR, PR, SD or PD per RECIST v1.1) assessment. In selecting this population, the patients that experience response of NE and non-CR/non-PD due to non-evaluable target lesions at baseline, have been excluded. This analysis set thus has a similar intention as the pre-specified PPS, i.e. to compare efficacy in a set of patients that is more sensitive than the ITT to elucidate a differential treatment effect. This analysis set includes 406 patients (64.8% of the ITT set; 197 patients in the MB02 arm and 209 patients in the Avastin arm) for the ORR analysis. The ORR RD was -2.66 (95% CI: -11.91 to 6.59). The RD for the primary endpoint ORR by IRRC review at Week 18 remained entirely within the predefined equivalence margin of [-12%, +12%].

Table 16: Summary of comparative analysis of primary efficacy endpoint (ORR by IRC) in ITT, mITT and PPS populations from study MB02-C-02-17

Population analysed	ORR Risk Difference, % (RD)			ORR Risk Ratio (RR)		
	Calculated value	90% CI	95% CI	Calculated value	90% CI	95% CI
ITT	**-4.02**	-10.51, 2.47	-11.76, 3.71	**0.910**	0.780, 1.060	0.758, 1.092
mITT	**-4.56**	-11.24, 2.12	-12.52, 3.40	**0.902**	0.776, 1.049	0.754, 1.080
PPS	**-4.27**	-11.53, 2.99	-12.92, 4.38	**0.915**	0.787, 1.065	0.764, 1.096

Abbreviations used: CI; Confidence interval: ITT; Intention to treat: mITT; Modified intention to treat: ORR; Objective response rate: PPS; Per Protocol Set
Source: Table 14.2.1.1.1, Table 14.2.1.1.2 and Table 14.2.1.1.3 CSR MB02-C-02-17

Post-hoc analyses

Best objective response rate (BORR):

A total of 332 (53.0%) subjects in the ITT population achieved BORR (CR or PR) based on IRC assessment. The number of subjects achieving BORR was slightly lower in the MB02 group compared with the Avastin group (160 subjects [50.8%; 95% CI: 45.1 to 56.4] in the MB02 group and 172 subjects [55.1%; 95% CI: 49.4 to 60.7] in the Avastin group). BORR RD was -4.04 (95% CI: -11.86 to 3.78).

Table 17: Best Overall Response Rate as determined by IRC assessment in study MB02-C-02-17 (ITT population)

	Avastin® N=312	MB02 N=315	Total N=627
Best Overall Response[a], n (%)			
CR	3 (1.0)	6 (1.9)	9 (1.4)
PR	169 (54.2)	154 (48.9)	323 (51.5)
SD	93 (29.8)	93 (29.5)	186 (29.7)
PD	11 (3.5)	10 (3.2)	21 (3.3)
Not evaluable	0	3 (1.0)	3 (0.5)
Early discontinuation[b, c]	36 (11.5)	49 (15.5)	85 (13.6)
ORR Risk Ratio up to Week 18[d, e]		**0.926**	
90% CI		(0.818, 1.049)	
95% CI		(0.799, 1.075)	
ORR Risk Difference up to Week 18[f, g]		**-4.04**	
90% CI		(-10.60, 2.53)	
95% CI		(-11.86, 3.78)	

Abbreviations: CI, confidence interval; CR, complete response; N, number of subjects in the intended set; n, number of subjects with data available; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria for Solid Tumors; SD, stable disease.

Note: Percentages are based on N.

[a] Objective response was assigned if a subject displayed either CR or PR per RECIST version 1.1.

[b] Early discontinuation includes subjects classified "NonCR/NonPD" (8 subjects in the MB02 group and 10 in the Avastin® group) at Week 18 and "missing" (41 subjects in MB02 group and 26 in Avastin® group).

[c] In case of missing evaluation (i.e., in case the subject was withdrawn from the study before Week 18), the subject was classified as a non-responder.

[d] The ORR estimate was adjusted for the actual randomization strata sex (male/female), smoking status (smoker/non-smoker), disease diagnosis (newly diagnosed/recurrent disease), and disease stage (Stage IIIB/Stage IV) using the Cochran-Mantel-Haenszel estimate of the risk ratio and corresponding 2-sided 90% CI.

[e] Equivalence is shown if the 90% CI was contained fully within [0.73; 1.36]. Confidence intervals calculated with the Mantel-Haenszel method.

[f] The ORR estimate was adjusted for the actual randomization strata sex (male/female), smoking status (smoker/non-smoker), disease diagnosis (newly diagnosed/recurrent disease) and stage (Stage IIIB/Stage IV) using the Cochran-Mantel-Haenszel estimate of the risk difference and corresponding 2-sided 90% CI.

[g] Equivalence is shown if the 90% CI is contained fully within [-12.0%; 12.0%]. Wald asymptotic CIs are specified.

Source: Table 14.2.1.1.14 CSR MB02-C-02-17

Comparing the updated primary ORR RD analysis based on the ITT set (-4.02; 95% CI: -11.76, 3.71) and the requested analysis based on best overall response up to week 18, BORR RD, as shown above (-4.04; 95% CI: -11.86, 3.78), there was almost no difference between these two analyses, which is considered reassuring.

ORR/BORR based on Multiple Imputation (MI)

Upon request, ORR at Week 18 was additionally analysed implementing a multiple imputation process for imputation of missing at random (MAR) and missing not at random (MNAR) data based on sum of target diameters.

An imputation of all data by a regression model for the missing sum of diameters was performed taking into account treatment and stratification factors and only including the distribution of data for which subjects either complete or withdraw for similar reasons. The outcome was forced to be imputed by an increase of the sum of diameters of 21% resulting in PD and, therefore, non-response for subjects that withdraw due to unacceptable toxicity, PD or death. Where a tumour response exists, it is used in the analysis regardless of whether target lesions (and thus sum of diameters) is present, otherwise the overall response is derived based on the imputed sum of diameters solely, per RECIST

v1.1. Subjects that were randomised erroneously with no sum of diameter or tumour response data, a non-responder imputation is applied.

In the ITT population, the ORR RD showed similarity at 95% CIs (-1.92; 95% CI: -10.02 to 6.19). In the mITT, the ORR difference was -2.77 (95% CI: -11.09 to 5.55) and showed also similar results.

In contrast to the ITT, the ORR was not met in the PPS.

As multiple imputation taking into account treatment and stratification factors was used for subjects without tumour response data or falling into the categories NonCR/NonPD or NE, additional analyses for this updated imputation process for the ITT set were presented.

For subjects with no baseline sum of target diameter data, a non-missing baseline sum of target diameters was randomly selected from the pool of data available for subjects with the same stratification factors. Once a baseline sum of target diameters is imputed, the remainder of the imputation process as previously conducted was implemented.

Table 18: Comparison of the OR results at Week 18 per IRRC assessment (ITT) –MI: adjustment for missing/NE

W18 IRRC Result	Latest MI Analysis: RD (95% CI)
ORR	-2.22 (-10.54 to 6.10)
BOR	-2.89 (-10.96 to 5.17)

Abbreviations: BOR = best overall response; CI = confidence interval; ORR = overall response rate; RD = risk difference
Source: Appendix 2 (Table 14.2.1.1.39) and Appendix 4 (Table 14.2.1.1.41)

An additional analysis was performed with a population set excluding only the patients for whom major protocol deviations affecting efficacy occurred up to and including Week 18 with non-responder and multiple imputation. The purpose of this analysis was to exclude those patients which had protocol violations that could have later resulted in biased efficacy outcomes, while preserving a larger sample size compared to the predefined PPS (thus resulting in more precision of the confidence intervals) through including those patients that had protocol violations unrelated to later efficacy outcome. This analysis included now 570 patients (91.0% of the ITT set), whereas the PPS included 511 patients (81.5% of the ITT set). No major imbalances in the individual reasons for exclusions between treatment arms were observed. The ORR RD under NR imputation was -6.04 (95% CI: -14.17 to 2.09) and under the preferred MI including adjustment for Missing/NE was -3.45 (95% CI: -12.04 to 5.13) at Week 18 by IRRC Review. Thus in the analysis set excluding only the patients for whom major protocol deviations affecting efficacy occurred up to and including Week 18, the results were close to the pre-specified equivalence margin of [-12%, 12%] using the preferred multiple imputation.

There are 33 subjects (n=18 (5.8%) for Avastin arm and n=15 (4.8%) for the MB02 arm based on the ITT Set) with missing sum of target lesion data at Baseline, leading to an OR outcome of missing, NE, or Non-CR/Non-PD in 25 subjects at Week 18 because where a tumour response exists, it is used in analysis regardless of whether target lesions (and thus sum of diameters) is present. As the number of outcomes affected by this update are minimal (n = 13 (4.2%) for Avastin arm and n = 12 (3.8%) for the MB02 arm based on the ITT Set), also the effects of this updated imputation process are minimal: ORR Risk Difference (RD) -2.22% (95% CI: -10.54% to 6.10) at Week 18 by IRRC, BORR RD -2.89% (95% CI: -10.96% to 5.17%) at Week 18 by IRRC Review (Table 18).
The RD of the ORR and BORR by IRRC review at Week 18 based on the ITT Set remained entirely within the equivalence margin of [-12%, +12%]. For the original and the updated information the point estimates of the RD shifted towards 0 when compared to the non-responder analysis, less for the new MI where also subjects without tumour response data or falling into the categories NonCR/NonPD or NE were imputed by MI instead of non-responder imputation. The number of missing values

imputed by MI instead of non-responder imputation is higher for Avastin than MB02 comparing original and new MI (12 MB02 and 13 Avastin) making the RD a bit higher.

Table 19: Tipping Point Analyses (ORR and BOR) at Week 18 (ITT)

W18 IRRC Result	No. of Subjects in the MB02 arm Switching from Responder to Non-Responder/ Risk Difference (95% CI)
ORR	5 subjects / -3.80 (-12.12 to 4.53)
BOR	4 subjects / -4.15 (-12.24 to 3.94)

Abbreviations: BOR= best overall response; CI = confidence interval; IRRC = Independent Radiological Review Committee; ITT = intention-to-treat; ORR = overall response rate.
Source: Appendix 3 (Table 14.2.1.1.40) and Appendix 5 (Table 14.2.1.1.42)

Tipping point analyses show no major changes in the number of subjects required to tip the response significantly in favour of Avastin (5 subject for ORR and 4 subjects for BOR) (Table 19).

ORR by investigator assessment

The results on the additional investigator assessment with non-responder imputation showed that the 95% CIs were outside of the proposed -12% lower bound of the margin for equivalence in the ITT, and also in the PPS and mITT population. With multiple imputation the results on the investigator assessment were: ITT RD of -5.99 (95% CI: -14.08 to 2.10), mITT RD of -6.61 (95% CI: -14.92 to 1.69), and PPS RD of -8.63 (95% CI: -17.35 to 0.10).–It should be noted that in the statistical analysis plan the investigator assessment is considered supportive analysis of the primary endpoint.

Concordance rates

The applicant provided data on concordance between the IRC and investigator assessments in ORR for the ITT population at the Week 18 time point. The concordance rate was quite low, with 62.5% and 55.0% for ORR in the MB02 and Avastin groups, but comparable between the groups.

ORR in ADA positive subjects

During the evaluation procedure the applicant provided an overview of ORR in ADA positive and ADA negative subjects in the ITT set.

Out of a total of 103 patients with positive TI-ADAs, 62 patients (60.2%) achieved OR at Week 18 (CR or PR; 28 patients [52.8%] in the MB02 arm and 34 [68.0%] in the Avastin arm) and 41 patients (39.8%) were non-responders (25 [47.2%] in the MB02 arm and 16 [32.0%] in the Avastin arm).

This difference may be explained by the low sample sizes and the imbalance in number of subjects with no efficacy evaluation at Week 18 ("Not evaluable", "Non CR/Non PD" and "Missing"; 18 subjects in total; 12 subjects in the MB02 arm [22.6%] and 6 subjects in the Avastin arm [12.0%]) Non-response per se (stable disease [SD] and progression of disease [PD]) would lead to a similar number of non-responders: 13 subjects in the MB02 [24.6%] arm and 10 [20.0%] subjects in the Avastin arm.

A total of 483 subjects were negative for ADAs (244 in the MB02 arm and 239 in the Avastin arm). Out of 483 subjects with negative ADAs, 191 subjects (39.5%) achieved OR at Week 18 (CR or PR; 92 subjects [37.7%] in the MB02 arm and 99 subjects [41.4%] in the Avastin arm) and 292 subjects (60.5%) were considered non-responders (152 subjects [62.3%] in the MB02 arm and 140 subjects [58.6%] in the Avastin arm).

The ORR at Week 18 per IRRC assessment in TI-ADA positive and ADA negative subjects were higher for the Avastin group than for MB02.

Overall, most subjects harboured low titres along the study period and titre levels between both treatment arms are highly similar. No relation between titre levels and ORR/BORR has been identified.

The number of ADA positive patients was generally low, increases only slightly over weeks 6, 12 and 18 and is comparable between treatment arms, whereas the difference in ORR gets more negative. Higher titre levels were not correlated with being a BORR non-responder.

Secondary outcomes

Progression free survival and Overall survival:

Progression free survival was defined as the time from randomization to subsequent confirmed progression per RECIST version 1.1 or death (whichever occurred first).

The Restricted Mean Survival Time [RMST] was defined as the area under the curve for the PFS and is estimated by the KM estimator for each treatment up to 52 weeks and the difference together with 95% CIs reported.

A total of 406 (64.8%) subjects had DP or died (205 subjects in the MB02 group and 201 subjects in the EU-Avastin group).

For PFS in the ITT set, the hazard ratio (HR) was 1.200 with 95% CI (0.985, 1.462) and a p-value of 0.0707. The median PFS was 43.00 weeks with 95% CI (36.14 to 45.14) for Avastin and 36.00 weeks with 95% CI (33.57, 36.86) for MB02. The analyses of PFS for ITT lead to a RMST of 37.29 weeks [95% CI: 36.14 to 45.14] for Avastin and a RMST of 36.0 weeks [95% CI: 33.00 to 36.43] for MB02. The difference in least square RMST between MB02 and Avastin for PFS ITT was -3.39 weeks (95% CI: -3.43 to -3.34). Note that the difference in least squares means are the difference in the group means after having controlled for covariates. Results were similar for mITT.

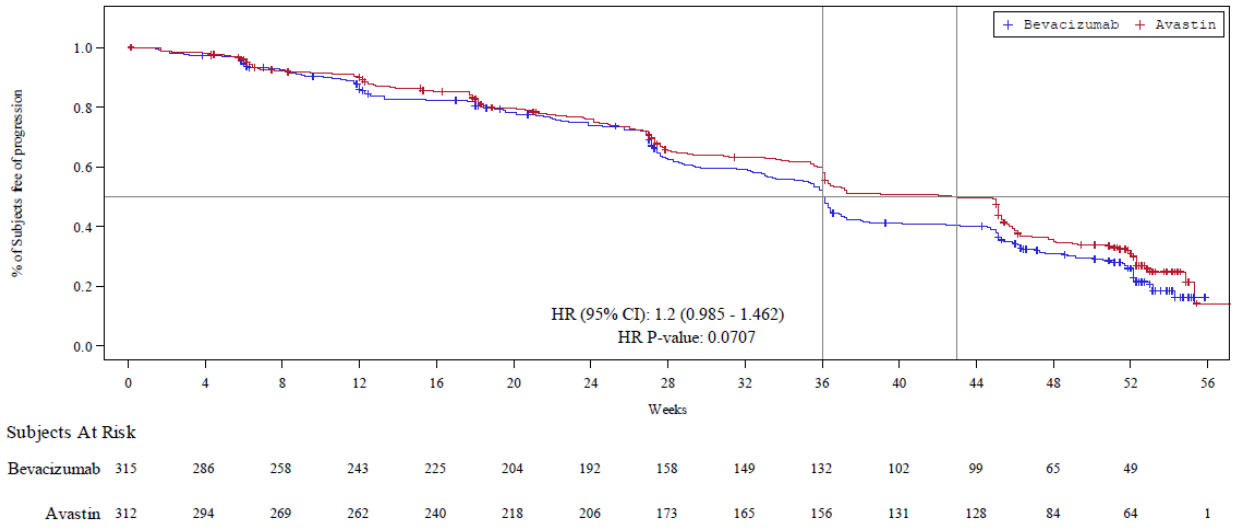


Figure 4: RtQ – 2 Kaplan Meier Plot – PFS – ITT set

The analysis of PFS in the mITT and PP populations showed similar results with those described in the primary ITT population. There was no significant difference in PFS between subjects treated with MB02 and Avastin.

For PFS in the PPS the HR was 1.233 with 95% CI (0.999 to 1.521) and a p-value of 0.0515. The median PFS was 45.00 weeks with 95% CI (36.29, 45.29) for Avastin and 36.00 weeks with 95% CI (33.43, 37.00) for MB02. The analyses of PFS for ITT lead to a RMST of 38.16 weeks [95% CI: 37.11 to 39.22] for Avastin and a RMST of 34.23 weeks [95% CI: 33.34 to 35.12] for MB02. The difference

in least square RMST between MB02 and Avastin for PFS PPS was -2.42 weeks [95% CI: -2.47 to -2.37].

Overall survival was defined as the time from randomization to subsequent death.

A total of 181 (28.9%) subjects died (91 and 90 subjects in the MB02 and EU-Avastin groups, respectively). Data for the remaining 446 (71.1%) subjects was censored (224 and 222 subjects in the MB02 and EU-Avastin groups, respectively).

For OS in the ITT set, the HR was 1.107 with 95% CI (0.826, 1.483) with a p-value of 0.49165. The median OS for Avastin and MB02 could not be calculated as well as the corresponding 95% CIs for both treatment groups. In both treatment groups more than 50% of subjects were still alive at the end of the trial (see corresponding Kaplan-Meier plot, Figure 5), therefore, no median OS could be calculated. The difference in least square RMST between MB02 and Avastin for OS ITT was -3.11 weeks (95% CI: -3.17 to -3.05).

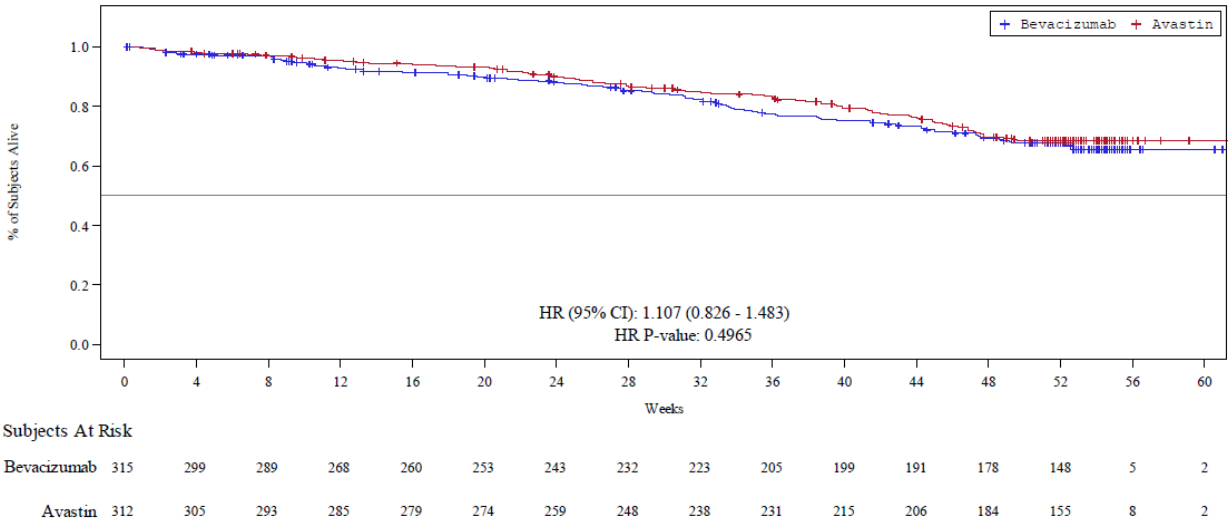


Figure 5: RtQ – 3 Kaplan Meier Plot – OS- ITT set

For OS in the PPS, the HR was 1.141 with 95% CI (0.835 to 1.560) and a p-value of 0.4085. The median OS provided by the Company for Avastin was 63.57 weeks. For MB02 the median OS could not be calculated, as well as the corresponding 95% CIs for both treatment groups. In both treatment groups more than 50% of subjects were still alive at the end of the trial, therefore, no median OS could be calculated. The difference in least square RMST between MB02 and Avastin for OS PPS was -2.11 weeks [95% CI: -2.17 to -2.05]).

OS results were consistent for mITT and PP Populations than those reported for the ITT set, with no notable difference between both treatment groups.

The time period the patients were not treated before death was comparable between the treatment arms with a median of 23.14 weeks for both treatment arms.

Other secondary outcomes, including duration of overall response (DOR), overall observational time (OT) and time to overall response (TOR) are summarized in the following tables:

Table 20: Summary of Median Survival and Hazard Ratio (Avastin compared to MB02) for Survival Analyses – ITT Set

Statistic	PFS	OS	DOR	OT	TOR

Median Survival Time (Weeks) [95% CI]	43.00 (36.14 to 45.14) vs. 36.00 (33.57 to 36.86)	n/a	37.14 (30.43 to 39.57) vs 30.29 (28.29 to 38.43)	52.29 (52.14 to 52.29) vs 52.29 (52.14 to 52.29)	12.29 (12.14 to 14.14) vs 12.43 (12.14 to 18.00)
Hazard Ratio [95% CI] p-value	1.200 (0.985 to 1.462) 0.0707	1.107 (0.826 to 1.483) 0.4965	1.195 (0.916 to 1.561) 0.1897	1.104 (0.916 to 1.331) 0.2989	0.949 (0.768 to 1.172) 0.6245

Abbreviations: CI = confidence interval; DOR = duration of response; ITT = intention-to-treat; OS = overall survival; OT = observation time; PFS = progression free survival; TOR = time to overall response

Sources: Appendix 14 (Table 14.2.2.2.14), Appendix 20 (Table 14.2.2.1.1), Appendix 21 (Table 14.2.2.3.1), Appendix 22 (Table 14.2.2.4.1), Appendix 23 (Table 14.2.2.5.1)

Table 21: Summary of Median Survival and Hazard Ratio for Survival Analyses – PPS Set

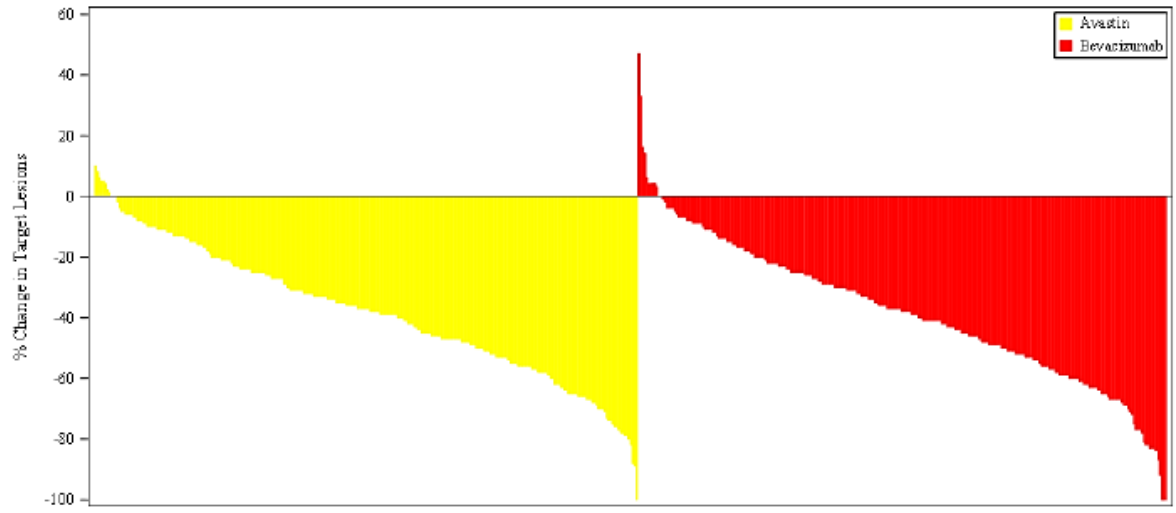
Statistic	PFS	OS	DOR	OTT	TOR
Median Survival Time (Weeks) [95% CI]	45.00 (36.29 to 45.29) vs 36.00 (33.43 to 37.00)	63.57 (63.57 to n/a) vs n/a (n/a to n/a)	37.14 (30.57 to 39.57) vs 30.29 (28.14 to 38.43)	52.29 (n/a to n/a) vs 52.29 (52.14 to 52.29)	12.29 (12.14 to 13.00) vs 12.43 (12.14 to 18.00)
Hazard Ratio [95% CI] p-value	1.233 (0.999 to 1.521) 0.0515	1.141 (0.835 to 1.560) 0.4085	1.258 (0.951 to 1.665) 0.1082	1.037 (0.84 to 1.28) 0.7348	0.878 (0.700 to 1.102) 0.2621

Abbreviations: CI = confidence interval; DOR = duration of response; OS = overall survival; OT = observation time; PFS = progression free survival; PPS = per-protocol set; TOR = time to overall response

Sources: Appendix 24 (Table 14.2.2.1.4), Appendix 25 (Table 14.2.2.2.4), Appendix 26 (Table 14.2.2.3.4), Appendix 27 (Table 14.2.2.4.4) Appendix 28 (Table 14.2.2.5.4)

DOR, OT and TOR results were consistent for the PP Population than those reported for the ITT set, with no notable difference between both treatments groups.

Lesion assessment:



Abbreviations: ITT = intention-to-treat
Note: "Bevacizumab" is used in this plot to display the MB02 arm.
Source: Final Analysis CSR MB02-C-02-17, Figure 14.2.1.5.3

Figure 6: Waterfall plot – Sum of Target Lesions – ITT Set

The waterfall plots show a sharp peak at the beginning for MB02 and represents the subjects who discontinued due to greater severity of target lesions. A higher number of subjects discontinued due to PD in the Avastin treatment arm, but tumour burden was greater in the MB02 arm. All of these patients should have been imputed as non-responders in the primary analysis.

For the MMRM analyses of the sum of diameters in the ITT set a difference in LSMeans and 95% CI at Week 18 (MB02 minus Avastin) of -0.892 (-4.828, 3.044) was seen.

For the MMRM analyses of the sum of diameters in the PPS a difference in LSMeans and 95% CI at Week 18 (MB02 minus Avastin) of -1.103 (-5.115, 2.910) was seen.

All seen differences, also for the other time points (week 6 and week 12), are negative, but non-significant. No monotone increase or decrease of the point estimate of the difference in the sum of diameters could be found.

ORR at different weeks:

ORR was also assessed by the IRC at Week 6 and Week 12 for ITT and PPS.

Table 22: Risk difference (95% CI) for ORR based on IRRC assessment (ITT)

Timepoint	Main Analysis with non-responder Imputation	Latest MI analysis
Week 6	4.75 (-2.33 to 11.83)	5.02 (-2.65 to 12.69)
Week 12	-3.48 (-11.18 to 4.21)	-0.96 (-9.13 to 7.20)
Week 18	-4.02 (-11.76 to 3.71)	-2.22 (-10.54 to 6.10)

Abbreviations: ORR = overall response rate; IRRC = Independent Radiological Review Committee; MI = multiple imputation
Source: Appendix 8 (Table 14.2.1.1.1), Appendix 9 (Table 14.2.1.1.33), Appendix 10 (Table 14.2.1.1.36) and Appendix 11 (Table 14.2.1.1.39)

The Applicant calculated the RD in ORR between the groups and corresponding 95% CIs at the time-points (Week 6, Week 12 and Week 18) for non-responder imputation (NR) and the updated multiple imputation (MI) analysis.

In the ITT set, the RD is positive at Week 6 (4.75 for NR and 5.02 for MI) and negative at Week 12 (-3.48 for NR and -0.96 for MI) and even more at Week 18 (-4.02 for NR and -2.22 for MI). The 95% CI stays within the margins of [-12%, 12%] calculated for week 18.

Table 23: RtQ – 11 ORR RD and BORR RD at Week 6, 12 and 18 (PPS)

Outcome	Evaluation	Week 6		Week 12		Week 18	
		MB02 N = 256	Avastin N = 255	MB02 N = 256	Avastin N = 255	MB02 N = 256	Avastin N = 255
ORR by IRRC (NR Imputation)	OR Responder	88 (34.4%)	75 (29.4%)	119 (46.5%)	127 (49.8%)	118 (46.1%)	129 (50.6%)
	RD	6.14		-2.89		-4.27	
	95% CI	(-1.88 to 14.16)		(-11.46 to 5.68)		(-12.92 to 4.38)	
ORR by IRRC (MI including adjustment for Missing/NE)	OR Responder	88 (34.4%)	75 (29.4%)	121 (47.3%)	128 (50.2%)	121 (47.3%)	132 (51.8%)
	RD	6.24		-2.49		-4.88	
	95% CI	(-1.81 to 14.29)		(-11.09 to 6.11)		(-13.55 to 3.80)	
BORR by IRRC (NR Imputation)	OR Responder	88 (34.4%)	75 (29.4%)	131 (51.2%)	138 (54.1%)	145 (56.6%)	158 (62.0%)
	RD	6.14		-2.30		-4.73	
	95% CI	(-1.88 to 14.16)		(-10.87 to 6.28)		(-13.23 to 3.77)	
BORR by IRRC (MI including adjustment for Missing/NE)	OR Responder	88 (34.4%)	75 (29.4%)	132 (51.6%)	139 (54.5%)	147 (57.4%)	160 (62.7%)
	RD	6.24		-2.18		-5.02	
	95% CI	(-1.81 to 14.29)		(-10.79 to 6.43)		(-13.53 to 3.50)	

Abbreviations: BORR = best objective response rate; CI = confidence interval; IRRC = Independent Radiological Review Committee; MI = multiple imputation; NE = not evaluable; NR = non-responder; ORR = objective response rate; RD = risk difference

Source: Q3 Appendix 1 (Table 14.2.1.35) for Week 6, NR Imputation, ORR, Q3 Appendix 5 (Table 14.2.1.1.55) for Week 6, NR Imputation, BORR, Q3 Appendix 2 (Table 14.2.1.1.38) for Week 12, NR Imputation, ORR, Q3 Appendix 6 (Table 14.2.1.1.57) for Week 12, NR Imputation, BORR, MB02-C-02-17 Table 14.2.1.1.3 for Week 18, NR Imputation, ORR, MB02-C-02-17 Table 14.2.1.1.16 for Week 18, NR Imputation, BORR, Q3 Appendix 7 (Table 14.2.1.1.86) for MI including adjustment for Missing/NE, ORR and Q3 Appendix 8 (Table 14.2.1.1.87) for MI including adjustment for Missing/NE, BORR

In the PPS, the RD in ORR is positive at Week 6 estimating a higher efficacy of MB02 [6.14 (95% CI: -1.88 to 14.16) for NR and 6.24 (95% CI:-1.81 to 14.29) for MI], but the estimates turn negative with Week 12 [-2.89 (95% CI: -11.46 to 5.68) for NR and -2.49 (95% CI: -11.09 to 6.11) for MI] and at Week 18 [-4.27 (95% CI: -12.92 to 4.38) for NR and -4.88 (95% CI: -13.55 to 3.80) for MI].

BORR tends to follow a similar pattern over time.

Discontinuations per cycle:

The discontinuation pattern per cycle shows that non-responder imputation favors the treatment arm with less missing data because Cycles 1-2 (18.1% vs 151%) and Cycles 3-4 (12.7% vs 9.6%) show a lower percentage of discontinuation for Avastin, whereas for Cycles 5-6 the Avastin arm has a higher percentage of discontinuation (8.6% vs 9.3%). This explains why for ITT there is a shift towards 0 and for the PPS there is a shift away from 0 when using MI instead of non-responder imputation (Table 30).

Table 24: Discontinuation per Cycle from Cycle 1 through Cycle 6 (ITT Set)

Cycle Reason for Discontinuation	MB02 N=315 n (%)	Avastin N=312 n (%)	Total N=627 n (%)
Cycles 1-2	**57 (18.1)**	**47 (15.1)**	**104 (16.6)**
Progression of disease	14 (4.4)	14 (4.5)	28 (4.5)
Unacceptable toxicity	14 (4.4)	11 (3.5)	25 (4.0)
Withdrawal of consent	13 (4.1)	9 (2.9)	22 (3.5)
Death	8 (2.5)	6 (1.9)	14 (2.2)
Investigator decision	3 (1.0)	5 (1.6)	8 (1.3)
Lost to follow-up	2 (0.6)	2 (0.6)	4 (0.6)
Protocol violation	3 (1.0)	0	3 (0.5)
Cycles 3-4	**40 (12.7)**	**30 (9.6)**	**70 (11.2)**
Progression of disease	11 (3.5)	15 (4.8)	26 (4.1)
Unacceptable toxicity	11 (3.5)	6 (1.9)	17 (2.7)
Death	7 (2.2)	6 (1.9)	13 (2.1)
Withdrawal of consent	3 (1.0)	1 (0.3)	4 (0.6)
Lost to follow-up	4 (1.3)	0	4 (0.6)
Investigator decision	2 (0.6)	1 (0.3)	3 (0.5)
Subject decision	2 (0.6)	1 (0.3)	3 (0.5)
Cycles 5-6	**27 (8.6)**	**29 (9.3)**	**56 (8.9)**
Progression of disease	12 (3.8)	17 (5.4)	29 (4.6)
Unacceptable toxicity	9 (2.9)	9 (2.9)	18 (2.9)
Withdrawal of consent	2 (0.6)	2 (0.6)	4 (0.6)
Investigator decision	4 (1.3)	0	4 (0.6)
Subject decision	0	1 (0.3)	1 (0.2)
Total	**124 (39.4)**	**106 (34.0)**	**230 (36.7)**

Abbreviations: N = number of subjects in intended set; n = number of subjects with data available.
Note: Percentages are based on N.
Source: CSR MB02-C-02-17, Listing 16.2.1.3, Listing 16.2.5.1.1

The Applicant provided the extent of study drug exposure for the PPS (Table 25). The mean duration of exposure to IMP was slightly lower in the MB02 arm: 201.2 days (SD 121.50) than in the Avastin arm: 215.6 days (SD 121.64). A slightly lower number of cycles were administered to subjects in the MB02 arm (mean of 10.1 cycles (SD 5.61)) compared with those in the Avastin arm (10.8 cycles (SD 5.65)). A slightly lower percentage of subjects received > 6 cycles of IMP in the MB02 arm (173 subjects; 67.6%) than in the Avastin arm (180 subjects; 70.5%). The dose per subject was higher in the Avastin arm than in the MB02 arm. (Table 32). Similar differences were also seen in the SAF set.

Table 25: Study Drug Exposure (PPS)

	MB02 N = 256	Avastin N = 255	Total N = 511
Duration of exposure (days) – IMP			
Mean (StD)	201.2 (121.50)	215.6 (121.64)	208.4 (121.66)
Median	209.5	233.0	224.0
Q1, Q3	89.5, 328.5	104.0, 344.0	102.0, 339.0
Number of cycles per subject – IMP			
Mean (StD)	10.1 (5.61)	10.8 (5.65)	10.4 (5.64)
Median	10.5	12.0	11.0
Q1, Q3	5.0, 15.5	6.0, 17.0	5.0, 16.0
Cycle categories – IMP			
1-2 cycles, n (%)	33 (12.9)	27 (10.6)	60 (11.7)
3-4 cycles, n (%)	29(11.3)	24(9.4)	53(10.4)
5-6 cycles, n (%)	21(8.2)	24(9.4)	45(8.8)
>6 cycles, n (%)	173 (67.6)	180 (70.5)	353 (69.1)

Abbreviations: IMP = investigational medicinal product; N = number of subjects in intended set; n = number of subjects with data available
Source: Appendix 12 (Table 14.3.4.5.17)

Similar differences are also seen in the SAF set (the difference between the ITT Set and the SAF Set was 6 subjects): The mean duration of exposure was slightly lower in the MB02 arm: 185.9 days (SD 126.01) than in the Avastin arm: 203.9 days (SD 126.25). The mean number of cycles received per subject was slightly lower in the MB02 arm (9.4 cycles) than in the Avastin arm (10.3 cycles). A

slightly lower proportion of subjects received > 6 cycles of IMP in the MB02 (191 subjects; 61.4%) than in the Avastin arm (206 subjects; 66.5%).

Number of chemotherapy cycles

Table 26: RtQ – 10 Number of cycles of chemotherapy received (SAF and PPS)

	SAF set		PPS	
	MB02 N=311	Avastin N=310	MB02 N=256	Avastin N=255
Number of Cycles per Subject				
N	311	310	256	255
Mean (sd)	4.9 (1.74)	5.1 (1.60)	5.1 (1.58)	5.3 (1.44)
Min – Max	1 - 6	1 - 6	1 – 6	1 – 6
Median	6.0	6.0	6.0	6.0
Q1 - Q3	4.0 - 6.0	5.0 – 6.0	5.0 – 6.0	6.0 – 6.0
Cycle Categories, n (%)				
1-2 cycles	53 (17.0)	45 (14.5)	33 (12.9)	27 (10.6)
3-4 cycles	40 (12.9)	30 (9.7)	29 (11.3)	24 (9.4)
5-6 cycles	218 (70.1)	235 (75.8)	194 (75.8)	204 (80.0)

Abbreviations: PPS = per protocol set; SAF = safety analysis set

Source: Q3 Appendix 13 (Table 14.3.4.5.2) and Q3 Appendix 14 (Table 14.3.4.5.18)

When comparing the number of chemotherapy cycles in the PPS set, more subjects of the MB02 arm were only exposed to chemotherapy cycles 1-2 (12.9% and 10.6% for MB02 and Avastin, respectively) and cycles 3-4 (11.3% and 9.4%) of chemotherapies, while more subjects from the Avastin arm received also the chemotherapy cycles 5-6 (75.8% and 80.0%). Similar differences were also seen in the SAF set.

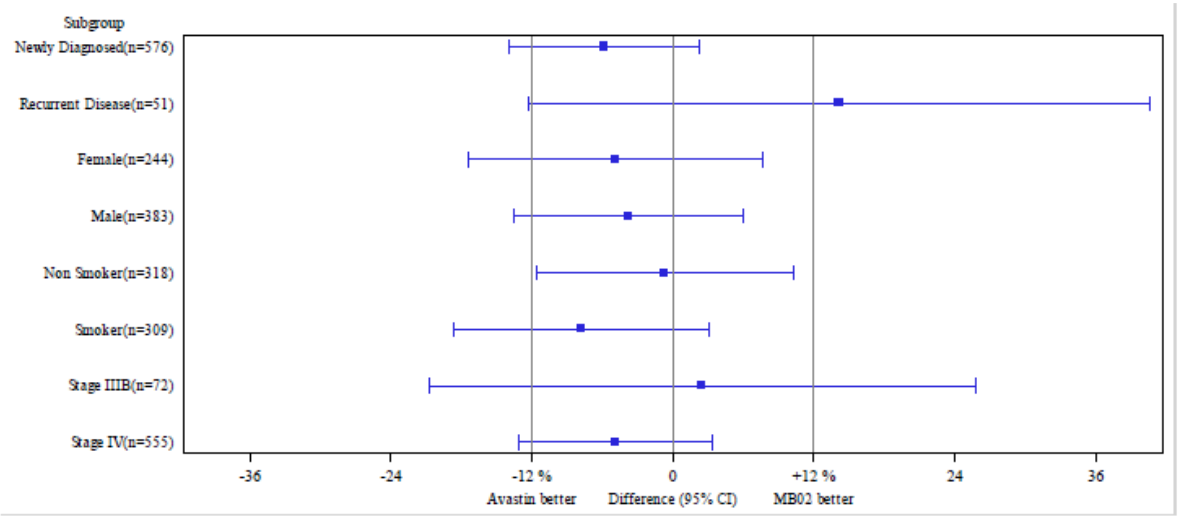
Ancillary analyses

Subgroup		**ORR Risk Difference (RD)** Equivalence range [-12%, 12%]			**ORR Risk Ratio (RR)** Equivalence range [0.73, 1.36]	
		Calculated value	90% CI	95% CI	Calculated value	90% CI
Sex	Male MB02 N =193 Avastin N =190	**-0.037**	-0.119, 0.044	-0.135, 0.060	**0.908**	0.734, 1.122
	Female MB02 N=122 Avastin N=122	**-0.049**	-0.154, 0.059	-0.174, 0.076	**0.903**	0.726, 1.123
Smoking status	Smoker MB02 N=157	**-0.0 78**	-0.169, 0.014	-0.186, 0.031	**0.821**	0.651, 1.037

	Avastin N=152					
	Non-smoker MB02 N=158 Avastin N=160	**-0.0069**	-0.099, 0.085	-0.116, 0.103	**0.985**	0.804, 1.206
Disease diagnosis	Newly diagnosed MB02 N=289 Avastin N=287	**-0.059**	-0.126, 0.009	-0.139, 0.022	**0.872**	0.743, 1.022
	Recurrent MB02 N=26 Avastin N=25	**0.142**	-0.081, 0.364	-0.123, 0.406	**1.442**	0.797, 2.609
Disease stage	Stage IIIB MB02 N=32 Avastin N=40	**0.025**	-0.17, 0.22	-0.207, 0.257	**1.053**	0.706, 1.569
	Stage IV MB02 N=283 Avastin N=272	**-0.049**	-0.117, 0.0198	-0.131, 0.033	**0.889**	0.753, 1.049

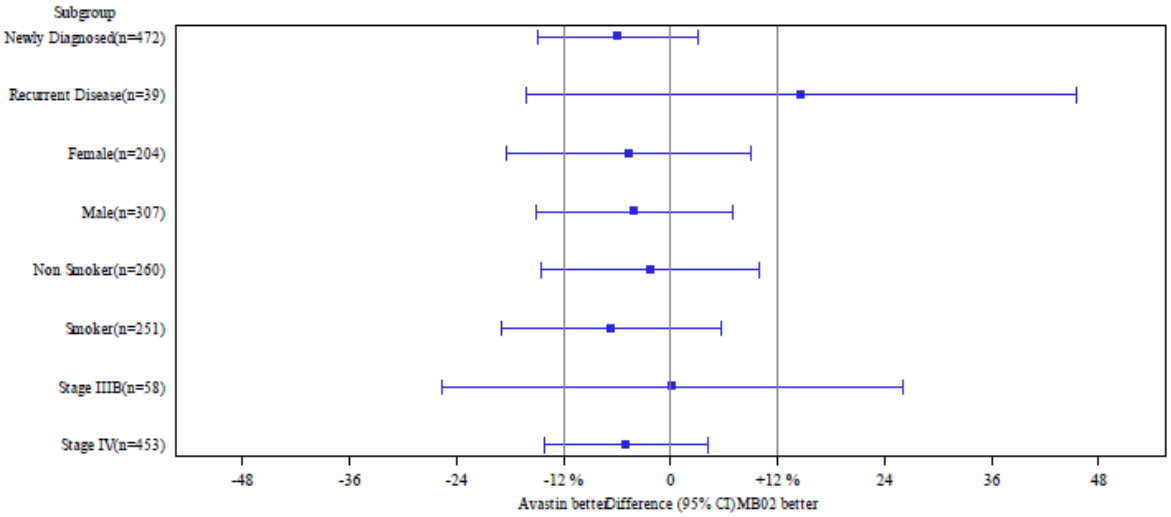
Forest plot for subgroup analyses of the difference in ORR:

Forest plots were provided for the subgroup analyses based on the ITT set and the PP set considering the factors Sex (male/female), Smoking status (smoker/non-smoker), Disease diagnosis (newly diagnosed/recurrent disease) and Disease stage (IIIB/IV).



Abbreviations: ITT = intention-to-treat, RD = risk difference
Source: Final Analysis CSR MB02-C-02-17, Figure 14.2.1.3.4

Figure 7: Forest plot – RD – ITT Set



Abbreviations: PPS = per-protocol set, RD = risk difference
Source: Final Analysis CSR MB02-C-02-17, Figure 14.2.1.3.10

Figure 8: Forest Plot – RD - PPS

The forest plots show a consistency in treatment effect with negative point estimates except for the subgroups "Recurrent disease" and "Stage IIIB" where there are relatively low sample sizes and the corresponding 95% CIs are large covering also the other treatment effects.

The point estimate of the subgroup "Recurrent disease" shows a higher response rate for MB02, but due to low sample size and as there is no medical explanation for a difference in treatment effect, this is likely to be attributed to chance.

No relevant difference in the magnitude of the treatment effect could be found between subgroups.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 27: Summary of efficacy for trial MB02-C-02-17

Title: STELLA – A Randomized, Multicenter, Multinational, Double-Blind Study to Assess the Efficacy and Safety of MB02 (Bevacizumab Biosimilar Drug) Versus Avastin in Combination with Carboplatin and Paclitaxel for the Treatment of Subjects with Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)			
Study identifier	EudraCT number: 2017-001769-26 Protocol number: MB02-C-02-17		
Design	Randomised, double blind, parallel group, multicentre study		
	Duration of main phase: Duration of maintenance phase:		Treatment cycles 1-6 (21-day treatment cycle each) Treatment cycle > 7 to EOS (52 weeks)
Hypothesis	Equivalence		
Treatments groups	A (N=315)		MB02, IV infusion, 15 mg/kg Q3W (6 cycles) with IV carboplatin AUC of 6 and paclitaxel (200 mg/m2) (6 cycles)
	B (N=312)		Avastin (EU), IV infusion, 15 mg/kg Q3W (6 cycles) with IV carboplatin AUC of 6 and paclitaxel (200 mg/m2) (6 cycles)
Endpoints and definitions	Primary endpoint	ORR by Week 18	Proportion of patients whose objective response rate was either CR or PR according to RECIST v1.1. criteria by 18 weeks
	Secondary Endpoint	PFS	Progression-free survival
	Secondary endpoint	OS	Overall survival
	Secondary endpoint	DOR	Duration of response
	Secondary endpoint	OT	Observation time
	Secondary endpoint	Time to OR	Time to overall response
Final database lock	31-March-2020		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat (ITT) PEP evaluation by w18, sec. EP evaluation by w18 and EOS w52		
Descriptive statistics and estimate variability	Treatment group	MB02	Avastin (EU)
	Number of subjects	315	312
Primary endpoint	ORR	127 (40.3%)	139 (44.6%)
	Difference (95% CI)	-4.02 (-11.76, 3.71)	
	ORR (PPS) Difference (95% CI)	-4.27(-12.92 to 4.38)	
Primary endpoint post-hoc	ORR (ITT) RD MI not adjusted for missing/NE (95% CI)	-1.92 (-10.02 to 6.19)	
	ORR (ITT) RD MI adjustment for missing/NE (95% CI)	-2.22 (-10.54 to 6.10)	
	ORR (complete cases[#]) RD (95% CI)	-2.66 (-11.91 to 6.59)	
	ORR (extended PPS [§]) RD (95% CI)	-3.45 (-12.04 to 5.13)	
Secondary endpoints	PFS Median (weeks) (95% CI)	36.0 (33.57 - 36.86)	43.0 (36.14 to 45.14)
	PFS HR (95% CI)	1.200 (0.985 - 1.462)	
	OS RMST Difference (weeks) (95% CI)	n/a	n/a
	OS HR (95% CI)	1.107 (0.826 to 1.483)	
	DOR RMST Difference (weeks) (95% CI)	30.29 (28.29 to 38.43)	37.14 (30.43 to 39.57)

DOR HR (95% CI)	1.195 (0.916 to 1.561)	
OT RMST Difference (weeks) (95% CI)	52.29 (52.14 – 52.29)	52.29 (52.14 to 52.29)
OT HR (95% CI)	1.104 (0.916 - 1.331)	
Time to OR Median (weeks) (95% CI)	12.43 12.14 to 18.00	12.29 12.14 to 14.14
Time to OR HR (95% CI)	0.949 (0.768 - 1.172)	

population set including only those patients in the ITT set that completed Week 18 and had overall response (OR/BOR of CR, PR, SD or PD per RECIST v1.1).
§ population set excluding only the patients for whom major protocol deviations affecting efficacy occurred up to and including Week 18 (and analysis with multiple imputation in case of Missing/NE ORR for the included patients).

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

Not applicable.

Clinical studies in special populations

Not applicable for biosimilars. According to inclusion criteria patients aged ≥18 years to ≤80 years were studied in the pivotal Phase III MB02-C-02-17 Study.

Supportive study(ies)

Not applicable.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme to demonstrate biosimilarity in efficacy between MB02 and EU-Avastin is based on one pivotal trial: MB02-C-02-17 was a multinational, multicentre, 2-armed, randomized, double-blind, parallel-group study in patients with newly diagnosed or recurrent stage IIIB/IV non-squamous NSCLC. Patients with non-squamous NSCLC are considered a relevant and sensitive population for the detection of potential differences between MB02 and the reference product.

No other clinical studies were conducted to demonstrate similarity in efficacy between MB02 and EU Avastin in other indications approved for EU Avastin. The applicant provided a justification on the extrapolation to the other approved indications.

The study was conducted in 16 countries and 93 study centres worldwide, including three EU Member States (Bulgaria, Greece and Hungary). The Applicant stated that the study was conducted in accordance with the ethical principles of the Declaration of Helsinki and consistent with ICH Guidance

and the applicable local regulatory requirements and laws. Two GCP inspections were conducted at two centres in Malaysia by the Medical Research and Ethics Committee (MREC). The respective inspection reports were provided; there were no critical GCP findings.

627 patients were randomized (1:1) to receive either MB02 or EU-Avastin. Eligible randomized patients received either MB02 or EU-Avastin (15 mg/kg by IV infusion) in combination with carboplatin and paclitaxel (administered by IV infusion at intended doses of 6 mg/mL x min [AUC6] and 200 mg/m2, respectively) on Day 1 of a 21-day treatment cycle.

Treatment cycles were repeated for up to 6 cycles, unless evidence of disease progression or other criteria for treatment discontinuation was observed. After 6 cycles, patients continued with monotherapy of MB02 or EU-Avastin until evidence of DP or unacceptable toxicity. Treatment was generally discontinued upon withdrawal of consent, death, lost to follow-up, protocol violation, termination by the sponsor or pregnancy.

The study design was generally in line with previous EMA-scientific advices and considered adequately powered to demonstrate equivalence with the reference product. The treatment regimens for bevacizumab and chemotherapy are in line with Avastin labelling and respective guidance.

Studied population

The selected study population with newly diagnosed or recurrent Stage IIIB/IV non-squamous NSCLC with at least 6 months from previous neoadjuvant/adjuvant treatment to randomization is considered sufficiently sensitive to identify a difference between the intended to be biosimilar MB02 and EU Avastin. The efficacy and safety profile of comparator treatment regimen with EU-Avastin in combination with paclitaxel and carboplatin approved for advanced non-squamous NSCLC is well understood.

Inclusion and exclusion criteria are based on those of the EU-Avastin reference trial and considered appropriate. The majority of patients had stage IV disease and were newly diagnosed patients. There were no findings in the medical history of clinical concern and no baseline signs/ symptoms of clinical concern prior to dosing.

Sex (female/ male), smoking status (smoker/ non-smoker), disease diagnosis (newly diagnosed/ recurrent disease) and disease stage (stage IIIB/ IV) were used as stratification factors and are considered clinically relevant prognostic factors for the underlying disease. The stratification by gender and smoking status was endorsed during SA procedure by CHMP (EMA/CHMP/SAWP/370625/2017). Following this SA procedure additional stratification by disease diagnosis (newly diagnosed/recurrent disease) and by disease stage (IIIB/IV) was undertaken.

Overall, baseline demographic and disease characteristics were well balanced between treatment arms.

Efficacy endpoints

The primary endpoint was the objective response rate (ORR) in the intention-to-treat (ITT) population by Week 18. The per-protocol-set (PPS) population was used as a supportive population for evaluation of the sensitivity of the main analysis; in an equivalence setting, the PPS should lead to similar results for a robust interpretation. Secondary endpoints were PFS and OS by Week 18 and 52. Further endpoints were DOR, OT and Time to OR by Week 52. The primary and secondary endpoints were in line with the recommendation in the scientific advice and biosimilar guidelines (CHMP/437/04 Rev.1, EMEA/CHMP/BMWP/42832/2005 Rev.1 and EMEA/CHMP/BMWP/403543/2010).

Based on the result of a meta-analysis of available RCTs of Avastin, an equivalence margin of ±12 % for the risk difference of ORR was defined, which is acceptable from a statistical point of view to ensure that in case of significance MB02 would be better than placebo. A margin of [-12%, +12%] corresponds to retaining approximately 20% of the conservative estimate of treatment effect sizes

relative to chemotherapy for MB02. For clinical justification of the chosen equivalence margin, the reference was made to other biosimilar bevacizumab applications with even higher pre-specified equivalence margins of (±12.5%, ±13%). With a margin of [-13%, +13%], approximately 12% of the treatment effect of the reference product would be preserved. The Applicant argued that a difference in efficacy on ORR within the 13% margin would correspond to a change in PFS of 2.6 months, and such was not considered clinically meaningful in the treatment of advanced NSCLC according to FDA guidance (FDA-2011-D-0432, "Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics"). Use of this reference deals with a different situation, i.e. eligibility for accelerated approval of new drugs, where treatment differences based on PFS had to be substantial (e.g., 3 months or more) in a superiority trial. Ultimately, however, the actual confidence interval limits are most important when it comes to deciding on equivalence.

The sample size calculations, randomisation and blinding procedures are considered adequately performed.

In general, the Applicant´s development programme for demonstrating similarity between MB02 and EU-Avastin with respect to efficacy is considered adequate to support a MAA. The study design, study population, inclusion/exclusion criteria, and dose regimen were in line with the guidance on similar biological products and were in general complied with scientific advice obtained from the EMA.

Efficacy data and additional analyses

The initial submission included the CSR data up to the Week 18 data cut-off (data cut-off: 03-July-2019). The final analysis CSR (11-August-2020) was provided during the evaluation procedure and includes a full analysis of EOS Week 52 data.

An unblinded study team independent from the blinded study team carried out the main analysis at Week 18. Tumour assessment is conducted by an independent central review for the primary analysis.

The number of patients with stable disease (SD) and disease progression (PD) was largely comparable between treatment arms. Early discontinuation was observed in 114 (36.2%) subjects in the MB02 group compared with 97 (31.1%) subjects in the EU Avastin group. The point estimate for the primary endpoint risk difference in ORR at week 18 in the ITT was -4.02 [95% CI: -11.76 to 3.71]. The two-sided 95% CI was contained within the pre-specified equivalence margin of [-12%, 12%]. The ORR risk difference at week 18 for the PPS population was -4.27 and the two-sided 95% CI [-12.92 to 4.38] was not fully contained within the pre-specified equivalence margin of [-12%, 12%].

Subjects who discontinued before week 18 were imputed as non-responders in both treatment arms, which would be anti-conservative in an equivalence setting. In addition, multiple imputation was performed by imputing all data by a regression model for the missing sum of diameters of target lesions. For certain discontinuation reasons associated with a negative outcome still non-responder imputation is performed making this a mixed and more realistic approach: In the ITT population, the ORR RD with the 95% CI remained within the 12% margins (-1.92; 95% CI: -10.02 to 6.19, MI not adjusted for missing/NE analysis) and similarly for the mITT, where the ORR difference was -2.77 (95% CI: -11.09 to 5.55). For the PPS the ORR difference was -5.0, and the 95% CI was (-13.68 to 3.68); the lower bound of the 95% CI exceeds the pre-defined equivalence margin of ±12% and also the argued 13% margin.

An additional sensitivity analysis was requested in order to see if results for the ITT set (with MI taking into account treatment and stratification factors for patients without tumour response data or falling into the categories NonCR/NonPD or NE) would violate the equivalence margin. The number of missing values imputed by MI instead of non-responder imputation was higher for Avastin than for MB02 in the

new MI analysis, making the ORR RD at week 18 slightly larger (-2.22), but the lower bound of the 95% CI still lies within 12% (95% CI: -10.54 to 6.10). Thus, the ITT ORR results seem fairly robust to different imputations, and thus supporting equivalence of MB02 to Avastin within the predefined acceptance range.

Following the final request from CHMP, the Applicant analysed a complete cases set, i.e. all patients of the ITT set that completed Week 18 and also had an OR of CR, PR, SD or PD according to RECIST v1.1, while excluding those subjects with non-evaluable disease and non- CR/non-PD response due to lack of target lesions at baseline. This analysis set has a similar intention as the pre-specified PPS, i.e. to assess differences in the treatments reducing the impact of unrelated factors on the outcome assessment, in this case based on the set of actual data that are generated over the course of treatment. The ORR RD was -2.66 (95% CI: -11.91 to 6.59) at Week 18 by IRRC Review, which is even fully contained within the predefined acceptance range of [-12%, +12%]. Though the interpretation of this result needs to be balanced against not fully respecting randomisation (as no PPS analysis does) and regarding multiplicity considering its post-hoc character, this analysis in a more sensitive model of completing patients supports similarity of MB02 and EU-Avastin with respect to the primary endpoint ORR.

Another relevant analysis approximating the PPS was provided that excluded only those patients from the PPS who had major protocol deviations with potential later impact on efficacy. This means that compared to the initial PPS definition those patients were included where the reason for the protocol violation was considered unrelated to later treatment efficacy. The intent of this request was to increase the sample size, and thereby to increase the precision of the information on the difference between the treatments, as based on a decreased sample size the PPS has by definition the property to have less statistical power. This analysis included 570 patients (91.0% of the ITT set), whereas the PPS included 511 patients (81.5% of the ITT set). In the thereby defined analysis set and under the preferred analysis using multiple imputation adjusting for missing/NE, the ORR RD was -3.45 (95% CI -12.04 to 5.13), and thus while again having in mind its post-hoc character this analysis like the complete cases set demonstrated comparable efficacy between the two treatments.
The discontinuation pattern per Cycle shows that non-responder imputation favors the treatment arm with less missing data because Cycles 1-2 and Cycles 3-4 show a lower percentage of discontinuation for Avastin (15.1% vs 18.1% and 9.6% vs 12.7%, for Avastin vs MB02, respectively), whereas for Cycles 5-6 the Avastin arm shows a higher percentage of discontinuation (9.3% vs 8.6%). This explains why for ITT there is a shift towards 0 and for the PPS there is a shift away from 0 when using MI instead of non-responder imputation.

The difference in best ORR in ITT was -4.04 (95% CI: -11.86 to 3.78) with non-responder imputation. In the analyses of BORR RD based on the PP set, the lower limit of the 95% CI was below -12% and for the PP analysis below also -13%. In addition to an independent central review for the primary analysis, assessment by investigator´s analysis is made, which is supported. ORR by the additional investigator assessment had a point estimate for the difference of -7.01 with a 95% CI of (-14.79 to 0.78) in the ITT analysis.

Additional time points (week 6 and week 12) for ORR evaluation were considered as well. It was shown that the difference in ORR favours MB02 at Week 6 (4.75 for NR and 5.02 for MI), but favours Avastin at Week 12 (-3.48 for NR and -0.96 for MI) and Week 18 (-4.02 for NR and -2.22 for MI) in the ITT set. The 95% CIs lie within the equivalence margin of 12% (set for the week 18 assessment), and the directions are inconsistent over time. When analysing the PPS, the same pattern is confirmed. This course over time does not reveal a consistent picture, however does not amount either to a doubt on a differential treatment effect. Aware of the post-hoc character of some of the PP results and the unknown direction the lack of randomised comparison actually has on the results, the observation of

an inconsistent pattern over time rather suggests a random component, respectively a component relating to effects imposed through study conduct (e.g. patient retainment/withdrawals).

The percentage change in tumour burden from baseline (sum of the diameters of the target lesions) was investigated post-hoc, showing no significant difference between the treatments: For the ITT set the mean of the percentage change from baseline in tumour burden by 18 weeks was −26.64 for MB02 and −25.75 for Avastin; the difference between the treatment groups was −0.892 (95% CI −4.828, 3.044). Results were comparable by Week 6 and Week 12 with a difference of −0.976 and −1.133, respectively. Analysis of the %change in tumour burden assessed by the investigator was comparable with the IRRC assessment. Consistent with the ITT set results, the point estimates of the difference between MB02 and Avastin in the means of %change from baseline in tumour burden on the PPS were all negative, but fairly consistent between week 6, 12 and 18.

Assessment of tumour burden on a continuous scale might be expected to increase sensitivity in terms of detecting potential treatment differences between a proposed biosimilar and its reference medicinal product and less prone to bias. All 95% CIs around the difference in means of %change in tumour burden show maintained response between [-5%, +5%] across both ITT and PPS. While it is critically noted that no margin was pre-specified for this endpoint, the extension of the confidence intervals for the difference in LSMeans is small in relation to the change from baseline, indicating good quantification of any differences between treatments, and thus supporting similarity of the two treatments across the analyses. Though in the lack of pre-specified equivalence margins this result cannot be used as a sole confirmatory result, it can be considered sensitive to detect differences between the treatments arms and adds supporting evidence of similarity. Therefore, tumour burden assessment strengthens the notion of similarity between MB02 and Avastin in the clinical assessment.

In the subgroup analyses of the ITT population, a significant effect of the randomization strata sex, smoking, diagnosis and disease status on the outcome OR at week 18 was observed. However, no relevant differences between the MB02 and EU-Avastin treatment arms were observed in these factors.

For the PPS, the mean duration of exposure to IMP was apparently slightly lower in the MB02 arm: 201.2 days (SD 121.50) than in the Avastin arm: 215.6 days (SD 121.64). A slightly lower number of cycles was administered to subjects in the MB02 arm (mean of 10.1 cycles (SD 5.61)) compared with those in the Avastin arm (10.8 cycles (SD 5.65)). A slightly lower percentage of subjects received > 6 cycles of IMP in the MB02 arm (173 subjects; 67.6%) than in the Avastin arm (180 subjects; 70.5%). The dose per subject was higher in the Avastin arm than in the MB02 arm. Similar differences are also seen in the SAF set.

In addition, when comparing the number of different chemotherapy cycles, more subjects of the MB02 arm were only exposed to chemotherapy cycles 1-2 (12.9% and 10.6% in the PPS set) and cycles 3-4 (11.3% and 9.4% in the PPS set), while more subjects from the Avastin arm received also the chemotherapy cycles 5-6 (75.8% and 80.0% in the PPS set). Similar differences in exposure were also seen in the SAF set and this imbalance did not lead to a crossing of the acceptance range in the ITT analysis for the ORR RD. In summary, the slightly lower exposure and number of cycles of IMP and chemotherapy in the MB02 arm than in the Avastin arm, could partly have contributed to the observed tendency and favoured Avastin in efficacy endpoints.

One reason that the 95% CIs were initially not contained within the equivalence margins for the PPS could be that the sample size was not adjusted for drop-outs, such that for the PPS the power to detect equivalence in case of similarity was lower. The calculated sample size to achieve 82% power was 300 subjects per treatment arm, 600 subjects in total. The ITT set consisted of 627 patients in total, 312 patients in the Avastin arm and 315 patients in the MB02 arm whereas the PP set had 511 patients, 255 patients in the Avastin arm and 256 patients in the MB02 arm. This is in line with the

requested results obtained for an extended PPS definition, where more narrow confidence intervals resulted extending only to around 12%.

The secondary endpoints PFS and OS were evaluated at EOS Week 52. At EOS, the median PFS was 36.43 weeks, and results were in favour of Avastin (36.0 weeks vs. 43.00 weeks with MB02 and Avastin, respectively). The PFS hazard ratio of the ITT set was 1.2 (95% CI: 0.985 to 1.462). The OS hazard ratio of the ITT was 1.107 (95% CI: 0.826 to 1.483). The PFS hazard ratio of the PPS was 1.233 (95% CI: 0.999 to 1.521). The OS hazard ratio was 1.141 (95% CI: 0.835 to 1.560). Overall the time-to-event endpoints are numerically consistently favouring Avastin and thereby match the results of the primary endpoint ORR, but are both less sensitive and especially over the longer observation period dependent on external factors, and are per se considered less informative for conclusions on biosimilarity.

2.5.4. Conclusions on clinical efficacy

The primary analysis of the RD in ORR at week 18 in the ITT set meets the predefined equivalence margins. While for the PPS the RD in ORR had a lower bound of the 95% CI around 13%, several supplementary analyses on the primary endpoint ORR that approximate the intention of the pre-specified PPS, showed comparable results between the treatment arms including the analysis of complete cases at week 18, and the analysis excluding only the patients who had major protocol deviations with potential impact on efficacy. Also, the ORR over time does not show a consistent pattern and could indicate a treatment effect seem implausible, but rather suggests a random element.

The change in tumour burden showed comparable results between the treatments and adds supporting evidence of similarity. Other secondary efficacy endpoints were in consistency with the primary endpoint, with point estimates favouring EU Avastin. As the observations are made on the same individuals, characteristics related to patients can influence such consistency. A further observation is that due to a slightly lower exposure and number of cycles of IMP and chemotherapy in the MB02 arm, subjects in the Avastin arm have received more IMP and chemotherapy than in the MB02 arm. This could also explain parts of the observed trend towards higher efficacy of Avastin.

In essence, all of the data provided upon request mitigate the previous concern, and while the 95% CI of the ORR RD analysis in the PPS extends somewhat beyond the predefined acceptance range, the provided respective supplementary analyses put these results into perspective. Overall, efficacy results support biosimilarity of MB02 and Avastin.

2.6. Clinical safety

Introduction

Pivotal comparative safety data was derived from two clinical studies: a comparative efficacy, safety and immunogenicity study in non-squamous NSCLC patients (MB02-C-02-17), and a single dose PK studies conducted in healthy volunteers in the EU (MB02-A-02-17). Safety evaluation is further supplemented by safety data from two single dose PK studies in healthy volunteers (MB02-A-04-18 and MB02-A-05-18) and a phase I, open label, repeat-dose, parallel arm PK study in mCRC patients (BEVZ92-A-01-13).

Study MB02-C-02-17 is a randomized, multicentre, multinational, double-blind study assessing the efficacy and safety of MB02 versus EU licensed Avastin, in combination with carboplatin and paclitaxel

for the treatment of subjects with stage IIIB/IV non-squamous non-small cell lung cancer (NSCLC) at 93 study sites in 16 countries.

MB02-A-02-17 is a randomised, double-blind, 3-arm, single dose, parallel study comparing the Pharmacokinetics, safety and immunogenicity of MB02, US-licenced Avastin and EU-approved Avastin..

Study **MB02-A-05-18** is a supportive, single-dose, randomised, double-blind study with three parallel arms to compare PK, safety and immunogenicity of MB02, EU-approved Avastin and US-licensed Avastin in healthy male volunteers. The design, conduct and analysis for this study are identical to that of study MB02-A-02-17.

Study **MB02-A-04-18** is a supportive, single-dose, randomised, double-blind study with two parallel arms to compare PK, safety and immunogenicity of MB02 and EU-approved Avastin. Study designs and methodology of these three Phase 1 studies are located in the efficacy section and in more detail in the respective sections of the Clinical Report.

Study **BEVZ92-A-01-13** is a supportive, open label, repeat-dose, parallel arm PK study in 142 mCRC patients for a duration of up to 88 weeks (for BEVZ92) or 122 weeks (for Avastin), respectively. This study, which was the FIH trial for MB02 clinical development, used a drug product (referred to as BEVZ92) manufactured according to GMP standards by a contract manufacturer at a different site to the one used for the rest of clinical development. This study was therefore only assessed for safety aspects but not for PK or efficacy parameters.

Both BEVZ92 and Avastin were to be administered at the initial dose of 5 mg/kg every 2 weeks, initially as a 90-minute intravenous (IV) infusion. If well tolerated, the next infusion was to be given over a 60-minute period; thereafter, these drugs were to be given over 30 minutes if well tolerated. Dose reduction of BEVZ92 or Avastin for adverse events (AEs) was not permitted, and therapy should be delayed or permanently discontinued if indicated. Special provisions were in place for AEs of interest, including hypertension, bleeding, proteinuria, thromboembolic events, posterior leukoencephalopathy, wound healing complications/dehiscence, gastrointestinal perforation, fistulae, and hypersensitivity reactions. FOLFOX (any) or FOLFIRI were to be chosen as per investigator criteria based on the hospital standard of care. The oxaliplatin dose was to be kept fixed at 85 mg/m2 in the first dose. Dose reductions were allowed for fluorouracil, oxaliplatin and irinotecan (depending the regimen selected – FOLFOX or FOLFIRI) according to the indications in the corresponding Summary of Product Characteristics. Each cycle of BEVZ92 and Avastin plus FOLFOX (any) or FOLFIRI was to be repeated every 2 weeks until progressive disease (PD), unacceptable toxicity, or withdrawal of consent.

Four immunogenicity samples were to be collected: on Day 1 of Cycles 1, 5 and 8, and 12 months after first drug administration.

Patient exposure

To date, 1037 subjects received at least one dose of IMP: 621 non-squamous NSCLC patients, 140 mCRC patients and 276 healthy volunteers.

Pharmacokinetic study MB02-A-02-17:

All 114 subjects enrolled in the study received the planned single dose of 3 mg/kg of MB02, US-Avastin or EU-Avastin, 38 subjects in each treatment arm. The total duration of trial participation for each subject (from Screening through to the final visit) was of 19 weeks. This dose is lower than the approved dose for Avastin, due to ethical concerns in a healthy study population and endoresed by the EMA Scientific advice earlier. Subjects in the US- and EU-Avastin arms received a dose of bevacizumab

approximately 12% to 14% lower than that administered to subjects in the MB02 arm. Nevertheless, comparison of safety data in this study seems possible.

Pharmacokinetic study MB02-A-05-18:

114 subjects received study treatment (3 mg/kg single dose of MB02, US-Avastin or EU-Avastin, 38 per treatment arm) and 113 subjects completed the study. One US Avastin subject withdrew before receiving any study treatment and was replaced. One EU Avastin subject received study treatment and was included in the safety and PK populations but was lost to follow-up on Day 56 and considered not to have completed the study. The total duration of clinical trial participation for all other subjects (from Screening through to the final visit) was approximately 19 weeks.

Pharmacokinetic study MB02-A-04-18:

All 48 subjects enrolled in the study received the planned single dose of 3 mg/kg of MB02 or EU-Avastin, 24 subjects in each treatment arm. The total duration of trial participation for each subject (from Screening through to the final visit) was 14 weeks.

Pharmacokinetic study BEVZ92-A-01-13:

A total of 140 patients, 69 in the BEVZ92 arm and 71 in the Avastin arm, comprehend the All treated (AT) population in this study and received 2350 cycles of treatment. In the BEVZ92 arm, 1007 cycles were administered, with a maximum of 44 cycles per patient; in the Avastin arm, 1343 cycles were administered, with a maximum of 61 cycles per patient. The mean and median cumulative dose of BEVZ92 were 73.0 and 65.0 mg/kg, whereas the corresponding figures were 94.6 and 71.0 mg/kg, respectively, for Avastin. The number of patients that withdrew treatment during the first 6 cycles of treatment was higher in the BEVZ92 arm (n=14) than in the Avastin arm (n=9). Afterwards, the unbalance increased in subsequent cycles. Nevertheless, most patients received up to 10 cycles of BEVZ92 or Avastin (81% vs 86%, respectively), and the proportion of patients receiving up to 15 cycles (67% and 72%), up to 20 cycles (33% and 47%) and, so on, was quite similar in the BEVZ92 or Avastin treatment groups.

In the AT population, FOLFOX was the chemotherapy regimen chosen by investigators in 45 patients in each arm (thus comprising 65% of patients in the BEVZ92 arm and 63% of patients in the Avastin arm). Two other patients in the BEVZ92 arm were randomized to FOLFOX but they did not receive any study treatment. Conversely, FOLFIRI was chosen in 24 (35%) patients in the BEVZ92 arm and in 26 (37%) patients in the Avastin arm.

Table 28: Extent of Exposure – AT Population

Characteristic	BEVZ92 (N=69)	Avastin® (N=71)	All (N=140)
Cumulative dose of bevacizumab (mg/kg)*			
Mean (SD)	73.0 (47.32)	94.6 (70.59)	83.9 (61.00)
Median (interquartile range; IQR)	65.0 (45.0; 99.0)	71.0 (45.0; 115.0)	70.0 (45.0; 105.0)
Minimum; maximum	5; 220	10; 305	5; 305
Number of cycles administered			
1 to 6	14 (20%)	9 (13%)	23 (16%)
7 to 10	9 (13%)	10 (14%)	19 (14%)
11 to 15	23 (33%)	18 (25%)	41 (29%)
16 to 20	10 (15%)	11 (16%)	21 (15%)
21 to 25	4 (6%)	8 (11%)	12 (9%)
26 to 30	5 (7%)	3 (4%)	8 (6%)
31 to 35	0	4 (6%)	
36 to 40	3 (4%)	0	3 (2%)
41 to 45	1 (1%)	2 (3%)	3 (2%)
46 to 50	0	3 (4%)	3 (2%)
51 to 55	0	0	0
56 to 60	0	1 (1%)	1 (<1%)
61 to 65	0	2 (3%)	2 (1%)
Patients with a least one interruption	5 (7%)	0	5 (4%)
Patients with at least one re-administration after interruption	5 (7%)	0	5 (4%)

*If the weight was missing at a visit, the weight at the previous visit was used.
Source: Table 14.3.1 (Section 14)

Study MB02-C-02-17:

As the safety profile of bevacizumab is well characterized, the sample size of the phase 3 study is considered acceptable to capture relevant safety signals.

A total of 427 (68.1%) subjects had completed treatment up to Week 18.

Subject demographics (gender, age, weight and height) were well balanced between treatment groups (see also 3.3.5). The mean duration of exposure was lower in the MB02 group (185.9 days compared with the Avastin group (203.9 days). Subjects in the MB02 group received a mean of 9.4 cycles of IMP compared with 10.3 cycles administered in the Avastin group. The mean amount of actual IMP doses administered was 1033.16 mg and the mean duration of infusion was 39.6 minutes, with no notable differences observed between groups. The frequency of subjects with IMP dose modifications (4 subjects vs 3 subjects), IMP dose delays (136 subjects vs 133 subjects), and IMP stops/interruptions (3 subjects each) was similar between the MB02 and Avastin groups, respectively. While not statistically significant, the lower duration of exposure in MB02-treated subjects was likely attributed to the slightly higher rate of discontinuations up at week 18 in the MB02 group than in Avastin group, particularly in the first cycles. The proportion of subjects in each treatment group that did not complete/discontinued the treatment up to Week 18 was as follows: 33.01% (104 subjects) and 28.84% (90 subjects) for the MB02 and EU-Avastin treatment groups, respectively. Other reasons, rather than toxicity, caused the imbalance at first cycles. After Week 18 (from cycle 7 to 18), discontinuations were slightly lower in the MB02 group, reverting the small imbalance observed during the first cycles.

Exposure to Carboplatin and Paclitaxel

A summary of administration of Carboplatin and Paclitaxel follows.

Table 29: Study Drug Exposure (SAF Set)

	Avastin® N = 310	MB02 N = 311	Total N = 621
Duration of exposure (days) – IMP			
Mean (StD)	203.9 (126.25)	185.9 (126.01)	194.9 (126.35)
Median	204.0	182.0	190.0
Q1, Q3	89.0, 343.0	64.0, 306.0	71.0, 335.0
Number of cycles per subject – IMP			
Mean (StD)	10.3 (5.84)	9.4 (5.79)	9.8 (5.83)
Median	10.0	9.0	9.0
Q1, Q3	5.0, 16.0	4.0, 15.0	4.0, 16.0
Cycle categories – IMP			
1-2 cycles, n (%)	45 (14.5)	53 (17.0)	98 (15.8)
3-4 cycles, n (%)	30 (9.7)	40 (12.9)	70 (11.3)
5-6 cycles, n (%)	29 (9.4)	27 (8.7)	56 (9.0)
>6 cycles, n (%)	206 (66.5)	191 (61.4)	397 (63.9)
Duration of exposure (days) – carboplatin			
Mean (StD)	92.2 (36.22)	88.2 (39.44)	90.2 (37.89)
Median	106.0	107.0	106.0
Q1, Q3	89.0, 112.0	64.0, 113.0	71.0, 112.0
Number of cycles per subject – carboplatin			
Mean (StD)	5.1 (1.60)	4.9 (1.74)	5.0 (1.68)
Median	6.0	6.0	6.0
Q1, Q3	5.0, 6.0	4.0, 6.0	4.0, 6.0
Cycle categories – carboplatin			
1-2 cycles, n (%)	45 (14.5)	53 (17.0)	98 (15.8)
3-4 cycles, n (%)	30 (9.7)	40 (12.9)	70 (11.3)
5-6 cycles, n (%)	235 (75.8)	218 (70.1)	453 (72.9)
Duration of exposure (days) – paclitaxel			
Mean (StD)	92.2 (36.07)	88.0 (39.44)	90.1 (37.83)
Median	106.0	107.0	106.0
Q1, Q3	89.0, 112.0	64.0, 113.0	70.0, 112.0
Number of cycles per subject – paclitaxel			
Mean (StD)	5.1 (1.60)	4.9 (1.74)	5.0 (1.67)
Median	6.0	6.0	6.0
Q1, Q3	5.0, 6.0	4.0, 6.0	4.0, 6.0
	Avastin® N = 310	**MB02 N = 311**	**Total N = 621**
Cycle categories – paclitaxel			
1-2 cycles, n (%)	45 (14.5)	53 (17.0)	98 (15.8)
3-4 cycles, n (%)	30 (9.7)	41 (13.2)[a]	71 (11.4)
5-6 cycles, n (%)	235 (75.8)	217 (69.8)	452 (72.8)

Abbreviations: IMP, investigational medicinal product; N, number of subjects on the intended set; n, number of subjects with data available; Q1, 25th percentile; Q3, 75th percentile; SAF, safety analysis set; StD, standard deviation.
Note: Percentages are based on N.
Note: Duration of study drug exposure = last dose date – first dose date + 1.
[a] One subject received paclitaxel but did not receive carboplatin.
Source: Table 14.3.4.5.1, 14.3.4.5.2

No notable differences were observed between IMP groups with regard to mean duration of exposure, total dose received, and duration of infusion. Likewise, the frequency of subjects with carboplatin or paclitaxel dose modifications, delays, and stops/interruptions was comparable between treatment groups.

Adverse events

MedDRA, version 20.1, was used for assigning System Organ Classes (SOC) and Preferred Terms in studies MB02-C-02-17 and MB02-A-02-17.

The most commonly reported adverse events across clinical trials in patients receiving Avastin were hypertension, fatigue or asthenia, diarrhoea and abdominal pain. The most serious adverse reactions reported were gastrointestinal perforations, haemorrhage, including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients and arterial thromboembolism.

PK study MB02-A-02-17:

Table 30: Overview of Treatment-emergent Adverse Events – Safety Population

	3 mg/kg MB02 IV (N = 38)	3 mg/kg US Avastin® IV (N = 38)	3 mg/kg EU Avastin® IV (N = 38)	Overall (N = 114)
Subjects with TEAEs	24 (63.2%)	28 (73.7%)	25 (65.8%)	77 (67.5%)
Fisher's exact test p-value vs US Avastin®	0.460		0.618	
Fisher's exact test p-value vs EU Avastin®	1.000			
Number of TEAEs	63	99	68	230
Subjects with SAEs	---	1 (2.6%) [1]	---	1 (0.9%) [1]
Subjects discontinued due to TEAEs	---	---	---	---
All TEAEs by Severity				
Grade 1: Mild	24 (63.2%) [59]	25 (65.8%) [78]	24 (63.2%) [62]	73 (64.0%) [199]
Grade 2: Moderate	4 (10.5%) [4]	10 (26.3%) [20]	5 (13.2%) [6]	19 (16.7%) [30]
Grade 3: Severe	---	1 (2.6%) [1]	---	1 (0.9%) [1]
Total	24 (63.2%) [63]	28 (73.7%) [99]	25 (65.8%) [68]	77 (67.5%) [230]
Related TEAEs (possible, probable, definitely related) by severity				
Grade 1: Mild	5 (13.2%) [9]	1 (2.6%) [2]	6 (15.8%) [10]	12 (10.5%) [21]
Grade 2: Moderate	1 (2.6%) [1]	1 (2.6%) [1]	3 (7.9%) [3]	5 (4.4%) [5]
Grade 3: Severe	---	1 (2.6%) [1]	---	1 (0.9%) [1]
Total	6 (15.8%) [10]	3 (7.9%) [4]	8 (21.1%) [13]	17 (14.9%) [27]

Abbreviations: N = number of subjects; SAE = serious adverse event; TEAE = treatment-emergent adverse event
( ) = percentage of subjects with adverse events; [ ] = number of adverse events
Source: Table 14.3.1-1a

Overall, 77 subjects (67.5%) reported 230 TEAEs, of which 17 subjects (14.9%) reported 27 events considered possible, probable or definitely related to study treatment. A similar number of subjects reported TEAEs in each treatment arm of the study, and Fisher's exact tests yielded p-values greater than 0.05 for all pairwise comparisons for the percentage of subjects with TEAEs.

Common Adverse events:

The most frequently reported TEAEs (incidence >10%) by Preferred Term were headache, (22 [19.3%] subjects reporting 29 TEAEs overall), upper respiratory tract infection (21 [18.4%] subjects reporting 23 TEAEs overall) and back pain (12 [10.5%] subjects reporting 13 TEAEs overall).

Table 31: Frequency of Treatment-emergent Adverse Events (All Causalities) Reported by >5% of Subjects Safety Population

MedDRA system organ class Preferred term	3 mg/kg MB02 IV (N = 38)	3 mg/kg US Avastin® IV (N = 38)	3 mg/kg EU Avastin® IV (N = 38)	Overall (N = 114)
Overall total	24 (63.2%) [63]	28 (73.7%) [99]	25 (65.8%) [68]	77 (67.5%) [230]
Infections and infestations	9 (23.7%) [10]	18 (47.4%) [25]	14 (36.8%) [17]	41 (36.0%) [52]
Upper respiratory tract infection	4 (10.5%) [4]	11 (28.9%) [12]	6 (15.8%) [7]	21 (18.4%) [23]
Nasopharyngitis	2 (5.3%) [2]	4 (10.5%) [6]	5 (13.2%) [6]	11 (9.6%) [14]
Conjunctivitis	2 (5.3%) [2]	1 (2.6%) [1]	---	3 (2.6%) [3]
Gingivitis	---	1 (2.6%) [1]	2 (5.3%) [2]	3 (2.6%) [3]
Gastrointestinal disorders	7 (18.4%) [17]	9 (23.7%) [10]	7 (18.4%) [9]	23 (20.2%) [36]
Nausea	4 (10.5%) [5]	---	1 (2.6%) [2]	5 (4.4%) [7]
Vomiting	2 (5.3%) [5]	1 (2.6%) [1]	---	3 (2.6%) [6]
Toothache	1 (2.6%) [1]	2 (5.3%) [2]	2 (5.3%) [2]	5 (4.4%) [5]
Diarrhoea	3 (7.9%) [3]	1 (2.6%) [1]	---	4 (3.5%) [4]
Dyspepsia	---	1 (2.6%) [1]	3 (7.9%) [3]	4 (3.5%) [4]
Gingival pain	---	3 (7.9%) [3]	---	3 (2.6%) [3]
Musculoskeletal and connective tissue disorders	6 (15.8%) [7]	14 (36.8%) [21]	8 (21.1%) [8]	28 (24.6%) [36]
Back pain	1 (2.6%) [1]	7 (18.4%) [8]	4 (10.5%) [4]	12 (10.5%) [13]
Pain in extremity	---	4 (10.5%) [4]	3 (7.9%) [3]	7 (6.1%) [7]
Muscle spasms	2 (5.3%) [2]	2 (5.3%) [2]	---	4 (3.5%) [4]
Musculoskeletal pain	2 (5.3%) [2]	1 (2.6%) [1]	---	3 (2.6%) [3]
Arthralgia	---	2 (5.3%) [2]	---	2 (1.8%) [2]
Nervous system disorders	7 (18.4%) [11]	9 (23.7%) [12]	8 (21.1%) [10]	24 (21.1%) [33]
Headache	6 (15.8%) [9]	8 (21.1%) [10]	8 (21.1%) [10]	22 (19.3%) [29]
Dizziness	2 (5.3%) [2]	1 (2.6%) [1]	---	3 (2.6%) [3]
Respiratory, thoracic and mediastinal disorders	5 (13.2%) [5]	6 (15.8%) [8]	9 (23.7%) [12]	20 (17.5%) [25]
Oropharyngeal pain	1 (2.6%) [1]	4 (10.5%) [5]	5 (13.2%) [5]	10 (8.8%) [11]
Cough	4 (10.5%) [4]	2 (5.3%) [2]	1 (2.6%) [1]	7 (6.1%) [7]
Nasal congestion	---	---	3 (7.9%) [3]	3 (2.6%) [3]
Epistaxis	---	---	2 (5.3%) [2]	2 (1.8%) [2]

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects ( ) = percentage of subjects with adverse events; [ ] = number of adverse events
Events were coded using MedDRA (Version 20.1)
Source: Table 14.3.1-2a

Table 32: Frequency of Treatment-emergent Adverse Events (All Causalities) Reported by >5% if Subjects Safety Population (Continued)

MedDRA system organ class Preferred term	3 mg/kg MB02 IV (N = 38)	3 mg/kg US Avastin® IV (N = 38)	3 mg/kg EU Avastin® IV (N = 38)	Overall (N = 114)
Injury, poisoning and procedural complications	3 (7.9%) [4]	3 (7.9%) [6]	3 (7.9%) [3]	9 (7.9%) [13]
Contusion	2 (5.3%) [2]	1 (2.6%) [1]	---	3 (2.6%) [3]
Skin and subcutaneous tissue disorders	3 (7.9%) [3]	4 (10.5%) [6]	2 (5.3%) [2]	9 (7.9%) [11]
Acne	2 (5.3%) [2]	---	1 (2.6%) [1]	3 (2.6%) [3]
Erythema	---	2 (5.3%) [2]	---	2 (1.8%) [2]
General disorders and administration site conditions	1 (2.6%) [1]	6 (15.8%) [6]	---	7 (6.1%) [7]
Influenza like illness	1 (2.6%) [1]	2 (5.3%) [2]	---	3 (2.6%) [3]
Investigations	1 (2.6%) [1]	1 (2.6%) [1]	3 (7.9%) [3]	5 (4.4%) [5]
Immune system disorders	---	---	2 (5.3%) [2]	2 (1.8%) [2]
Seasonal allergy	---	---	2 (5.3%) [2]	2 (1.8%) [2]
Reproductive system and breast disorders	---	2 (5.3%) [2]	---	2 (1.8%) [2]

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects( ) = percentage of subjects with adverse events; [ ] = number of adverse events
Source: Table 14.3.1-2a

The incidence and severity of TEAEs in PK study MB02-A-02-17 was comparable between MB02 and EU Avastin. The majority of TEAEs were considered mild in severity and were reported in a comparable number of subjects in the MB02, US-Avastin and EU-Avastin arm. The most frequently reported TEAEs Terms were headache (19.3%), upper respiratory tract infection, (18.4%), and back pain (10.5%), with slightly higher incidence in the EU Avastin arm compared to the MB02 arm for each of the terms.

Study drug-related TEAEs:

Table 33: Frequency of Treatment-emergent Adverse Events (Possible, Probable, or Related to Study Drug) Reported by ≥5% of Subjects – Safety Population

MedDRA system organ class Preferred term	3 mg/kg MB02 IV (N = 38)	3 mg/kg US Avastin® IV (N = 38)	3 mg/kg EU Avastin® IV (N = 38)	Overall (N = 114)
Overall Total	6 (15.8%) [10]	3 (7.9%) [4]	8 (21.1%) [13]	17 (14.9%) [27]
Gastrointestinal disorders				
Nausea	3 (7.9%) [3]	---	1 (2.6%) [2]	4 (3.5%) [5]
Total	3 (7.9%) [6]	1 (2.6%) [2]	3 (7.9%) [4]	7 (6.1%) [12]
Musculoskeletal and connective tissue disorders				
Back pain	---	---	2 (5.3%) [2]	2 (1.8%) [2]
Total	1 (2.6%) [1]	---	3 (7.9%) [3]	4 (3.5%) [4]
Nervous system disorders				
Headache	1 (2.6%) [1]	---	2 (5.3%) [2]	3 (2.6%) [3]
Total	2 (5.3%) [2]	---	2 (5.3%) [2]	4 (3.5%) [4]

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects ( ) = percentage of subjects with adverse events; [ ] = number of adverse events
Source: Table 14.3.1-4a

The number of TEAEs considered possible, probable or definitely related to the study drug was low (17; 14.9% overall) and was comparable between treatment groups (6 subjects vs 8 subjects with MB02 and EU Avastin, respectively). The majority of possibly related TEAEs were Grade 1 (mild) in severity.

PK study MB02-A-05-18:

Table 34: Summary of TEAEs reported in study MB02-A-05-18 – Safety population

Number of patients (%) experiencing at least one of the following:	MB02 (N=38)	EU-Avastin® (N=38)	US-Avastin® (N=38)	All (N=114)
TEAE	30 (78.9%)	25 (65.8%)	32 (84.2%)	87 (76.3%)
Grade 1 TEAE (mild)	20 (52.6%)	10 (26.3%)	23 (60.5%)	53 (46.5%)
Grade 2 TEAE (moderate)	10 (10.5%)	14 (36.8%)	9 (23.7%)	33 (28.9%)
Grade 3 TEAE (severe)	0 (0%)	1 (2.6%)	0 (0%)	1 (0.9%)
TEAEs leading to study discontinuation	0 (0%)	0 (0%)	0 (0%)	0(0%)
Fatal TEAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Serious TEAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Serious TEAEs (Grade 3)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment-related TEAEs (considered possibly, probably or definitely-related)	10 (26.3%)	11 (28.9%)	12 (31.6%)	33 (28.9%)
Grade 1 TEAE (mild)	9 (23.7%)	9 (23.7%)	10 (26.3%)	28 (24.6%)
Grade 2 TEAE (moderate)	1 (2.6%)	2 (5.3%)	2 (5.3%)	5(4.4%)
Grade 3 TEAE (severe)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations used: N; Number of subjects in the analysis population: TEAE; Treatment-emergent adverse event
Source: Table 14.3.1.1 and Table 14.3.1.10 CSR MB02-A-05-18

Overall, 199 TEAEs were reported in 87 (76.3%) study subjects. In the MB02 arm of the study, 30 subjects experienced at least one TEAE with a total of 60 TEAEs reported. In the EU-Avastin arm, 25 subjects experienced at least one TEAE with a total of 72 TEAEs reported. In the US-Avastin arm, 32 subjects experienced at least one TEAE with a total of 67 events.

In terms of severity, the majority of TEAEs reported in the study were considered mild (149 of 199 events; 46 of 60 events in the MB02 treatment arm, 48 of 72 events in the EU-Avastin treatment arm and 55 of 67 events in the US-Avastin treatment arm) or moderate (49 of 199 events; 14 of 60 events in the MB02 treatment arm, 23 of 72 events in the EU-Avastin treatment arm and 12 of 67 events in the US-Avastin treatment arm). Likewise, the majority of treatment-related TEAEs were considered mild in severity (13 of 14 events in the MB02 treatment arm, 19 of 22 events in the EU-Avastin treatment arm and 18 of 20 events in the US-Avastin treatment arm).TEAEs considered to be treatment-related (possibly, probably or definitely-related) were reported in 33 (28.9%) study subjects from all arms of the study. In the MB02 and EU-Avastin treatment arms, 21 subjects experienced a total of 36 treatment-related TEAEs (10 subjects/14 events and 11 subjects/22 events in the MB02 and EU-Avastin treatment arms, respectively).

Only one severe TEAE was reported; a subject in the EU-Avastin treatment arm experienced an upper respiratory tract infection. This severe TEAE, which resolved by the end of the study, was not considered to be treatment-related by the Investigator and was not classified as a SAE. There were no deaths reported in this study.

PK study MB02-A-04-18:

Table 35: Summary of TEAEs reported in study MB02-A-04-18 – Safety population

Number of patients (%) experiencing at least one of the following:	MB02 (N=24)	EU-Avastin® (N=24)	All (N=48)
TEAE	8 (33.3%)	12 (50.0%)	20 (41.7%)
Grade 1 TEAE (mild)	8 (33.3%)	9 (37.5%)	17 (35.4%)
Grade 2 TEAE (moderate)	2 (8.3%)	6 (25.0%)	8 (16.7%)
Grade 3 TEAE (severe)	0 (0%)	0 (0%)	0 (0%)
TEAEs leading to study discontinuation	0 (0%)	0 (0%)	0(0%)
Fatal TEAEs	0 (0%)	0 (0%)	0 (0%)
Serious TEAEs	0 (0%)	0 (0%)	0 (0%)
Serious TEAEs (Grade 3)	0 (0%)	0 (0%)	0 (0%)
Treatment-related TEAEs (considered possibly, probably or definitely-related)	0 (0%)	2 (8.3%)	2 (4.2%)
Grade 1 TEAE (mild)	0 (0%)	2 (8.3%)	2 (4.2%)
Grade 2 TEAE (moderate)	0 (0%)	0 (0%)	0 (0%)
Grade 3 TEAE (severe)	0 (0%)	0 (0%)	0 (0%)

Abbreviations used: N; Number of subjects in the analysis population: TEAE; Treatment-emergent adverse event
Source: Table 14.3.1-1 CSR MB02-A-04-18

An overall total of 47 TEAEs were reported by 20 of the 48 subjects participating in the study (41.7%). The incidence of TEAEs in the MB02 treatment group was slightly lower compared to the EU-Avastin treatment group (8 of 24 subjects [33.3%] and 12 of 24 subjects [50.0%] in the MB02 and EU-Avastin treatment groups, respectively). The number of TEAEs was comparable between the MB02 and EU-Avastin treatment groups (22 and 25 events in the MB02 and EU-Avastin treatment groups, respectively).

Of the 47 TEAEs reported, the majority were classified as mild (Grade 1) in severity (37 TEAEs; 20 and 17 for the MB02 and EU-Avastin treatment groups, respectively). The remainder were classified as moderate (Grade 2) in severity (10 TEAEs; 2 and 10 for the MB02 and EU-Avastin treatment groups, respectively). No severe (Grade 3) TEAEs were reported in the study.

Only 3 of the 47 reported TEAEs were considered to be treatment-related (possibly, probably or definitely-related). All 3 treatment-related TEAEs were observed in the EU-Avastin treatment group, with no treatment-related TEAEs observed in the MB02 treatment group.

Of note, the number of TEAE was distinctly lower in study MB02-A-04-18 compared to the other PK studies in healthy volunteers which may be explained by differences in baseline characteristics (age, BMI) and a known trend towards occasionally lower reporting of TEAEs in Asian countries.

Study BEVZ92-A-01-13:

A summary of TEAEs reported during the study is displayed in Table 36.

Table 36: Summary of TEAE – AT population

No. Patients (%) with at least one	BEVZ92 (N=69)	Avastin® (N=71)	All (N=140)
TEAE[a]	66 (96%)	71 (100%)	137 (98%)
Grade 1 or 2 TEAEs [a]	65 (94%)	71 (100%)	136 (97%)
Grade 3 or 4 TEAEs [a]	44 (64%)	49 (69%)	93 (66%)
TEAEs leading to permanent discontinuation of any study treatment regimen [a]	13 (19%)	6 (8%)	19 (14%)
Fatal TEAEs [b]	8 (12%)	5 (7%)	13 (9%)
Serious TEAEs [b]	19 (28%)	21 (30%)	40 (29%)
Serious TEAEs grade 3 or 4 [a]	14 (20%)	15 (21%)	29 (21%)
Treatment-related TEAEs [a,c]			
to any study treatment (bevacizumab or chemotherapy)	63 (91%)	70 (99%)	133 (95%)
to both study treatments (bevacizumab and chemotherapy)	27 (39%)	39 (55%)	66 (47%)
only to bevacizumab (BEVZ92/Avastin®)	24 (35%)	26 (37%)	50 (36%)
only to FOLFOX/FOLFIRI	63 (91%)	64 (90%)	127 (91%)
TEAEs of bleeding	14 (20%)	19 (27%)	33 (24%)
Grade 3 or 4 TEAEs of bleeding [a]	1 (1%)	2 (3%)	3 (2%)

TEAE: Treatment-Emergent Adverse Event
All AEs occurring on or after the first dose of any study treatment are included.
[a] Source: Table 14.3.02.01 (Section 14). Multiple occurrences of the same adverse event in one individual are counted only once.
[b]Source: PV database
[c]Related to BEVZ92/Avastin® or FOLFOX/FOLFIRI (relationship is 'Unlikely', 'possible', 'Probable', 'Definite' or with missing relationship). AEs occurring multiple times for the same patient are sometimes reported as related and sometimes as non-related hence they are counted once for each table (related AEs and unrelated AEs).

All 71 patients in the EU-Avastin arm and 66 patients (96%) in the BEVZ92 arm experienced at least one TEAE.

A similar number of TEAEs considered related to administration of IMP were reported in each treatment arm; 24 (35%) and 26 (37%) of patients experienced at least one TEAE considered related only to IMP administration in the BEVZ92 and EU-Avastin arms, respectively.

The SOCs with the largest number of patients reporting TEAEs (≥ 50 patients for each SOC) were gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, blood and lymphatic system disorders, metabolism and nutrition disorders, infections and infestations and investigations.

Grade 3 or 4 TEAEs were reported in similar proportions of patients in both arms (44 [64%] in the BEVZ92 arm and 49 [69%] in the EU-Avastin arm). The most common (> 20%) treatment related TEAEs were those commonly seen with chemotherapy, including diarrhoea, nausea, neutropenia, anaemia, vomiting, asthenia, fatigue, decreased appetite and abdominal pain and their incidence was similar in both treatment arms. Other events commonly described in patients treated with bevacizumab, such as hypertension, proteinuria, thrombocytopenia and bleeding, were also reported in similar proportion in both treatment arms. Finally, serious TEAEs were reported in 40 (29%) patients overall, 19 (28%) in the BEVZ92 arm and 21 (30%) in the EU-Avastin arm. Despite a larger number of

serious TEAEs in the EU-Avastin arm (56 compared to 34 in the BEVZ92 arm), there was no obvious pattern regarding the types of serious TEAEs in both arms.

When TEAEs were analyzed according to an exposure-adjusted incidence rate to see if the nominal differences in exposure to study treatment have an influence on the incidence of TEAEs observed in each treatment arm (events per 100 patient months [PM]), the incidence of TEAEs was comparable and supported the previous analysis for TEAEs considering any causality. Similarly, no remarkable difference was observed in serious TEAEs based on the total exposure time – per 100 PM.

Comparative analysis of the number of patients with particular AEs in the BEVZ92 and EU-Avastin arms of the study suggests a similar profile of AEs in the two treatment groups. The safety profiles were within expectations given the underlying disease and concomitant chemotherapy and consistent with the labelling information for Avastin

The numbers of patients in study BEVZ92-A-01-13 that reported at least one TEAE, regardless of causality, in each treatment group is displayed by SOC in Table 37.

Table 37: Summary of TEAEs by SOC and causality in study BEVZ92-A-01-13

SOC	BEVZ92 (N=69)		EU-approved Avastin® (N=71)		All (N=140)	
	Treatment related	Any causality	Treatment related	Any causality	Treatment related	Any causality
All body systems	63 (91%)	66 (96%)	70 (99%)	71 (100%)	133 (95%)	137 (98%)
Gastrointestinal disorders	43 (62%)	49 (69%)	54 (76%)	55 (77%)	97 (69%)	104 (74%)
General disorders and administrations site disorders	39 (57%)	48 (70%)	39 (55%)	47 (66%)	78 (56%)	95 (68%)
Nervous system disorders	38 (55%)	41 (59%)	45 (63%)	47 (66%)	83 (59%)	88 (63%)
Blood and lymphatic system disorders	39 (57%)	39 (57%)	44 (62%)	46 (65%)	83 (59%)	85 (61%)
Metabolism and nutrition disorders	20 (29%)	39 (57%)	27 (38%)	41 (58%)	47 (34%)	80 (57%)
Infections and infestations	13 (19%)	36 (52%)	11 (15%)	31 (44%)	24 (17%)	67 (48%)
Investigations	15 (22%)	27 (39%)	24 (34%)	34 (48%)	39 (28%)	61 (44%)
Vascular disorders	17 (25%)	21 (30%)	22 (31%)	24 (34%)	39 (28%)	45 (32%)
Skin and subcutaneous tissue disorders	16 (23%)	22 (32%)	19 (27%)	22 (31%)	35 (25%)	44 (31%)
Respiratory, thoracic and mediastinal disorders	13 (19%)	19 (28%)	15 (21%)	20 (28%)	28 (20%)	39 (28%)
Musculoskeletal and connective tissue disorders	9 (13%)	17 (25%)	10 (14%)	16 (23%)	19 (14%)	33 (24%)
Renal and urinary disorders	7 (10%)	15 (22%)	6 (8%)	6 (8%)	13 (9%)	21 (15%)
Injury, poisoning and procedural complications	7 (10%)	12 (17%)	6 (8%)	12 (17%)	13 (9%)	24 (17%)
Cardiac disorders	2 (3%)	6 (9%)	1 (1%)	8 (11%)	3 (2%)	14 (10%)
Reproductive system and breast disorders	0 (0%)	3 (4%)	2 (3%)	6 (8%)	2 (1%)	9 (6.4%)
Hepatobiliary disorders	1 (1%)	3 (4%)	3 (4%)	5 (7%)	4 (3%)	8 (6%)
Psychiatric disorders	1 (1%)	3 (4%)	3 (4%)	5 (7%)	4 (3%)	8 (6%)
Immune system disorders	2 (3%)	2 (3%)	3 (4%)	4 (6%)	5 (4%)	6 (4%)
Neoplasms benign, malignant and unspecified	0 (0%)	2 (3%)	1 (1%)	1 (1%)	1 (< 1%)	3 (2%)
Eye disorders	0 (0%)	1 (1%)	2 (3%)	7 (10%)	2 (1%)	8 (6%)
Ear and labyrinth disorders	1 (1%)	1 (1%)	2 (3%)	4 (6%)	3 (2%)	5 (4%)
Congenital, familial and genetic disorders	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	2 (1%)
Surgical and medical procedures	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (< 1%)

Notes: Multiple occurrences of the same adverse event (AE) in one individual are only counted once.
The numbers in parentheses represent the number of patients with TEAEs regardless of causality.
Source: Table 14.3.2.2, Table 14.3.2.5.1 Addendum CSR BEVZ92-A-01-13. MedDRA version: 18.1

Study MB02-C-02-17:

Adverse events were collected and classified according to MedDRA v20.1 and severity was graded according to NCI-CTCAE version 4.03.

Table 38: Overall Summary of Treatment-Emergent Adverse Events (SAF Set)

	Avastin® N=310 n (%) [Events]	MB02 N=311 n (%) [Events]	Total N=621 n (%) [Events]	p-Value
Treatment-Emergent Adverse Events				
Subjects with ≥1 TEAE	288 (92.9) [2166]	288 (92.6) [2174]	576 (92.8) [4340]	0.89
Subjects with Grade 3 or 4 TEAE	125 (40.3) [269]	131 (42.1) [271]	256 (41.2) [540]	0.65
Subjects with ≥1 Study Drug-Related TEAE[a]				
MB02/Avastin®	125 (40.3) [397]	125 (40.2) [412]	250 (40.3) [809]	0.97
Carboplatin	255 (82.3) [1234]	246 (79.1) [1188]	501 (80.7) [2422]	0.32
Paclitaxel	259 (83.5) [1345]	251 (80.7) [1293]	510 (82.1) [2638]	0.36
Subjects with Grade 3 or 4 study-drug related TEAE[a]	91 (29.4) [190]	98 (31.5) [187]	189 (30.4) [377]	0.56
Serious TEAEs				
Subjects with ≥1 serious TEAE	54 (17.4) [86]	58 (18.6) [88]	112 (18.0) [174]	0.69
Serious Study Drug Related Serious TEAEs				
Subjects with ≥1 serious drug-related TEAE[a]	33 (10.6) [52]	33 (10.6) [51]	66 (10.6) [103]	0.99
MB02/Avastin®	18 (5.8) [27]	21 (6.8) [26]	39 (6.3) [53]	
Carboplatin or paclitaxel	27 (8.7) [43]	24 (7.7) [37]	51 (8.2) [80]	
Fatal TEAEs				
All	24 (7.7) [24]	23 (7.4) [23]	47 (7.6) [47]	0.87
Study drug-related fatal TEAEs[a,]	5 (1.6) [5]	7 (2.3) [7]	12 (1.9) [12]	0.56
Subjects with TEAEs leading to permanent treatment discontinuation				
All	63 (20.3) [79]	72 (23.2) [116]	135 (21.7) [195]	0.39
Study drug-related TEAEs leading to permanent treatment discontinuation[a,b]	33 (10.6) [42]	42 (13.5) [54]	75 (12.1) [96]	0.27

Abbreviations: AE, adverse event; IMP, investigational medicinal product; N, number of subjects on intended set; n, number of subjects with data available; SAF, safety analysis set; TEAE, treatment-emergent adverse event.

Note: Percentages were based on N.

Note: More than one category could apply for the same event.

[a] An AE was related if assessment of causality was possible, probable, or very likely/certain.

[b] This total is different than the 72 total subjects with discontinuation due to toxicity reported in Figure 2 (Table 14.1.1.1); 2 subjects with toxicity who discontinued were not included in the safety population; 3 subjects who discontinued had toxicity but no treatment-related TEAEs; for 8 subjects who discontinued due to a treatment-related TEAE, toxicity was not reported as the reason for discontinuation.

Source: Table 14.3.1.1

Common adverse events:

The majority of the patients in this study had at least one TEAE (all causality). The subject incidence was balanced between treatment arms, 92.6% subjects in the MB02 group and 92.9% subjects in the Avastin group.

The most common TEAEs (reported in ≥ 5% of subjects) were those commonly reported with the use of carboplatin/paclitaxel (e.g., alopecia, nausea, and neuropathy), as well as PTs related to myelosuppression (e.g., anaemia, leukopenia, neutropenia and thrombocytopenia). Other TEAEs were those commonly reported with the use of bevacizumab (e.g., hypertension and proteinuria), and were similarly distributed between treatment groups.

The most common TEAEs by preferred term (PT) were alopecia (51.2%) and anaemia (31.4%), with no considerable differences between treatment groups.

Table 39: Summary of subjects experiencing TEAEs by SOC and PT (≥5%) of subjects) by decreasing frequency in Safety population of study MB02-C-02-17

System Organ Class Preferred Term	Avastin® N=310 n (%)	MB02 N=311 n (%)	Total N=621 n (%)
All TEAEs	288 (92.9)	288 (92.6)	576 (92.8)
Skin and subcutaneous tissue disorders	**174 (56.1)**	**164 (52.7)**	**338 (54.4)**
Alopecia	163 (52.6)	155 (49.8)	318 (51.2)
Blood and lymphatic system disorders	**131 (42.3)**	**135 (43.4)**	**266 (42.8)**
Anaemia	94 (30.3)	101 (32.5)	195 (31.4)
Thrombocytopenia	42 (13.5)	41 (13.2)	83 (13.4)
Neutropenia	45 (14.5)	34 (10.9)	79 (12.7)
Leukopenia	18 (5.8)	24 (7.7)	42 (6.8)
Nervous system disorders	**106 (34.2)**	**119 (38.3)**	**225 (36.2)**
Neuropathy peripheral	41 (13.2)	38 (12.2)	79 (12.7)
Peripheral sensory neuropathy	23 (7.4)	22 (7.1)	45 (7.2)
Paraesthesia	13 (4.2)	21 (6.8)	34 (5.5)
General disorders and administration site conditions	**104 (33.5)**	**110 (35.4)**	**214 (34.5)**
Fatigue	36 (11.6)	39 (12.5)	75 (12.1)
Asthenia	29 (9.4)	39 (12.5)	68 (11.0)
General physical health deteriortion	29 (9.4)	23 (7.4)	52 (8.4)
Investigations	**104 (33.5)**	**105 (33.8)**	**209 (33.7)**
Weight decreased	27 (8.7)	23 (7.4)	50 (8.1)
Platelet count decreased	19 (6.1)	26 (8.4)	45 (7.2)
Alanine aminotransferase increased	21 (6.8)	15 (4.8)	36 (5.8)
Aspartate aminotransferase increased	22 (7.1)	14 (4.5)	36 (5.8)
Neutrophil count decreased	18 (5.8)	18 (5.8)	36 (5.8)
Gastrointestinal disorders	**91 (29.4)**	**104 (33.4)**	**195 (31.4)**
Nausea	44 (14.2)	47 (15.1)	91 (14.7)
Diarrhoea	27 (8.7)	29 (9.3)	56 (9.0)
Vomiting	11 (3.5)	22 (7.1)	33 (5.3)
Musculoskeletal and connective tissue disorders	**76 (24.5)**	**75 (24.1)**	**151 (24.3)**
Myalgia	30 (9.7)	23 (7.4)	53 (8.5)
Arthralgia	20 (6.5)	19 (6.1)	39 (6.3)
Infections and infestations	**69 (22.3)**	**72 (23.2)**	**141 (22.7)**
Respiratory tract infection viral	16 (5.2)	16 (5.1)	32 (5.2)
Respiratory, thoracic and mediastinal disorders	**66 (21.3)**	**69 (22.2)**	**135 (21.7)**
Cough	22 (7.1)	20 (6.4)	42 (6.8)
Metabolism and nutrition disorders	**43 (13.9)**	**44 (14.1)**	**87 (14.0)**
Decreased appetite	20 (6.5)	14 (4.5)	34 (5.5)
Vascular disorders	**37 (11.9)**	**36 (11.6)**	**73 (11.8)**
Hypertension	26 (8.4)	24 (7.7)	50 (8.1)
Renal and urinary disorders	**38 (12.3)**	**26 (8.4)**	**64 (10.3)**
Proteinuria	25 (8.1)	18 (5.8)	43 (6.9)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in intended set; n, number of subjects with data available; SAF, safety; TEAE, treatment-emergent adverse event.
Note: Percentages were based on N.
Note: TEAEs were AEs with onset date/time at or after the first IMP infusion until the subject's last visit.
AEs were coded to MedDRA version 20.1.
Source: Table 14.3.1.2 CSR MB02-C-02-17

TEAEs were also analysed by study period (i.e. the combination period with chemotherapy up to Week 18 and the monotherapy period from Week 18 through to Week 52), see following table.

Table 40: Treatment-Emergent Adverse Events Reported in ≥5% of Subjects, by Combination Therapy and Monotherapy, by System Organ Class and Preferred Term (SAF Set)

System Organ Class Preferred Term	Avastin® N = 310 n (%)		MB02 N = 311 n (%)		Total N = 621 n (%)	
	Combination Therapy	Monotherapy	Combination Therapy	Monotherapy	Combination Therapy	Monotherapy
Skin and subcutaneous tissue disorders	**173 (55.8)**	22 (7.1)	**163 (52.4)**	12 (3.9)	**336 (54.1)**	34 (5.5)
Alopecia	163 (52.6)	17 (5.5)	155 (49.8)	7 (2.3)	318 (51.2)	24 (3.9)
Blood and lymphatic system disorders	**114 (36.8)**	**56 (18.1)**	**124 (39.9)**	**45 (14.5)**	**238 (38.3)**	**101 (16.3)**
Anaemia	77 (24.8)	41 (13.2)	91 (29.3)	24 (7.7)	168 (27.1)	65 (10.5)
Thrombocytopenia	37 (11.9)	15 (4.8)	39 (12.5)	19 (6.1)	76 (12.2)	34 (5.5)
Neutropenia	36 (11.6)	17 (5.5)	29 (9.3)	14 (4.5)	65 (10.5)	31 (5.0)
Leukopenia	15 (4.8)	7 (2.3)	21 (6.8)	7 (2.3)	36 (5.8)	14 (2.3)
Nervous system disorders	**95 (30.6)**	**25 (8.1)**	**106 (34.1)**	**28 (9.0)**	**201 (32.4)**	**53 (8.5)**
Neuropathy peripheral	39 (12.6)	3 (1.0)	36 (11.6)	4 (1.3)	75 (12.1)	7 (1.1)
Peripheral sensory neuropathy	20 (6.5)	4 (1.3)	20 (6.4)	5 (1.6)	40 (6.4)	9 (1.4)
Paraesthesia	12 (3.9)	2 (0.6)	21 (6.8)	6 (1.9)	33 (5.3)	8 (1.3)
Gastrointestinal disorders	**84 (27.1)**	**22 (7.1)**	**88 (28.3)**	**30 (9.6)**	**172 (27.7)**	**52 (8.4)**
Nausea	41 (13.2)	6 (1.9)	41 (13.2)	10 (3.2)	82 (13.2)	16 (2.6)
Diarrhoea	22 (7.1)	6 (1.9)	24 (7.7)	5 (1.6)	46 (7.4)	11 (1.8)
Investigations	**78 (25.2)**	**49 (15.8)**	**81 (26.0)**	**49 (15.8)**	**159 (25.6)**	**98 (15.8)**
Platelet count decreased	13 (4.2)	8 (2.6)	22 (7.1)	13 (4.2)	35 (5.6)	21 (3.4)
Neutrophil count decreased	16 (5.2)	6 (1.9)	16 (5.1)	6 (1.9)	32 (5.2)	12 (1.9)
General disorders and administration site conditions	**75 (24.2)**	**38 (12.3)**	**78 (25.1)**	**42 (13.5)**	**153 (24.6)**	**80 (12.9)**
Fatigue	32 (10.3)	7 (2.3)	29 (9.3)	15 (4.8)	61 (9.8)	22 (3.5)
Asthenia	18 (5.8)	11 (3.5)	26 (8.4)	14 (4.5)	44 (7.1)	25 (4.0)
System Organ Class Preferred Term	**Avastin® N = 310 n (%)**		**MB02 N = 311 n (%)**		**Total N = 621 n (%)**	
	Combination Therapy	**Monotherapy**	**Combination Therapy**	**Monotherapy**	**Combination Therapy**	**Monotherapy**
Musculoskeletal and connective tissue disorders	**69 (22.3)**	**22 (7.1)**	**66 (21.2)**	**16 (5.1)**	**135 (21.7)**	**38 (6.1)**
Myalgia	30 (9.7)	2 (0.6)	23 (7.4)	3 (1.0)	53 (8.5)	5 (0.8)
Arthralgia	18 (5.8)	2 (0.6)	18 (5.8)	1 (0.3)	36 (5.8)	3 (0.5)
Vascular disorders	**26 (8.4)**	**14 (4.5)**	**29 (9.3)**	**10 (3.2)**	**55 (8.9)**	**24 (3.9)**
Hypertension	17 (5.5)	12 (3.9)	19 (6.1)	7 (2.3)	36 (5.8)	19 (3.1)
Renal and urinary disorders	**19 (6.1)**	**26 (8.4)**	**15 (4.8)**	**15 (4.8)**	**34 (5.5)**	**41 (6.6)**
Proteinuria	12 (3.9)	19 (6.1)	7 (2.3)	12 (3.9)	19 (3.1)	31 (5.0)

Abbreviations: AE, adverse event; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects on the intended set; n, number of subjects with data available; SAF, safety analysis set; TEAE, treatment-emergent adverse event.
Note: Percentages were based on N.
Note: TEAEs were AEs with onset date/time at or after the first IMP infusion until the subject's last study visit.
Note: An AE was related if assessment of causality was possible, probable, or very likely/certain.
Note: For AEs that changed severity rating, the AE was included only once under the maximum severity.
Note: Subjects may have experienced the same event PT with multiple CTCAE grades.
Note: Each subject only contributed once to each of the incidence rates, regardless of the number of occurrences. Subjects are counted once under a preferred term with worst severity.
Note: AEs were coded to MedDRA version 20.1.
Source: Table 14.3.1.19

Alopecia (318 subjects [51.2%]; 155 subjects [49.8%] and 163 subjects [52.6%] in the MB02 and EU-Avastin treatment groups, respectively), anaemia (168 subjects [27.1%]; 91 [29.3%] and 77 subjects [24.8%] in the MB02 and EU-Avastin treatment groups, respectively), and nausea (82 subjects [13.2%]; 41 [13.2%] subjects each in the MB02 and EU-Avastin treatment groups), were the most commonly reported TEAEs during combination therapy (up to Week 18).

Between study Week 18 and Week 52 (i.e. the monotherapy period) the most commonly reported TEAEs were anaemia (65 subjects [10.5%]; 24 subjects [7.7%] in the MB02 and 41 subjects [13.2%] in the MB02 and EU-Avastin treatment groups, respectively), and thrombocytopenia (34 subjects

[5.5%]; 19 subjects [6.1%] and 15 subjects [4.8%] in the MB02 and EU-Avastin treatment groups, respectively).

Severity of TEAEs:

Table 41: Summary of Treatment-Emergent Adverse Events, by Maximum Severity (SAF Set)

	Avastin® N=310 n (%)	MB02 N=311 n (%)	Total N=621 n (%)	p-Value
TEAE Maximum Severity by NCI-CTCAE				
Subjects with at least one TEAE	288 (92.9)	288 (92.6)	576 (92.8)	0.89
Grade 1	230 (74.2)	225 (72.3)	455 (73.3)	
Grade 2	241 (77.7)	252 (81.0)	493 (79.4)	
Grade 3	117 (37.7)	126 (40.5)	243 (39.1)	
Grade 4	24 (7.7)	22 (7.1)	46 (7.4)	
Grade 5[a]	19 (6.1)	20 (6.4)	39 (6.3)	

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; IMP, investigational medicinal product; N, number of subjects on the intended set; n, number of subjects with data available; NCI, National Cancer Institute; SAF, safety analysis set; TEAE, treatment-emergent adverse event.
Note: Percentages were based on N.
Note: TEAEs were AEs with onset date/time at or after the first IMP infusion until the subject's last study visit.
Note: More than one category could apply for the same event.
[a] Eight subjects with fatal outcome events maintained their initial grade of severity as per investigator decision, further details in Section 12.3.1.1.
Source: Table 14.3.1.1

The most commonly Grade ≥3 reported events included anaemia (26 subjects [8.4%] in the MB02 group and 21 subjects [6.8%] in the Avastin group) and neutropenia (16 subjects [5.1%] in the MB02 group and 21 subjects [6.8%] in the Avastin group), followed by asthenia (14 subjects [4.5%] in the MB02 group and 11 subjects[3.5%] in the Avastin group) and thrombocytopenia (10 subjects [3.2%] in the MB02 group and 6 subjects [1.9%] in Avastin group).

More patients experienced grade 3 or 4 TEAEs with MB02 compared to Avastin (39.9% vs 38.1%, respectively). Grade 5 TEAEs were generally low in incidence and comparable between treatment groups (6.4% versus 6.1%). Of note, 3 fatal TEAEs were not classified as Grade 5 events (2 subjects with general physical health deterioration [Grade 2 and Grade 3] and one subject with dyspnoea [Grade 3]). The applicant provided a brief explanation and a table with all fatal AEs up to Week 52 not classified as Grade 5.

A total of 576 (92.8%) subjects, who were treated with the study drug in study MB02-C-02-17, experienced at least 1 TEAE, with no statistical difference between treatment groups (p=0.89). Between treatment groups at each severity level, the distribution of events was similar. A total of 256 (41.2%) subjects experienced a total of 540 TEAEs with a severity of Grade 3 or Grade 4 (131 [42.1%] in the MB02 group [271 events] and 125 [40.3%] in the Avastin group [269 events]). A total of 39 subjects (6.3%) experienced a TEAE with a severity of Grade 5 (20 [6.4%] in the MB02 group and 19 [6.1%] in the Avastin group).

IMP-related TEAEs:

The most commonly reported IMP-related TEAEs were hypertension (40 subjects [6.4%]; 19 subjects [6.1%] and 21 subjects [6.8%] in the MB02 and EU-Avastin treatment groups, respectively) and anaemia (33 subjects [5.3%]; 16 subjects [5.1%] and 17 subjects [5.5%] in the MB02 and EU-Avastin treatment groups, respectively).

The most commonly reported Grade 3 or 4 IMP-related TEAEs reported were hypertension (12 subjects [3.9%]; 7 [2.3%] in the MB02 group and 5 [1.6%] in the Avastin group) and anaemia (9 subjects [2.9%]; 2 [0.6%] in the MB02 group and 7 [2.3%] in the Avastin group). For IMP-related TEAEs reported by ≥1% of subjects, Grade 5 PTs of haemoptysis (one event in the EU-Avastin treatment group) and pulmonary embolism (one event in the MB02 treatment group) were reported.

No clear treatment group-related trends were observed for IMP-related TEAEs. In all cases, the risk difference between treatment groups in subjects reporting IMP-related TEAEs was <2%.

Table 42: Summary of IMP-related TEAEs (≥1%) reported in the Safety population of Study MB02-C-02-17 by SOC, PT and Maximum severity

System Organ Class Preferred Term	Avastin® N=310 n (%)				MB02 N=311 n (%)			
	Any	Grade 1 or 2	Grade 3 or 4	Grade 5	Any	Grade 1 or 2	Grade 3 or 4	Grade 5
Gastrointestinal disorders	**31 (10.0)**	**30 (9.7)**	**1 (0.3)**	**0**	**29 (9.3)**	**27 (8.7)**	**1 (0.3)**	**1 (0.3)**
Nausea	11 (3.5)	11 (3.5)	0	0	11 (3.5)	11 (3.5)	0	0
Diarrhoea	6 (1.9)	6 (1.9)	0	0	8 (2.6)	8 (2.6)	0	0
Vomiting	4 (1.3)	4 (1.3)	0	0	7 (2.3)	7 (2.3)	0	0
Constipation	4 (1.3)	4 (1.3)	0	0	6 (1.9)	6 (1.9)	0	0
Blood and lymphathic system disorders	**29 (9.4)**	**18 (5.8)**	**11 (3.5)**	**0**	**26 (8.4)**	**20 (6.4)**	**6 (1.9)**	**0**
Anaemia	17 (5.5)	10 (3.2)	7 (2.3)	0	16 (5.1)	14 (4.5)	2 (0.6)	0
Neutropenia	10 (3.2)	7 (2.3)	3 (1.0)	0	5 (1.6)	4 (1.3)	1 (0.3)	0
Thrombocytopenia	5 (1.6)	5 (1.6)	0	0	9 (2.9)	7 (2.3)	2 (0.6)	0
Leukopenia	2 (0.6)	2 (0.6)	0	0	4 (1.3)	3 (1.0)	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	**22 (7.1)**	**14 (4.5)**	**6 (1.9)**	**2 (0.6)**	**32 (10.3)**	**26 (8.4)**	**4 (1.3)**	**2 (0.6)**
Epistaxis	9 (2.9)	8 (2.6)	1 (0.3)	0	13 (4.2)	13 (4.2)	0	0
Haemoptysis	4 (1.3)	3 (1.0)	1 (0.3)	0	8 (2.6)	7 (2.3)	0	1 (0.3)
Pulmonary embolism	4 (1.3)	0	3 (1.0)	1 (0.3)	5 (1.6)	1 (0.3)	4 (1.3)	0
Vascular disorders	**26 (8.4)**	**19 (6.1)**	**7 (2.3)**	**0**	**27 (8.7)**	**16 (5.1)**	**11 (3.5)**	**0**
Hypertension	21 (6.8)	16 (5.2)	5 (1.6)	0	19 (6.1)	12 (3.9)	7 (2.3)	0
Nervous system disorders	**22 (7.1)**	**18 (5.8)**	**4 (1.3)**	**0**	**27 (8.7)**	**26 (8.4)**	**1 (0.3)**	**0**
Paraesthesia	5 (1.6)	4 (1.3)	1 (0.3)	0	10 (3.2)	10 (3.2)	0	0
Neuropathy peripheral	5 (1.6)	4 (1.3)	1 (0.3)	0	8 (2.6)	8 (2.6)	0	0
Headache	7 (2.3)	7 (2.3)	0	0	2 (0.6)	2 (0.6)	0	0
General disorders and administration site conditions	**24 (7.7)**	**19 (6.1)**	**5 (1.6)**	**0**	**24 (7.7)**	**23 (7.4)**	**1 (0.3)**	**0**
Fatigue	10 (3.2)	8 (2.6)	2 (0.6)	0	14 (4.5)	14 (4.5)	0	0
Asthenia	7 (2.3)	6 (1.9)	1 (0.3)	0	8 (2.6)	8 (2.6)	0	0
Pyrexia	4 (1.3)	3 (1.0)	1 (0.3)	0	3 (1.0)	3 (1.0)	0	0
Investigations	**22 (7.1)**	**17 (5.5)**	**5 (1.6)**	**0**	**19 (6.1)**	**14 (4.5)**	**5 (1.6)**	**0**
Platelet count decreased	3 (1.0)	2 (0.6)	1 (0.3)	0	4 (1.3)	4 (1.3)	0	0
Renal and urinary disorders	**20 (6.5)**	**15 (4.8)**	**4 (1.3)**	**1 (0.3)**	**13 (4.2)**	**10 (3.2)**	**2 (0.6)**	**1 (0.3)**
Proteinuria	18 (5.8)	14 (4.5)	4 (1.3)	0	12 (3.9)	11 (3.5)	1 (0.3)	0
Metabolism and nutrition disorders	**10 (3.2)**	**7 (2.3)**	**3 (1.0)**	**0**	**9 (2.9)**	**5 (1.6)**	**4 (1.3)**	**0**
Decreased appetite	6 (1.9)	5 (1.6)	1 (0.3)	0	2 (0.6)	2 (0.6)	0	0
Skin and subcutaneous tissue disorders	**10 (3.2)**	**8 (2.6)**	**2 (0.6)**	**0**	**9 (2.9)**	**8 (2.6)**	**1 (0.3)**	**0**
Infections and infestations	**8 (2.6)**	**6 (1.9)**	**2 (0.6)**	**0**	**10 (3.2)**	**9 (2.9)**	**1 (0.3)**	**0**
Musculoskeletal and connective tissue disorders	**9 (2.9)**	**9 (2.9)**	**0**	**0**	**7 (2.3)**	**6 (1.9)**	**1 (0.3)**	**0**
Arthralgia	4 (1.3)	4 (1.3)	0	0	5 (1.6)	4 (1.3)	1 (0.3)	0

Abbreviations: AE, adverse event; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in intended set; n, number of subjects with data available; SAF, safety; TEAE, treatment-emergent adverse event.
Note: Percentages were based on N.
Note: TEAEs were AEs with onset date/time at or after the first IMP infusion until the subject's last visit.
Note: An AE was related if assessment of causality was possible, probable, or very likely/certain.
Note: For AEs that changed severity rating, the AE was included only once under the maximum severity.
Note: Subjects may have experienced the same event PT with multiple CTCAE grades.
Note: AEs were coded to MedDRA version 20.1.
Source: CSR MB02-C-02-17 Table 14.3.1.9

Other significant adverse events:

PK Study MB02-A-02-17:

No AEs were classified as other significant AEs.

PK study MB02-A-05-18:

No AEs were classified as other significant AEs.

PK study MB02-A-04-18:

No AEs were classified as other significant AEs.

Study BEVZ92-A-01-13:

All haemorrhagic and cardiovascular events were considered "Important Medical Events" as per the protocol for study BEVZ92-A-01-13.

In relation to the SOC cardiac events, 17 TEAEs in this class were reported in 14 patients (6 in the BEVZ92 arm and 8 in the Avastin arm). However, none of these events were considered to be related to bevacizumab treatment.

Overall, 33 (24%) of patients in the study reported at least one bleeding event (14 in the BEVZ92 arm and 19 in the Avastin arm). The most frequent bleeding event was epistaxis (7 [10%] in the BEVZ92 arm and 11 [15%] in the Avastin arm) followed by gastrointestinal haemorrhage events (8% overall; mainly rectal, anal or haemorrhoidal).

All bleeding events were graded 1–2 except for one event in the BEVZ92 arm (lower gastrointestinal haemorrhage) and two events in the Avastin arm (subdural haematoma and tumour haemorrhage) that were graded 3–4.

Overall, the adjusted event rate per patient-month (0.0030 in the BEVZ92 arm and 0.0037 in the Avastin arm) was similar in both treatment groups.

Study MB02-C-02-17

Overall, the number, type, and severity of TEAEs of special interest was in alignment with the safety profile reported in the bevacizumab SmPC for this patient population. However, some events were reported as SUSARs, as discussed below. For all TEAEs of special interest, the difference in frequency between treatment groups of TEAEs reported was <5%. The most commonly reported TEAEs of special interest were identified by the searches for events associated with neutropenia and infections (191 subjects [30.8%]). A total of 61 (9.8%) subjects experienced TEAEs associated with haemorrhage, pulmonary haemorrhage, and/or haemoptysis, with no observable risk difference between treatment groups with regard to subjects reporting TEAEs. Hypertension-related TEAEs were identified in 60 (9.7%) subjects; proteinuria-related TEAEs were identified in 46 (7.4%) subjects, with no observable risk difference between treatment groups with regard to subjects reporting TEAEs.

Treatment-related TEAEs of special interest occurring in >1% of subjects and with higher reports in MB02-treated subjects compared with Avastin-treated subjects included leukopenia (6 subjects in total; 1.0%), epistaxis (22 subjects in total; 3.5%) and haemoptysis (12 subjects in total; 1.9%). Treatment-related TEAEs occurring in >1% of subjects and with higher reports in Avastin-treated subjects compared with MB02-treated subjects included neutropenia (19 subjects in total; 3.1%) and proteinuria (31 subjects in total; 5.0%). Other treatment-related TEAEs occurring in >1% of subjects included hypertension (40 subjects in total; 6.4%) and pulmonary embolism (9 subjects in total; 1.4%) and were reported in similar frequency in both treatment groups.

Serious adverse events and deaths

PK study MB02-A-02-17:

Serious TEAEs: A single subject reported an SAE. This subject was allocated to US Avastin and reported a Grade 3 (severe) TEAE of purpura, with no other symptoms on Day 82. Two weeks before, the subject had an upper respiratory tract infection. Clinical laboratory assessments were normal. No treatment was prescribed, and the event resolved without sequelae. The subject was negative for ADA and nAb at all timepoints. This SAE was unexpected and thus, the case was considered and expedited as a Suspected Unexpected Serious Adverse Reaction (SUSAR) as per regulatory reporting requirements.

Deaths: There were no deaths reported in this study.

PK study MB02-A-05-18:

No deaths or other SAEs were reported in study MB02-A-05-18.

PK study MB02-A-04-18:

No deaths or other SAEs were reported in study MB02-A-04-18.

Study BEVZ92-A-01-13:

At the completion of study BEVZ92-A-01-13, a total of 37 deaths were reported in the AT (safety) population: 19 (28%) in the BEVZ92 arm and 18 (25%) in the Avastin arm. The majority of the deaths (24) were due to disease progression: 11 (16%) and 13 (18%) in the BEVZ92 and Avastin arms, respectively. The deaths due to disease progression reported in the study were well balanced between both treatment arms and are expected events in the study population.

The remaining 13 patients (8 [10%] and 5 [6%] in the BEVZ92 and Avastin arms, respectively) experienced at least one serious TEAE with fatal outcome.

Fatal events were considered related to any of the study treatments (bevacizumab, chemotherapy or both) in four patients (two in each treatment arm). Only in one patient in the Avastin arm the fatal events were considered to be related exclusively to bevacizumab by the investigator.

The distribution of SAEs across the treatment arms by SOC were similar, as were the total number of patients reporting SAEs (19 [28%] in the BEVZ92 treatment arm and 21 [30%] in the Avastin arm). SAEs by PT that were reported in > 5% patients included intestinal obstruction (9%) in the BEVZ92 group; and diarrhoea (7%), neutropenia (8%) and anaemia (6%) in the Avastin group.

Most common treatment-related SAEs included neutropenia and diarrhoea (each one in one patient in the BEVZ92 arm and four patients in the Avastin arm), anaemia (in one patient in the BEVZ92 arm and three patients in the Avastin arm), leukopenia and sepsis (each one in two patients in the Avastin arm), and hypotension (in two patients in the Avastin arm).

Three events merited attention: one asymptomatic thromboembolism in the right trunk of the pulmonary artery in a patient in the BEVZ92 group that was considered "probably related" to bevacizumab and was detected while the patient was undergoing a scheduled CT scan, which led to discontinuation of the study treatment; a superior vena cava thrombosis that was considered "possibly related" to Avastin and "possibly related" to FOLFOX and was ongoing at the time of patient withdrawal due to progression of the disease under study, and a large intestinal perforation ("transverse colon perforation") in the Avastin arm, which led to a fatal outcome and was considered by the investigator to be "probably related" to Avastin and "not related" to FOLFOX.

Study MB02-C-02-17:

Serious TEAEs:

Through study Week 52, a total of 112 (18.0%) subjects experienced a total of 174 serious TEAEs during the study. No statistically significant difference (p=0.69) in serious TEAEs was observed between the MB02 (58 subjects [18.6%]; 88 events) and EU-Avastin (54 subjects [17.4%]; 86 events) treatment groups. No SAEs were reported during study drug infusion.

A total of 66 (10.6%) subjects experienced study drug-related serious TEAEs during the study (33 subjects in each treatment group); the difference was not statistically significant (p=0.99). Of these cases, 39 (6.3%) subjects experienced serious TEAEs related to MB02 (21 subjects [6.8%]) or EU-Avastin (18 subjects [5.8%]). A total of 51 (8.2%) subjects experienced serious TEAEs related to carboplatin and/or paclitaxel (24 subjects [7.7%] in the MB02 group compared to 27 subjects [8.7%] in the EU-Avastin group).

Table 43: Summary of Related Serious Treatment-Emergent Adverse Events (SAF Set)

	Avastin® N=310 n (%)	MB02 N=311 n (%)	Total N=621 n (%)	p-Value
Serious TEAEs				
Subjects with ≥1 serious drug-related TEAE	33 (10.6)	33 (10.6)	66 (10.6)	0.99
IMP	18 (5.8)	21 (6.8)	39 (6.3)	
Carboplatin/paclitaxel	27 (8.7)	24 (7.7)	51 (8.2)	

Abbreviations: AE, adverse event; IMP, investigational medicinal product; N, number of subjects in intended set; n, number of subjects with data available; SAF, safety; TEAE, treatment-emergent adverse event.
Note: Percentages were based on N.
Note: An AE was related if assessment of causality was possible, probable, or very likely/certain.
Note: More than one category could apply for the same event.
Source: Table 14.3.1.1

The most common serious TEAEs were pneumonia (16 subjects [2.6%]), febrile neutropenia (11 subjects [1.8%]), pulmonary embolism (10 subjects [1.6%]), and neutropenia (9 subjects [1.4%]). All other serious TEAEs were experienced by < 1% of subjects overall. The incidence of serious TEAEs observed between treatment groups was comparable, and no notable trends were observed in the reported PTs.

Suspected unexpected serious adverse reaction: Study MB02-C-02-17:

Among all TEAEs, 16 SUSARs were reported, 9 in the MB02 treatment group and 7 in the Avastin group.

Per definition SUSARs are suspected to be related to the administration of the study drug, but unexpected as not being consistent with the applicable product information (i.e., investigators´ brochure for an unauthorized investigational medicinal product or SmPC for an authorized product).

Following up on these cases, a detailed explanation of all SUSAR cases including patient narratives and information on the patients' medical history and concomitant medication was provided. Thus it was demonstrated that all cases could be explained by one or more of the following: side effects of concomitant medication; confounding by medical history or underlying disease; additional data on Avastin from published literature or the EudraVigilance database where similar events were observed. Based on the provided evaluation it is concluded that no new safety signals or observable trends have

been identified in either treatment arm in the pivotal efficacy and safety study MB02-C-02-17 compared with the known safety profile of Avastin.Deaths: Study MB02-C-02-17:

A total of 47 (7.6%) fatal TEAEs were reported in study MB02-C-02-17, of which 23 (7.4%) occurred in subjects randomized to receive MB02 and 24 (7.7%) occurred in subjects randomized to receive EU-Avastin.

Of these 47 subjects, 25 (4.0%) reported fatal TEAEs in the SOC general and administration site conditions (13 subjects [4.2%] in the MB02 group and 12 subjects [3.9%] in the EU-Avastin group). No fatal TEAEs were reported during study drug infusion. The most commonly reported fatal TEAE was general physical health deterioration (disease progression), reported by 8 (2.6%) subjects in the MB02 group and 11 (3.5%) subjects in the EU-Avastin group.

Other fatal TEAEs experienced in more than one subject were sudden death (2 [0.6%] subjects in the MB02 treatment group (not fulfilling clinical definition).

As summarized in Table 44, the fatal TEAE was considered related to any study drug in 12 subjects with no statistical significance between the groups (p=0.56); 7 subjects and 5 subjects in the MB02 and EU-Avastin treatment groups, respectively. A total of 6 subjects had fatal TEAEs considered related to MB02 and three subjects had fatal TEAEs related to EU-Avastin.

Table 44: Fatal TEAEs considered related to study treatment in study MB02-C-02-17 (Safety Population)

Case number	Age / sex of subject	Preferred Term	Day of death relative to last dose	Relationship to treatment
MB02-related				
19GR000777	60 / Male	Nephrotic syndrome	56	Very likely / Certainly
19HU000785	57 / Female	Haemoptysis	17	Possibly
19RS000981	65 / Male	Gastric ulcer	57	Possibly
19RU000915	61 / Male	Pulmonary haemorrhage	15	Possibly
19TH000888	68 / Male	Acute myocardial infarction	30	Probably
MB02 and Carboplatin / Paclitaxel-related				
18IN000757	48 / Female	Cardio-respiratory arrest	15	MB02: Probably related Carboplatin / Paclitaxel: Unknown
EU-Avastin®-related				
18CL000718	65 / Male	Acute kidney injury	38	Very likely / Certainly
18RU000690	65 / Male	Pulmonary haemorrhage	16	Possibly
EU-Avastin® and Carboplatin / Paclitaxel-related				
18UA000736	55 / Male	Pulmonary embolism	11	EU-Avastin®: Possibly Carboplatin: Not-related Paclitaxel: Possibly
Carboplatin / Paclitaxel-related				
18CL000600	62 / Male	Dehydration	10	Carboplatin: Very likely / Certainly Paclitaxel: Not-related
19UA000916	62 / Male	Enterocolitis	7	Carboplatin / Paclitaxel: Possibly
19IN000917	56 / Female	Disease progression	32	Carboplatin / Paclitaxel: Unknown

Source: CSR MB02-C-02-17 Listing 16.2.7.2 and Listing 16.2.5.1.1

Preferred Term	Day of Death Relative to Last Dose	Relationship to Treatment
MB02-Related		
Nephrotic syndrome	56	Very likely/certainly
Hemoptysis	17	Possibly
Gastric ulcer	57	Possibly
Pulmonary hemorrhage	15	Possibly
Acute myocardial infarction	30	Probably
MB02 and carboplatin / Paclitaxel-Related		
Cardio-respiratory arrest	15	MB02: Probably related Carboplatin/Paclitaxel: Unknown
EU-Avastin®-Related		
Acute kidney injury	38	Very likely/certainly
Pulmonary hemorrhage	16	Possibly
EU- Avastin® and Carboplatin/Paclitaxel-Related		
Pulmonary embolism	11	EU-Avastin®: Possibly Carboplatin: Not related Paclitaxel: Possibly
Carboplatin/Paclitaxel-Related		
Dehydration	10	Carboplatin: Very likely/certainly Paclitaxel: Not related
Enterocolitis	7	Carboplatin/Paclitaxel: Possibly
Disease progression	32	Carboplatin/Paclitaxel: Unknown

Source: CSR MB02-C-02-17 Listing 16.2.7.2, Listing 16.2.5.1.1

According to the data provided by the Applicant in the final CSR, out of the 39 patients in the SAF set discontinued due to death, 11 were discontinued due to death caused by disease progression, (6 subjects in the MB02 arm and 5 subjects in the Avastin arm) and the rest of 28 subjects were discontinued due to death caused by fatal TEAEs. Out of total 47 subjects with fatal TEAEs throughout

the study, 28 subjects with fatal TEAEs were discontinued due to death and are reported in subject disposition flowchart in the category of the patients discontinued due to death.

Laboratory findings

PK study MB02-A-02-17:

Clinical laboratory evaluations: Five subjects (4.4%, one with MB02, one with US Avastin and three subjects with EU Avastin) experienced AEs related to out-of-range clinical laboratory evaluations. Most of them were increased hepatic enzyme, which were unlikely/ not related to study drug. The elevations in all 5 subjects were grade 1 or grade 2, transient and resolving without intervention by the next scheduled clinical laboratory evaluation.

There were no apparent treatment or time-related differences or trends in mean clinical laboratory measurements during the study. Sporadic out-of-range values occurred for multiple subjects in evaluations of various clinical laboratory measurements but not considered clinically significant.

Vital signs, ECG, and local tolerability: One subject (administered US Avastin) experienced a TEAE of pyrexia, which was considered Grade 1 (mild) and not related to the study drug by the Investigator. No other TEAEs related to vital signs measurements were reported.

PK study MB02-A-05-18:

All clinically significant changes reported in clinical laboratory assessments were considered by the Investigator to be resolved by the end of the study and none were considered related to study treatment.

PK study MB02-A-04-18:

Clinically significant changes in clinical laboratory assessment parameters were observed; however, these were transient, resolved without intervention, and no treatment arm-related trends were observed.

Study BEVZ92-A-01-13:

The majority of laboratory anomalies reported in study BEVZ92-A-01-13 were of grade 1 or 2 and the distribution of grade 3–4 abnormalities was similar between the BEVZ92 and Avastin study arms. The only grade 3–4 abnormalities reported in > 10% of patients were high uric acid (21 [30%] and 23 [32%], respectively) and low neutrophil counts (16 [23%] and 21 [30%] in the MB02 and Avastin arms, respectively).

Low total serum protein levels were reported in 37 (54%) patients in the BEVZ92 arm and 33 (46%) patients in the Avastin arm.

Study MB02-C-02-17:

Changes in the haematology, clinical chemistry, urinalysis, and coagulation parameters were those corresponding to the TEAEs reported under the SOCs investigations (alanine aminotransferase increased, aspartate aminotransferase increased and haemoglobin decreased), blood and lymphatic system disorders (anaemia, thrombocytopenia, febrile neutropenia), and renal disorders (proteinuria and protein urine), as the most representative.

There were no apparent trends or remarkable differences between the treatment groups in mean baseline measurements or changes from baseline at each vist/cycle through the end of the study (Week 52) for any variable measured, including haematology, clinical chemistry, urinanalysis and coagulation variables.

12-lead electrocardiogram (ECG) parameters: ECG measurements are presented for Screening, Baseline, at Cycle 3, Cycle 5, Cycle 6, End of Treatment, and at End of Study There were no apparent trends or remarkable differences between the treatment groups in mean baseline measurements, numbers of subjects with abnormal clinically significant measurements, or changes from baseline to the worst grade or at each visit/cycle for any variable measured. (mean heart rate, PR interval, QRS duration, QT interval, and QTcF interval). All abnormal ECG measurements that met criteria of an AE or SAE are discussed in the respective sections of this report.

Left Ventricular Ejection Fraction: LVEF at Baseline and End-of-Treatment are presented as descriptive statistics by treatment group. At Baseline, mean (StD) LVEF measurements for 618 of 621 subjects in the SAF population were 63.1% (6.04). End-of-Treatment LVEF measurements of 62.4% (6.98) were observed for 365 of 621 subjects in the SAF population. No clinically significant differences were apparent between treatment groups. Measurements of LVEF that met criteria of an AE or SAE are discussed in the respective sections of this report.

Eastern Cooperative Oncology Group Performance Status: ECOG performance status is presented for Screening, Baseline, at Day 1 of each cycle, at the End-of-Treatment Visit, at additional follow-up visits, and at the End-of-Study Visit. All subjects entering the study were rated Grade 0 or 1 in ECOG status at baseline. A general worsening in ECOG status was observed as expected due to the disease outcome and was comparable between treatment groups.

Clinical laboratory evaluation:

Blood and Urine parameters: Changes in the haematology, clinical chemistry, urinalysis, and coagulation parameters were those corresponding to the TEAEs reported under the SOCs investigations (alanine aminotransferase increased, aspartate aminotransferase increased and haemoglobin decreased), blood and lymphatic system disorders (anaemia, thrombocytopenia, febrile neutropenia), and renal disorders (proteinuria and protein urine), as the most representative.

There were no apparent trends or remarkable differences between the treatment groups in mean baseline measurements or changes from baseline at each vist/cycle through the end of the study (Week 52) for any variable measured, including haematology, clinical chemistry, urinanalysis and coagulation variables.

Other observations:

12-Lead Electrocardiogram: There were no apparent trends or remarkable differences between the treatment groups in mean baseline measurements, numbers of subjects with abnormal clinically significant measurements, or changes from baseline to the worst grade or at each visit/cycle for any variable measured.

Left Ventricular Ejection Fraction: No clinically significant differences were apparent between treatment groups.

Eastern Cooperative Oncology Group Performance Status: subjects entering the study were rated Grade 0 or 1 in ECOG status at baseline. A general worsening in ECOG status was observed as expected due to the disease outcome and was comparable between treatment groups.

Safety in special populations

The applicant has not conducted specific safety studies in special populations. MB02 will therefore rely on the information available for the RMP, Avastin.

Immunological events

Analytics:

Immunogenicity assay validation

Screening and confirmation assayTo obtain data with regards to the immunogenicity of MB02 and Avastin in the phase I study MB02-A-02-17, MB02-A-05-18, MB02-A-04-18 and the efficacy and safety study MB02-C-02-17, determination of ADAs was performed using an electrochemiluminescence (ECL) method validated with respect to sensitivity, specificity, intra- and inter-assay precision, and short- and long-term stability. Assay selectivity was shown in the presence of haemolysed and lipaemic matrix components. Drug tolerance was established in the presence of varying concentrations of MB02. To mitigate VEGF interference, samples were neutralised with VEGF Receptor 1 neutralisation buffer after the acid dissociation step.

Calculation of the screening cut point followed recent recommendations (testing for normality, selection of non-parametric approach). Calculation of confirmatory cut point is in accordance with recent guidance.

Neutralization assay

The assay for determination of neutralising antibodies (nAbs) was comprehensively validated according to recent guidance. nAbs in the clinical Phase I studies and Phase III study were determined using assays validated with regard to sensitivity, selectivity, short- and long-term stability, inter- and intra-assay precision, drug tolerance and interference.

Haemolytic samples (10% haemolysis) were found to interfere with nAb determination in normal as well as in NSCLC human serum, thus potentially causing false positive results. No hook effect was observed.

Due to insufficient volumes of negative control pool and labelled reagents to complete new upcoming clinical studies (Covance studies 8412384 and 8412385, MB02-A-05-18, MB02-A-04-18 respectively), a partial re-validation was conducted.

Pharmacokinetic Study MB02-A-02-17:

Immunogenicity Sampling was performed at baseline, d14, 28, 56 and day 78.

At the baseline visit (study Day -1), one subject in each of the MB02 and EU-Avastin treatment arms tested positive for ADA.

Treatment-induced ADA were reported in both the MB02 and EU-Avastin arms of the study (2 subjects and 1 subject, respectively). The majority of positive tests for ADA were transient, occurring at a single time point with a low titre value.

No discernible trend or correlation between ADA status and the measured values for PK parameters (AUC0-inf, Cmax and CL) could be observed for either the MB02 or EU-Avastin treatment arms. Those subjects who developed an ADA or nAb response did not report any treatment-emergent adverse events (TEAEs) related to infusion reactions or any TEAEs considered temporally associated with the development of ADA or nAbs.

Pharmacokinetic Study MB02-A-05-18:

Immunogenicity Sampling was performed at baseline, d14, 28, 56 and day 78.

A total of 3 subjects (2.6%) tested positive for ADA at baseline (2 [5.2%] subjects in the MB02 treatment group and 1 [2.6%] subject in the EU-Avastin treatment group). All three positive baseline

samples were negative for NAb response and were low titre. One of the subjects in the MB02 treatment group who was ADA positive at baseline showed a NAb response at study Day 78.

Treatment-induced ADA (TI-ADA), defined as an ADA which developed following drug administration, were developed in a total of 35 (30.7%) subjects. The distribution of ADA positive subjects was similar between the MB02 and EU-Avastin treatment groups; 12 subjects (31.5%) and 14 subjects (36.8%) in the MB02 and the EU-Avastin treatment groups, respectively. The presence of TI-ADA was distinctly higher in this study than in all other clinical studies. Although the reasons for this observation could not be elucidated, similar incidences of TI-ADAs where observed between treatments arms within each individual study. Moreover, almost all ADAs were transient and appeared not to have effects on PK or safety.

All subjects that were ADA positive in both the MB02 and EU-Avastin treatment groups exhibited a transient response, with only one subject (in the MB02 treatment group) showing a NAb response at a single timepoint (Day 78).

No discernible trend or correlation between ADA status and the measured values for PK parameters (AUC0-inf, Cmax and CL) could be observed for either the MB02 or EU-Avastin treatment arms.

Those subjects who developed an ADA or NAb response did not report any treatment-emergent adverse events (TEAEs) related to infusion reactions or any TEAEs considered temporally associated with the development of ADA or NAbs.

Pharmacokinetic Study MB02-A-04-18:

The majority of study subjects tested negative for ADA at all timepoints. A total of two subjects tested positive for ADA at baseline, one in each treatment arm.

Only one subject in the EU-Avastin treatment arm tested positive for treatment-induced ADA during the study. The positive result was transient.

The subjects testing positive for ADA at baseline did not report any TEAEs related to infusion reactions.

No discernible trend or correlation between ADA status and total clearance was observed. The incidence of ADA and NAb was not considered to have any effect on PK parameter estimates.

Pharmacokinetic Study BEVZ92-A-01-13:

Immunogenicity of BEVZ92 is not assessed.

Study MB02-C-02-17:

Through study Week 52, a total of 2811 samples have been analysed, corresponding to 621 subjects from the Safety population (311 and 310 for MB02 and EU-Avastin groups, respectively).

Initially, an increased frequency of ADA positive baseline samples in the screening tier of the trial (17.4%) had been measured. This led to further investigations and new analyses with cut-points, which better reflected the disease matrix (NSCLC serum) but may still have included a certain level of false positives, thus leading to the relatively high number of ADA positive patients at baseline. However, it was shown that the observed ADA baseline levels are in line with historical data for bevacizumab across different patient populations.

A total of 38 (6.1%) subjects tested positive for ADA at baseline (Cycle 1 prior to treatment), 16 (5.1%) subjects in the MB02 group and 22 (7.1%) subjects in the EU-Avastin group. Among these positive baseline samples, 4 NAb positive responses were detected, all in the EU-Avastin group.

The majority of subjects tested negative for ADA at all timepoints.

A total of 103 subjects (16.6%) developed TI-ADA, defined as an ADA which developed in a subject who had tested negative for ADA at baseline. Similar proportions of subjects developed treatment-induced ADA in the MB02 (53 subjects [17.0%]) and EU-Avastin (50 subjects [16.1%]) treatment groups, respectively. Most subjects positive for TI-ADA harboured low titres and the median titre in both treatment arms was observed to be similar.

In both the MB02 and EU-Avastin treatment groups the majority of the TI-ADA positive subjects exhibited a transient response (for MB02, 50 of 53 subjects [94.3%]; for EU-Avastin 40 of 50 subjects [80.0%]). These transient responses generally occurred at a single timepoint or at two timepoints occurring less than 16 weeks apart. A small number of subjects demonstrated a persistent response (3 of 53 subjects [5.7%] and 10 of 40 subjects [20.0%] in the MB02 and EU-Avastin treatment groups, respectively).

Less than 5% of subjects tested positive for TI-NAb, 10 of 292 (3.2%) of subjects in the MB02 treatment group and 13 of 297 subjects (4.2%) in the EU-Avastin treatment group.

Table 45: Summary of ADA incidence by treatment group in the Safety Population of study MB02-C-02-17

Table 61: Summary of ADA Incidence by Treatment Group (SAF Set)

Sample Time Point	Criteria	Avastin® N=310 n (%)	MB02 N=311 n (%)	Total N=621 n (%)
Baseline				
Cycle 1 predose	n	305	307	612
	Positive	22 (7.1)	16 (5.1)	38 (6.1)
	Negative	283 (91.3)	291 (93.6)	574 (92.4)
Overall				
Post-Treatment	n	297	292	589
	Positive	50 (16.1)	53 (17.0)	103 (16.6)
	Negative	247 (79.7)	239 (76.8)	486 (78.3)

Abbreviations: ADA, anti-drug antibody; N, number of subjects in intended set; n, number of subjects with data available; SAF, safety population.

Note: Post-treatment positive represents patients with treatment-induced (transient + persistent) ADAs. It refers to all ADA-positive patients who had a baseline negative result and a subsequent positive result at any time point after treatment with MB02 or Avastin®.

Note: Post-treatment negative represents all patients with at least one sample analyzed post-treatment, with the exclusion of post-treatment ADA-positive patients.

Percentages are based on N.

Source: Table 14.3.4.1.5.1, Appendix 16.2.5

Table 46: Summary of NAb incidence by treatment group (SAF Set)

Sample Time Point	Criteria	Avastin® N=310 n (%)	MB02 N=311 n (%)	Total N=621 n (%)
Baseline				
Cycle 1 predose	n	22	18	40
	Positive	4 (1.3)	0	4 (0.6)
	Negative	18 (5.8)	18 (5.8)	36 (5.8)
Post-treatment	n	73	66	139
	Positive	13 (4.2)	10 (3.2)	23 (3.7)
	Negative	60 (19.4)	56 (18.0)	116 (18.7)

Abbreviations: ADA, anti-drug antibody; N, number of subjects in intended set; n, number of subjects with data available; SAF, safety population.
Note: Post-treatment positive represents patients with treatment-induced NAb (transient + persistent). It is defined as any Nab-positive patient who had a baseline negative NAb result and a subsequent positive result at any time point after treatment with MB02 or Avastin®.
Note: Post-treatment negative represents all patients with at least one sample analyzed post-treatment, with the exclusion of post-treatment Nab-positive patients.
Note. Two additional patients (2604028 and 2812002) were analyzed/reported for neutralizing antibodies at baseline as they were ADA baseline positive prior to the reassessment of the cut-points in the ADA assay (study ID: 8372443).
Percentage are based on N.

Source: Table 14.3.4.1.5.2, Appendix 16.2.5

Of the 103 patients with TI-ADAs, 62 patients (60.2%) achieved ORR at Week 18 (CR or PR; 28 [patients [52.8%] in the MB02 arm and 34 [68.0%] in the Avastin® arm) and 41 patients (39.8%) were non-responders (25 [47.2%] in the MB02 arm and 16 [32.0%] in the Avastin® arm). Although a difference in the number of patients achieving ORR between both treatment arms was observed, this difference was not statistically significant (RD -15.17, 95% CI: -32.82 to 3.48 treatment p-value 0.11) and it was overall concluded that the findings do not account for any differences in efficacy between the products.

No discernible trend or correlation between ADA status and safety was seen. The presence of ADAs was apparently not associated with serious infusion-related reactions or anaphylactic reactions.

Safety related to drug-drug interactions and other interactions

Not applicable for biosimilars.

Discontinuation due to Adverse Events

Pharmacokinetic Study MB02-A-02-17: No subject discontinued due to TEAEs.

Pharmacokinetic studies MB02-A-04-18 and MB02-A-05-18: No subject discontinued due to AEs.

Pharmacokinetic Study BEVZ92-A-01-13:

A total of 19 patients (13 in the BEVZ92 arm and six in the Avastin arm) reported a total of 21 (14 and seven in the BEVZ92 and Avastin arms, respectively) TEAEs leading to permanent discontinuation of study treatment.

The TEAEs leading to discontinuation were considered related to one of the study drugs in 15 patients (10 in the BEVZ92 arm and five in the Avastin arm) and discontinuation was attributed to bevacizumab alone or bevacizumab in combination with FOLFOX/FOLFIRI in 9 patients (5 in the BEVZ92 arm and four in the Avastin arm).

The bevacizumab-related TEAEs leading to discontinuation in the BEVZ92 arm were wound bleeding, wound dehiscence, aortic thrombosis and aortic dissection (all considered non-serious), along with one case of serious embolism. In the Avastin arm, hypertension, portal vein thrombosis and abdominal abscess (all considered non-serious) and one serious case of hypotension and dystonia, were responsible for study discontinuation.

Study MB02-C-02-17:

Through study week 52, there were slight but statistically non-significant differences between treatment groups in the total number of subjects who experienced TEAEs leading to discontinuation (23.2% in MB02 vs 20.3% in Avastin; p=0.39) or in the total discontinuations due to study-drug related TEAEs (13.5% in MB02 group vs 10.6% in Avastin group; p=0.27).

A slightly higher number of patients in the MB02 group than in the Avastin group discontinued due to study drug-related and IMP-related serious TEAE, mostly while receiving 3-4 cycles or after receiving more than 6 cycles. The median dose administered per patient over the entire study was similar between the arms. The median exposure time was approximately three times longer in the MB02 group than in the Avastin group, while the median number of cycles administered was slightly higher for this category of patients in the MB02 group. This can be explained either by more dose delays in the MB02 group or by a better tolerability to MB02 in the early cycles allowing the patients to continue the treatment for a longer time while a longer time of exposure increases the risk for higher incidents of serious adverse events or deaths. When analysing the fatal TEAEs study drug-related and IMP-related, 3 fatal cases were reported in the MB02 vs 0 in the Avastin group. Regarding the number of MB02 cycles administered in the 3 fatal cases, in 1 case up to 4 cycles and in the other 2 fatal cases more than 6 cycles were administered (median number of cycles 8). Based on the data presented, no clear conclusion on the relationship between exposure in time or dose intensity and the pattern of discontinuation due to toxicity or death can be drawn.

Table 47: Exposure to Study Treatments – Subjects that Discontinued due to Serious TEAEs, Serious Study Drug-Related TEAEs, and Serious-IMP Related TEAEs up to Week 52 – SAF Set

Category	Parameter		MB02 N=311 (100%)	Avastin N=310 (100%)	Overall N=621 (100%)
All subjects	Median exposure (days)		182.0	204.0	190.0
	Cycle categories n (%)	1-2 cycles	53 (17.0)	45 (14.5)	98 (15.8)
		3-4 cycles	40 (12.9)	30 (9.7)	70 (11.3)
		5-6 cycles	27 (8.7)	29 (9.4)	56 (9.0)
		> 6 cycles	191 (61.4)	206 (66.5)	397 (63.9)
Serious TEAEs,	n/N (%) with serious TEAEs		27/311 (8.7)	16/310 (5.2)	43/621 (6.9)
	Number of cycles, median		3.0	2.5	3.0
	Cycle categories n (%)	1-2 cycles	12 (3.9)	8 (2.6)	20 (3.2)
		3-4 cycles	7 (2.3)	3 (1.0)	10 (1.6)
		5-6 cycles	4 (1.3)	2 (0.6)	6 (1.0)
		> 6 cycles	4 (1.3)	3 (1.0)	7 (1.1)
	Exposure time, median (days) [a]		49.0	33.0	44.0
	Dose, median (mg) [b]		1035.00	1104.00	1054.50
Serious study drug-related TEAEs	n/N (%) with serious TEAEs		16/311 (5.1)	10/310 (3.2)	26/621 (4.2)
	Number of cycles, median		3.5	2.0	2.5
	Cycle categories n (%)	1-2 cycles	6 (1.9)	7 (2.3)	13 (2.1)
		3-4 cycles	5 (1.6)	1 (0.3)	6 (1.0)
		5-6 cycles	1 (0.3)	2 (0.6)	3 (0.5)
		> 6 cycles	4 (1.3)	0	4 (0.6)
	Exposure time, median (days) [a]		61.0	22.0	37.5
	Dose, median (mg) [b]		1054.50	1125.00	1089.50
Serious IMP-related TEAEs,	n/N (%) with serious IMP-related TEAEs		14/311 (4.5)	6/310 (1.9)	20/621 (3.2)
	Number of cycles, median		3.5	2.0	3.0
	Cycle categories n (%)	1-2 cycles	5 (1.6)	4 (1.3)	9 (1.4)
		3-4 cycles	4 (1.3)	0	4 (0.6)
		5-6 cycles	1 (0.3)	2 (0.6)	3 (0.5)
		> 6 cycles	4 (1.3)	0	4 (0.6)
	Exposure time, median (days) [a]		61.0	22.5	53.5
	Dose, median (mg) [b]		1025.25	1125.00	1125.00

Table 48: Exposure to Study Treatments – Subjects that Discontinued Due to Fatal TEAEs, Fatal Study Drug-Related TEAEs, and Fatal IMP-Related TEAEs up to Week 52, SAF Set

Category	Parameter		MB02 N=311 (100%)	Avastin N=310 (100%)	Overall N=621 (100%)
All subjects	Median exposure (days)		182.0	204.0	190.0
	Cycle categories n (%)	1-2 cycles	53 (17.0)	45 (14.5)	98 (15.8)
		3-4 cycles	40 (12.9)	30 (9.7)	70 (11.3)
		5-6 cycles	27 (8.7)	29 (9.4)	56 (9.0)
		> 6 cycles	191 (61.4)	206 (66.5)	397 (63.9)
Fatal TEAEs	n/N (%) with fatal TEAEs		9/311 (2.9)	7/310 (2.3)	16/621 (2.6)
	Number of cycles, median		7.0	9.0	7.0
	Cycle categories n (%)	1-2 cycles	3 (1.0)	0	3 (0.5)
		3-4 cycles	1 (0.3)	3 (1.0)	4 (0.6)
		5-6 cycles	0	0	0
		> 6 cycles	5 (1.6)	4 (1.3)	9 (1.4)
	Exposure time, median (days) [a]		133.0	176.0	137.0
	Dose, median (mg) [b]		1110.00	810.00	900.00
Fatal study drug-related TEAEs	n/N (%) with study drug-related TEAEs		3/311 (1.0)	0/310 (0)	3/621 (0.5)
	Number of cycles, median		8.0	-	8.0
	Cycle categories n (%)	1-2 cycles	0	0	0
		3-4 cycles	1 (0.3)	0	1 (0.2)
		5-6 cycles	0	0	0
		> 6 cycles	2 (0.6)	0	2 (0.3)
	Exposure time, median (days) [a]		149.0	-	149.0
	Dose, median (mg) [b]		1350.0	-	1350.0
Fatal IMP-related TEAEs	n/N (%) with serious TEAEs		3/311 (1.0)	0/310 (0)	3/621 (0.5)
	Number of cycles, median		8.0	-	8.0
	Cycle categories n (%)	1-2 cycles	0	0	0
		3-4 cycles	1 (0.3)	0	1 (0.2)
		5-6 cycles	0	0	0
		> 6 cycles	2 (0.6)	0	2 (0.4)
	Exposure time, median (days) [a]		149.0	-	149.0
	Dose, median (mg) [b]		1350.0	-	1350.0

The most commonly reported TEAEs leading to treatment discontinuation were general physical health deterioration (31 subjects [5.0%]; 13 [4.2%] subjects in the MB02 group and 18 [5.8%] in the Avastin® group) and anemia (12 subjects [1.9%]; 7 [2.3%] subjects in the MB02 group and 5 [1.6%] in the Avastin® group) and the associated event of hemoglobin decreased (2 subjects [0.3%], both in the Avastin® group). No clear treatment group–related trends were observed for TEAEs leading to treatment discontinuation. In all cases, the risk difference between treatment groups in subjects reporting TEAEs leading to treatment discontinuation was <2%.

The Applicant also presented the proportion of subjects with drug-related TEAEs, any combination drug-related TEAEs, IMP-related TEAEs and chemotherapy-related AEs leading to treatment discontinuation. In general, less than 5% of subjects discontinued due to TEAEs in any specific SOCs. A difference between treatments was observed in IMP-related TEAEs in the SOC "Nervous system disorders" where five patients discontinued treatment in the MB02 arm as opposed to zero in the Avastin arm. Regarding IMP-related TEAEs, it is noticed that, though in general comparable between

treatment arms, in the two SOCs "Respiratory, thoracic and mediastinal disorders" and "Nervous system disorders" more events were observed in the MB02 arm. Most were limited to mild events and were confounded by the concomitant chemotherapy medication. They do therefore not represent an impediment in the comparative safety assessment of MB02 and Avastin.

Upon request from EMA, drug exposure in subjects who discontinued due to TEAEs were analysed, observing an slight higher proportion of discontinuations due to serious TEAEs in MB02 group than in Avastin group (8.7 % vs 5.2 %). The serious TEAE leading to discontinuation was drug-related or IMP-related in a slightly higher number of patients in the MB02 group than in Avastin group, mostly while receiving 3-4 cycles or after receiving more than 6 cycles. In all cases differences were less than 5%. Drug exposure was assessed in these subjects, observing that the median dose administered per patient over the entire study was similar between the arms. The median exposure time to the study drug for subjects who discontinued due to serious TEAEs was longer and the median number of cycles administered was slightly higher in the MB02 group than in the Avastin group. As to regard to the fatal TEAEs study drug-related and IMP-related, 3 fatal cases were reported in the MB02 vs 0 in the Avastin group. These subjects received a median number of 8 cycles of MB02 in combination with chemotherapy.

Based on the data presented, no clear conclusion on the relationship between exposure in time or dose intensity and the pattern of discontinuation due to toxicity or death can be drawn.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

The safety population consisted of all subjects who received at least one dose of bevacizumab in any of the following studies:

- The pivotal phase 3 comparative efficacy, safety and immunogenicity study in non-squamous NSCLC patients (MB02-C-02-17),
- the pivotal three-arm single dose PK study conducted in healthy volunteers in the UK (MB02-A-02-17),
- an additional three-arm single dose PK study conducted in healthy volunteers in Germany (MB02-A-05-18),
- an additional two-arm single dose PK study conducted in healthy volunteers in Japan (MB02-A-04-18),
- and a phase I, open label, repeat-dose, parallel arm PK study in mCRC patients (BEVZ92-A-01-13).

Exposure: In total, 1037 subjects received at least one dose of IMP: 621 non-squamous NSCLC patients, 140 mCRC patients and 276 healthy volunteers. In the pivotal efficacy and safety study MB02-C-02-17 the mean duration of exposure was lower in the MB02 group (185.9 days compared with the Avastin group (203.9 days). While not statistically significant, the lower duration of exposure in MB02-treated subjects was likely attributed to the slightly higher rate of discontinuations up at week 18 in the MB02 group than in Avastin group, particularly in the first cycles. Incidence of dose modifications or infusion interruption was low and balanced between treatment arms.

Adverse events: The incidence and severity of TEAEs in PK study MB02-A-02-17 was comparable between MB02 and EU Avastin. The most frequently reported TEAEs were mild in severity and included headache (19.3%), upper respiratory tract infection, (18.4%), and back pain (10.5%), with slighty higher incidence with EU Avastin compared to MB02 in each of these terms. The incidence of ADRs was low and comparable between treatment arms (6 subjects vs. 8 subjects with MB02 and EU Avastin, respectively).

A similar picture was observed in the PK study MB02-A-05-18 where the majority of TEAEs were mild or moderate in severity and treatment-related TEAEs were evenly distributed between the study arms. TEAEs considered to be treatment-related (possibly, probably or definitely-related) were reported in 33 (28.9%) study subjects from all arms of the study.

In PK study MB02-A-04-18, the incidence of TEAEs in the MB02 treatment group was slightly lower compared to the EU-Avastin treatment group (8 [33.3%] and 12 subjects [50.0%] in the MB02 and EU-Avastin treatment groups, respectively). The number of TEAEs was comparable between the MB02 and EU-Avastin treatment groups. Only 3 of the 47 reported TEAEs were considered to be treatment-related. All of them were observed in the EU-Avastin treatment group, with no treatment-related TEAEs observed in the MB02 treatment group. All of the 47 TEAEs reported in this study were classified as mild or moderate in severity. Of note, the number of TEAE was distinctly lower in study MB02-A-04-18 compared to the other PK studies in healthy volunteers probably caused by slight differences in baseline characteristics (age, BMI) and a known trend towards occasionally lower reporting of TEAEs in Asian countries.

Study BEVZ92-A-01-13: All 71 patients in the EU-Avastin arm and 66 patients (96%) in the BEVZ92 arm experienced at least one TEAE. A similar number of TEAEs considered related to administration of IMP were reported in each treatment arm; 24 (35%) and 26 (37%) of patients experienced at least one TEAE considered related only to IMP administration in the BEVZ92 and EU-Avastin arms, respectively. The SOCs with the largest number of patients reporting TEAEs (≥ 50 patients for each SOC) were gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, blood and lymphatic system disorders, metabolism and nutrition disorders, infections and infestations and investigations. Comparative analysis of the number of patients with particular AEs in the BEVZ92 and EU-Avastin arms of the study suggests a similar profile of AEs in the two treatment groups. The safety profiles were within expectations given the underlying disease and concomitant chemotherapy and consistent with the labelling information for Avastin.

In Study MB02-C-02-17 the subject incidence was balanced between treatment arms, 92.6% subjects in the MB02 group and 92.9% subjects in the Avastin group (p = 0.89). The most common TEAEs were those commonly reported with the use of carboplatin/paclitaxel (e.g., alopecia, nausea, and neuropathy), as well as PTs related to myelosuppression (e.g., anaemia, thrombocytopenia, leukopenia, and neutropenia). Other TEAEs were those commonly reported with the use of bevacizumab (e.g., hypertension and proteinuria), and were similarly distributed between treatment groups. The most common TEAEs by preferred term (PT) were alopecia (51.2%) and anaemia (31.24%), with no considerable differences between treatment groups. More patients experienced grade 3 or 4 TEAEs with MB02 compared to Avastin (39.9% vs 38.1%, respectively). Grade 5 TEAEs were generally low in incidence and comparable between treatment groups. No clear treatment group-related trends were observed for IMP-related TEAEs. In all cases, the risk difference between treatment groups in subjects reporting IMP-related TEAEs was <2%.

Overall, the number, type, and severity of TEAEs of special interest was in alignment with the safety profile reported in the bevacizumab SmPC for this patient population. There were no new safety signals or observable trends reported for MB02-treated subjects. For all TEAEs of special interest, the difference in frequency between treatment groups of TEAEs reported was <5%. The most commonly

reported TEAEs of special interest were identified by the searches for events associated with neutropenia and infections (191 subjects [30.8%]). A total of 61 (9.8%) subjects experienced TEAEs associated with haemorrhage, pulmonary haemorrhage, and/or haemoptysis, with no observable risk difference between treatment groups with regard to subjects reporting TEAEs. Hypertension-related TEAEs were identified in 60 (9.7%) subjects; proteinuria-related TEAEs were identified in 46 (7.4%) subjects, with no observable risk difference between treatment groups with regard to subjects reporting TEAEs.

Serious events and deaths:

In PK study MB02-A-02-17, only one subject treated with US-Avastin experienced a serious TEAE. The event of purpura was considered as SUSAR and resolved without sequelae. No death occurred in this study.

In study MB02-A-05-18 and in study MB02-A-04-18 no SAE or deaths occurred.

Study BEVZ92-A-01-13: A total of 37 deaths were reported in the AT (safety) population. The majority of the deaths (24) were due to disease progression and were well balanced between both treatment arms and are expected events in the study population. 13 patients (8 [10%] and 5 [6%] in the BEVZ92 and Avastin arms, respectively) experienced at least one serious TEAE with fatal outcome. Fatal events were considered related to any of the study treatments (bevacizumab, chemotherapy or both) in four patients (two in each treatment arm). Only in one patient in the Avastin arm the fatal events were considered to be related exclusively to bevacizumab.

The distribution of SAEs across the treatment arms by SOC were similar, as were the total number of patients reporting SAEs (19 [28%] in the BEVZ92 treatment arm and 21 [30%] in the Avastin arm). SAEs by PT that were reported in > 5% patients included intestinal obstruction (9%) in the BEVZ92 group; and diarrhoea (7%), neutropenia (8%) and anaemia (6%) in the Avastin group. Most common treatment-related SAEs included neutropenia and diarrhoea, anaemia, leukopenia and sepsis, and hypotension. These events were more common in the Avastin arm, which may be a result of the relatively small sample size.

In study MB02-C-02-17, serious TEAEs were observed in 58 (18.6%) and 54 (17.4%) of patients treated with MB02 or Avastin, respectively. No statistically significant difference (p=0.69) in serious TEAEs was observed between the MB02 and EU-Avastin treatment groups. No SAEs were reported during study drug infusion. A total of 66 (10.6%) subjects experienced study drug-related serious TEAEs during the study (33 subjects in each treatment group); the difference was not statistically significant (p=0.99). Of these cases, 39 (6.3%) subjects experienced serious TEAEs related to MB02 (21 subjects [6.8%]) or EU-Avastin (18 subjects [5.8%]). A total of 51 (8.2%) subjects experienced serious TEAEs related to carboplatin and/or paclitaxel (24 subjects [7.7%] in the MB02 group compared to 27 subjects [8.7%] in the EU-Avastin group). The most common serious TEAEs were pneumonia (16 subjects [2.6%]), febrile neutropenia (11 subjects [1.8%]), pulmonary embolism (10 subjects [1.6%]), and neutropenia and general physical health deterioration (9 subjects [1.4%] each). All other serious TEAEs were experienced by < 1% of subjects overall. The incidence of serious TEAEs observed between treatment groups was comparable, and no notable trends were observed in the reported PTs.

Fatal TEAEs in study MB02-C-02-17 were observed in 23 (7.4%) and 24 (7.7%) of subjects with MB02 and Avastin, respectively. Fatal TEAEs considered related to any study drug occurred in 12 subjects with no statistical significance between the groups (p=0.56); 7 subjects and 5 subjects in the MB02 and EU-Avastin treatment groups, respectively. A total of 6 subjects had fatal TEAEs considered related to MB02 and three subjects had fatal TEAEs related to EU-Avastin. Reported fatal TEAEs are known ADR for bevacizumab.

In total, 16 SUSARs were reported during the study, of which 5 were fatal. Upon EMA request, a detailed explanation of all SUSAR cases including patient narratives and information on the patients' medical history and concomitant medication was provided. Thus it was demonstrated that all cases could be explained by one or more of the following: side effects of concomitant medication; confounding by medical history or underlying disease; additional data on Avastin from published literature or the EudraVigilance database where similar events were observed. Based on the provided evaluation it is concluded that no new safety signals or observable trends have been identified in either treatment arm in the pivotal efficacy and safety study MB02-C-02-17 compared with the known safety profile of Avastin. A minor imbalance in discontinuation due to toxicity or death was observed in the group of patients who discontinued due to SAEs. A slightly higher number of patients in the MB02 group than in Avastin group discontinued due to study drug-related and IMP-related serious TEAE, mostly while receiving 3-4 cycles or after receiving more than 6 cycles. The median dose administered per patient over the entire study was similar between the arms. Based on the data presented, no clear conclusion on the relationship between exposure in time or dose intensity and the pattern of discontinuation due to toxicity or death can be drawn.

The Applicant also presented the proportion of subjects with drug-related TEAEs, any combination drug-related TEAEs, IMP-related TEAEs and chemotherapy-related AEs leading to treatment discontinuation. In general, less than 5% of subjects discontinued due to TEAEs in any specific SOCs. A small difference between treatments was observed in IMP-related TEAEs in two SOCs "Respiratory, thoracic and mediastinal disorders" and "Nervous system disorders" where more events were observed in the MB02 arm. During the evaluation procedure it was concluded that differences in IMP-related TEAEs between treatment arms in the two SOCs "Respiratory, thoracic and mediastinal disorders" and "Nervous system disorders" in study MB02-C-02-17 were limited to mild events and were confounded by the concomitant chemotherapy medication. They do therefore not represent an impediment in the comparative safety assessment of MB02 and Avastin.

Immunogenicity: Total treatment-induced ADAs were mainly transient and were similar between products (MB02 and EU Avastin) across all studies for which immunogenicity data were submitted. In all studies, ADAs were present at baseline in some subjects. In the pivotal phase 3 study, a total of 38 subjects (6.2%) tested positive for ADAs at baseline, although previous treatment with Avastin or other VEGF inhibitors was an exclusion criterion. Initially, an increased frequency of ADA positive baseline samples in the screening tier of the trial (17.4%) had been measured. This led to further investigations and new analyses with cut-points which better reflected the disease matrix (NSCLC serum) but may still have included a certain level of false positives, thus leading to the relatively high number of ADA positive patients at baseline. However, it was shown that the observed ADA baseline levels are in line with historical data for bevacizumab across different patient populations.

The range of TI-ADAs was different between studies with the highest number in the supportive phase 1 study conducted in Germany (MB02-A-05-18), where TI-ADAs were detected in 12 (31.5%) and 14 (36.8%) subjects in the MB02 and EU-Avastin arm, respectively. Although the reasons for this observation could not be elucidated, it is acknowledged that similar incidences of TI-ADAs were observed between treatments arms within each individual study. Moreover, almost all ADAs were transient and appeared not to have effects on PK or safety.

No impact on the safety in general and no immune-related safety risks in particular, seem to be correlated with treatment related antibodies.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on clinical safety

The applicant provided comprehensive safety and immunogenicity data including the final CSR of the pivotal phase 3 study. The totality of the safety results supports biosimilarity of MB02 and Avastin.

2.7. Risk Management Plan

Safety concerns

No safety concerns are identified for Alymsys.

Pharmacovigilance plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of Alymsys.

Risk minimisation measures

Routine risk minimisation measures are considered sufficient to manage the risks of Alymsys.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 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. New Active Substance

The CHMP, based on the available data, considers that bevacizumab is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union. Bevacizumab is contained in the marketing authorisation Avastin which was authorised in the Union on 12 January 2005.

2.10. Product information

2.10.1. 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.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Alymsys (bevacizumab) is included in the additional monitoring list 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

Alymsys (also referred to as MB02) is developed as a biosimilar to the reference product Avastin. The administration route (i.v.), posology, and indications are according to the reference product as described in the Avastin SmPC except for one concerning platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

The marketing authorization is claimed for

- Alymsys in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.
- Alymsys 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.
- Alymsys 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.
- Alymsys, 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.
- Alymsys, 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.
- Alymsys in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer.

- Alymsys, 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 III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- Alymsys, 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.
- Alymsys, in combination with topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.
- Alymsys, 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 similarity

The design of the analytical similarity exercise has been discussed in two CHMP advices (procedures EMEA/H/SA/3471/1/2017/III and EMEA/H/SA/3471/1/FU/2/2019/I). The Applicant generally followed the recommendations and relevant guidelines and performed a sound and comprehensive biosimilarity exercise using sensitive orthogonal state-of-the-art analytical methods that addressed the relevant quality attributes. Primary and higher order structure, post-translational modifications, size and charge variants, larger aggregates, general attributes, as well as Fab- or Fc-mediated biological functions were compared between MB02 and the reference product EU-Avastin. The Fab-mediated mechanism of action was evaluated by a range of biological assays at different levels (binding to various VEGF isoforms, competitive binding ELISA, HUVEC anti-proliferation assay, VEGF blocker reporter gene assay, receptor dimerization assay). Biological characteristics were further compared with regard to Fc receptor and mannose receptor binding, C1q binding, and CDC and ADCC activity. Size and charge variants were thoroughly characterised for both MB02 and EU-Avastin. A sufficient number of lots, which can be expected to sufficiently reflect product variability of both the proposed biosimilar and the reference product, was included.

Summary of non-clinical data

Non-clinical studies supported biosimilarity between MB02 and Avastin. The cynomolgus monkey repeated dose toxicity study BEVZ92-NC-01, conducted for MAA in non-EU regions, showed no relevant differences between BEVZ92 and EU-Avastin in mortality, clinical signs, body weights, ophthalmology, electrocardiography, haematology, clinical chemistry, urine analysis, organ weights, macroscopic and microscopic findings. Consequently, the study appears to support biosimilarity of BEVZ92 and EU-Avastin; however, the small group size and occasionally high inter-individual variability in this study make it unreliable in terms of demonstrating biosimilarity. Therefore, results of this study should only be regarded as supplementary data.

Summary of clinical data

The design of the clinical studies has been discussed in two CHMP advices. From a clinical point of view the Applicant mostly followed EMA guidelines and the CHMP SA, except for additional PK sampling in the efficacy and safety study in patients, which was omitted.

The clinical developmental program compromised of

- **MB02-A-02-17:** The pivotal PK-study was a randomised (1:1:1), double-blind, single dose (3 mg/kg per IV infusion) parallel group study for a duration of up to 100 days comparing the pharmacokinetics, safety and immunogenicity between MB02, EU- and US-Avastin in 114 healthy male volunteers.

- **MB02-C-02-17:** A multi-centre, double-blind, parallel group, randomised (1:1), one-year clinical study comparing the efficacy, safety, and immunogenicity of MB02 to EU-Avastin (15 mg/kg every 3 weeks Q3W) in 627 patients with Stage IIIB/IV non-squamous non-small cell lung cancer (NS-NSCLC).

Supportive information for PK, immunogenicity and safety was provided from two phase I, single-dose studies: **MB02-A-05-18** was conducted in Germany with 114 healthy volunteers, comparing MB02 to EU Avastin and US Avastin with a study design similar to the completed study MB02-A-02-17 to support FDA filing and **MB02-A-04-18** had also a similar design and was conducted in 48 healthy Japanese volunteers comparing MB02 to EU Avastin to support PMDA filing.

The applicant also provided supportive safety information from a phase I study BEVZ92-A-01-13 (open label repeat-dose parallel arm PK study) in 142 mCRC patients. 5 mg/kg BEVZ92 or EU-Avastin was administered in combination with FOLFOX or FOLFIRI by IV infusion once every two weeks.

3.2. Results supporting biosimilarity

Quality

In summary, the presented analytical data show similarity of the proposed biosimilar MB02 and the reference product EU-Avastin. Quality attributes related to the mechanism of action of bevacizumab were highly similar. The minor analytical differences observed for several quality attributes have been appropriately addressed by the Applicant and justified with regard to their potential impact on clinical performance of the product.

Clinical

- *Pharmacokinetics*

Similarity between MB02 and EU-Avastin was demonstrated in study MB02-A-02-17, as the 90% CI for the geometric LS means ratios of protein-unadjusted AUCs and Cmax parameters were fully contained within the predefined bioequivalence limits of 0.80 to 1.25. Results for the difference in AUC0-∞ were 1.16 with a 90% CI of [1.09, 1.22] and for Cmax 1.12 [1.03, 1.22], respectively. Results showed a statistically significant difference, as "1" was not included in the ratio, suggesting slight overexposure.

Review of the protein concentrations administered to subjects demonstrated that subjects in the MB02 arm received a dose of bevacizumab approximately 12 to 14% higher compared to the US and EU Avastin arms, due to the higher protein concentrations in the MB02 vials. The additionally performed sensitivity analysis correcting for actual protein content confirmed PK similarity, showing no statistically significant difference, with the point estimates near "1". Although, which is seen with some caution, this analysis is supportive of PK similarity. A bioequivalence assessment on protein-unadjusted PK parameters was also performed including the actual protein in the model as a nested parameter of treatment. The point estimates for AUC0-inf, AUC0-t and Cmax were 0.892, 0.885 and 0.897 respectively, with an upper limit of the 90% CI excluding "1" for all three parameters, suggesting slight underexposure, which is explained by the unbalanced strata in the nested model (29 vs 9 subjects) and the magnitude of the differences which could lead to an inability to estimate the model parameters due to a lack of variability in the protein content.

The secondary endpoints were in support of PK similarity. The terminal elimination half-life was 451h with MB02 and 449h with EU Avastin, the elimination rate constant was also similar. Tmax was slightly longer with EU-Avastin compared to MB02: 3h vs. 2.51h, respectively.

Similarity was also demonstrated between MB02 and EU Avastin in the supportive studies MB02-A-04-18 and MB02-A-05-18. In study MB02-A-05-18, the ratio of geometric least squares mean for AUC0-inf was 1.07 (90% CI: 1.00, 1.14) and for Cmax was 1.06 (90% CI: 0.976, 1.16). The 90% CIs were fully contained within the predefined equivalence limits of 0.80 to 1.25. The resulting 90% CI for AUC0-inf, where the lower limit covers exactly "1", even indicates a slight overexposure of MB02. The secondary endpoints were in support of PK similarity. Results from the MB02-A-04-18 study demonstrated equivalence in healthy Japanese male subjects, as the 90% CI for the geometric LS mean ratio for AUC0-inf (1.04; 90% CI: 0.981, 1.11) was fully contained within the predefined equivalence limits of 0.80 to 1.25. The secondary endpoints were also in support of PK similarity.

- *Efficacy*

Primary endpoint: In the ITT population, the ORR by IRC was 40.3% (127/315) in the MB02 group and 44.6% (139/312) in the EU-Avastin group resulting in the point estimate of -4.02 (95% CI: -11.76 to 3.71) for the risk difference. The 95% CI for the risk difference was contained within the pre-determined equivalence margin of ±12%. Under multiple imputation, the ORR RD showed similarity at 95% CIs (-1.92; 95% CI: -10.02 to 6.19) and using the multiple imputation for subjects without tumour response data (missing, NonCR/NonPD or NE), the ORR RD was -2.22 with 95% CI of (-10.54 to 6.10) at Week 18 in the ITT. In the mITT, the ORR difference was -2.77 (95% CI: -11.09 to 5.55) and showed also similar results. While the pre-defined equivalence range was not fully met for the initial PPS, when only the complete cases with overall response at week 18 were analysed, the RD of the ORR remained entirely within the equivalence margin (-2.66; 95% CI: -11.91 to 6.59). Additionally, by excluding only those patients from the PPS who had major protocol deviations with potential impact on efficacy, the ORR RD was -3.45 (95% CI -12.04 to 5.13) under the preferred analysis using multiple imputation adjusting for missing/NE.

Similar efficacy between MB02 and Avastin was observed in analyses of best ORR in the ITT set based on the IRC assessments with a RD -4.04 (95% CI: -11.86 to 3.78).

No relevant differences between treatment arms MB02 and Avastin were identified in patient subgroups.

Secondary endpoints:

The percentage change in tumour burden from baseline (sum of the diameters of the target lesions) was investigated post-hoc, showing no significant difference between the treatments. The mean of the %change from baseline in tumour burden by week 18 was −26.64 for MB02 and −25.75 for Avastin; the difference between the treatment groups was −0.892 (95% CI of −4.828, 3.044). Results were comparable by Week 6 and Week 12, with a difference of −0.976 and −1.133, respectively. Analysis of the %change in tumour burden assessed by the investigator was comparable with the IRRC assessment.
For PFS in the ITT set, the HR was 1.200 with 95% CI (0.985, 1.462). For PFS in the PPS, the HR was 1.233 with 95% CI (0.999 to 1.521). For OS in the ITT set, the HR was 1.107 with 95% CI (0.826, 1.483) and in the PPS, the HR was 1.141 with 95% CI (0.835, 1.560).

- *Safety*

In PK study MB02-A-02-17, incidence and severity of TEAEs was comparable between MB02 and EU Avastin. TEAEs occurred in 63.2% and 65.5% of subjects, respectively. The incidence of ADRs was low and also comparable between treatment arms (6 subjects vs. 8 subjects with MB02 and EU Avastin, respectively). The only serious event (purpura) was rated as SUSAR and occurred in the US-Avastin

treatment arm. It developed after an upper respiratory tract infection and resolved without sequelae. Only few patients had out-of-range laboratory values. They were transient and comparable between treatment arms, resolving without intervention by the next scheduled clinical laboratory evaluation.

A similar picture was observed in the PK study MB02-A-05-18 where the majority of TEAEs were mild or moderate in severity and treatment-related TEAEs were evenly distributed between the study arms. TEAEs considered to be treatment-related were reported in 33 (28.9%) study subjects from all arms of the study.

In PK study MB02-A-04-18, the number of TEAEs was comparable between the MB02 and Avastin treatment groups. Only 3 of the 47 reported TEAEs were considered to be treatment-related. All of them were observed in the Avastin treatment group, with no treatment-related TEAEs observed in the MB02 treatment group. All of the 47 TEAEs reported in this study were classified as mild or moderate in severity.

In Study BEVZ92-A-01-13, 24 (35%) and 26 (37%) of patients experienced at least one TEAE considered related only to IMP administration in the BEVZ92 and Avastin arms, respectively. Comparative analysis of the number of patients with particular AEs in the BEVZ92 and Avastin arms of the study suggests a similar profile of AEs in the two treatment groups. The safety profiles were within expectations given the underlying disease and concomitant chemotherapy and consistent with the labelling information for Avastin. A total of 37 deaths were reported in the all treated (= safety) population. The majority of the deaths (24) were due to disease progression and were well balanced between both treatment arms and are expected events in the study population. 13 patients (8 [10%] and 5 [6%] in the BEVZ92 and Avastin arms, respectively) experienced at least one serious TEAE with fatal outcome. Fatal events were considered related to any of the study treatments (bevacizumab, chemotherapy or both) in four patients (two in each treatment arm). Only in one patient in the Avastin arm the fatal events were considered to be related exclusively to bevacizumab. The distribution of SAEs across the treatment arms by SOC were similar, as were the total number of patients reporting SAEs (19 [28%] in the BEVZ92 treatment arm and 21 [30%] in the Avastin arm).

In Study MB02-C-02-17, the subject incidence of TEAEs was balanced between treatment arms, with 92.6% subjects in the MB02 group and 92.9% subjects in the Avastin group. The most common TEAEs were those commonly reported with the use of carboplatin/paclitaxel (e.g., alopecia, nausea, and neuropathy), as well as PTs related to myelosuppression (e.g., anaemia, leukopenia, thrombocytopenia and neutropenia). Other TEAEs were those commonly reported with the use of bevacizumab (e.g., hypertension and proteinuria), and were similarly distributed between treatment groups. The majority of subjects experienced TEAEs classified as NCI CTCAE severity Grade 1 or 2 events. No clear treatment group-related trends were observed for IMP-related TEAEs.

Serious TEAEs were observed in 58 (18.6%) and 54 (17.4%) of patients treated with MB02 or Avastin, respectively. No statistically significant difference (p=0.69) in serious TEAEs was observed between the MB02 and Avastin treatment groups. No SAEs were reported during study drug infusion. A total of 66 (10.6%) subjects experienced study drug-related serious TEAEs during the study (33 subjects in each treatment group); the difference was not statistically significant (p=0.99). Of these cases, 39 (6.3%) subjects experienced serious TEAEs related to MB02 (21 subjects [6.8%]) or Avastin (18 subjects [5.8%]). A total of 51 (8.2%) subjects experienced serious TEAEs related to carboplatin and/or paclitaxel (24 subjects [7.7%] in the MB02 group compared to 27 subjects [8.7%] in the Avastin group).

Fatal TEAEs were observed in 7.4% and 7.7% of subjects with MB02 and Avastin, respectively. Fatal TEAEs considered related to any study drug occurred in 12 subjects with no statistical significance between the groups (p=0.56) – 7 subjects and 5 subjects in the MB02 and Avastin treatment groups, respectively. A total of 6 subjects had fatal TEAEs considered related to MB02 and three subjects had fatal TEAEs related to Avastin. The majority of the reported fatal TEAEs are known ADR for bevacizumab.

Immunogenicity: Total treatment-induced ADAs were mainly transient and were similar between products (MB02 and EU Avastin) across all studies for which immunogenicity data were submitted. In all studies, ADAs were present at baseline in some subjects. No impact on the safety in general and no immune-related safety risks in particular, seem to be correlated with treatment related antibodies.

3.3. Uncertainties and limitations about biosimilarity

Quality

The presented analytical data show similarity of the proposed biosimilar MB02 and the reference product EU-Avastin. Quality attributes related to the mechanism of action of bevacizumab were highly similar. The minor analytical differences observed for several quality attributes have been appropriately addressed by the Applicant and justified with regard to their potential impact on clinical performance of the product.

The samples used in the analytical similarity exercise have been stored frozen prior to analysis. However, based on the available data, it is deemed unlikely that freezing will specifically impact the reference product.

A partial metabolic amino acid substitution is observed for MB02, which affects the formation of disulphide bridges. These variants are not present in Avastin. However, the extent of replacement is low. As demonstrated by analytical data the exchange has no effect on biological activity and structure under native conditions. An impact on immunogenicity appears unlikely; indeed, the clinical data show comparable immunogenicity of MB02 and Avastin.

Clinical

Efficacy

Primary endpoint: For the PP set, the pre-defined equivalence margin for the difference in ORR at week 18 was not met, with a 95% CI of (-12.92 to 4.38) under non-responder imputation and a 95% CI of (-13.68 to 3.68) under multiple imputation.

Secondary endpoints: The Kaplan-Meier plots for PFS and OS in both ITT set and PPS set show a consistent trend for better outcomes for subjects in the Avastin group than subjects in the MB02 group, although in a statistically non-significant manner.

Safety

Study MB02-C-02-17:

A slight imbalance in discontinuation due to toxicity or death was observed between the treatment arms (median duration of exposure: 182 days in MB02 group vs 204 days in Avastin group). A slightly higher number of patients in the MB02 group than in Avastin group discontinued due to study drug-related and IMP-related serious TEAE, mostly while receiving 3-4 cycles or after receiving more than 6 cycles. Based on the data presented, no clear conclusion on the relationship between exposure in time or dose intensity and the pattern of discontinuation due to toxicity or death can be drawn.

Although IMP-related TEAEs were in general comparable between treatment arms, in the two SOCs "Respiratory, thoracic and mediastinal disorders" and "Nervous system disorders" more events were observed in the MB02 arm. However, these findings were limited to mild events and were confounded by the concomitant chemotherapy medication.

The occurrence of SUSARs in the setting of a similar biological medicinal product application, where a known active substance with a well-described safety profile is investigated, required further evaluation.

The Applicant acknowledged that three events should not have been reported as SUSARs as they are clearly listed in the RSI as expected events. Also, the remaining cases were explained retrospectively by one or more of the following: side effects of concomitant medication; confounding by medical history or underlying disease; additional data on Avastin from published literature or the EudraVigilance database where similar events were observed.

Immunogenicity:

In all studies, ADAs were present at baseline in some subjects. In the pivotal phase 3 study, a total of 38 subjects (6.1%) tested positive for ADAs at baseline, although previous treatment with Avastin or other VEGF inhibitors was an exclusion criterion. Initially, an increased frequency of ADA positive baseline samples in the screening tier of the trial (17.4%) had been measured. This led to further investigations and new analyses with cut-points, which better reflected the disease matrix (NSCLC serum) but may still have included a certain level of false positives, thus leading to the relatively high number of ADA positive patients at baseline. However, it was shown that the observed ADA baseline levels are in line with historical data for bevacizumab across different patient populations.

The range of TI-ADAs was different between studies with the highest number in the supportive phase 1 study conducted in Germany (MB02-A-05-18), where TI-ADAs were detected in 12 (31.5%) and 14 (36.8%) subjects in the MB02 and EU-Avastin arm, respectively. Although the reasons for this observation could not be elucidated, it is acknowledged that similar incidences of TI-ADAs were observed between treatments arms within each individual study.

Furthermore, a difference in efficacy in terms of ORR at Week 18 was observed in TI-ADA positive subjects between the treatments (ORR 52.8% and 68% for the MB02 arm and the Avastin arm, respectively) in study MB02-C-02-17. In response to outstanding issues the applicant provided further analyses on the difference in ORR between TI-ADA positive subjects and it was overall concluded that the findings were minimal and do not account for any differences in efficacy between the products.

3.4. Discussion on biosimilarity

Overall, the design of the analytical similarity exercise is considered adequate. The results demonstrate high analytical similarity between MB02 and EU-Avastin. Analytical differences observed between MB02 and the reference product have been adequately justified with regard to their potential impact on clinical performance. Notably, molecule variants with partial amino acid substitution are present in MB02 that are not observed in Avastin; however, the extent of the substitution is low and hence, an impact on clinical performance is not expected. The quantitative differences in free thiol content, basic peak 2, and mannose content have been adequately addressed.

Pharmacokinetic similarity of MB02 to EU-Avastin was demonstrated in the pivotal single dose PK study MB02-A-02-17 in HV, based on primary PK parameters. The post-hoc performed protein-corrected analysis supports the primary results. The two supportive studies MB02-A-04-18 and MB02-A-05-18 also demonstrated similarity of the pharmacokinetics of MB02 and EU-Avastin, based on the primary PK parameters. Therefore, biosimilarity on PK level can be concluded from three independent PK studies.

Generally, the Applicant has established in compliance with the relevant guidelines a comprehensive program for the purpose of investigating the similarity between MB02 and EU-Avastin. Based on the analytical data and the PK studies performed, no differences have been identified that give rise to uncertainty over the expected clinical performance.

The pivotal efficacy and safety study in non-squamous NSCLC patients was adequately designed and the chosen primary and secondary efficacy outcomes and equivalence criteria are deemed acceptable.

The results of the ORR risk difference at week 18 in the ITT population demonstrated biosimilarity between MB02 and EU Avastin within the equivalence margin of 12%. In the initial PP population under multiple imputation that does not favour the treatment arm with less missing values, the 95% CI of the ORR RD (-13.68, 3.68) did go below -13%, however.

Additional analyses were presented by including only those patients from the ITT set that completed Week 18 and had overall response (OR of CR, PR, SD or PD per RECIST v1.1). In selecting this population, the patients that experience response of NE and non-CR/non-PD due to non-evaluable target lesions at baseline, have been excluded. This analysis set has a similar intention as the pre-specified PPS, i.e. to assess differences in the treatments reducing the impact of unrelated factors on the outcome assessment, in this case based on the set of actual data that are generated over the course of treatment. The ORR RD was fully contained within the predefined acceptance range of [-12%, +12%]. Though the interpretation of this result needs to be balanced against not fully respecting randomisation (as no PPS analysis does) and regarding multiplicity considering its post-hoc character, this analysis in a more sensitive model of completing patients supports similarity of MB02 and Avastin with respect to the primary endpoint ORR.

Another relevant analysis approximating the per-protocol set was provided that excluded only those patients from the PPS who had major protocol deviations with potential impact on efficacy. This means that compared to the initial PPS definition those patients were included where the reason for the protocol violation was considered unrelated to later treatment efficacy. The intent of this request was to increase the sample size, and thereby to increase the precision of the information on the difference between the treatments, as based on a decreased sample size the PPS has by definition the property to have less statistical power. In the thereby defined analysis set and under the preferred analysis using multiple imputation adjusting for missing/NE, the ORR RD was -3.45 (95% CI -12.04 to 5.13) and thus like the complete cases set demonstrated comparable between the two treatments.

The ORR over time (Week 6, 12 and 18) does not show a consistent pattern and makes the suspicion of a treatment effect seem implausible, but rather suggests a random element.

Tumour burden on a continuous scale might be expected to increase sensitivity in terms of detecting potential treatment differences and is less prone to a biased assessment than ORR. All 95% CIs around the difference in means of %change in tumour burden show maintained response within +5/-5%, across both ITT and PPS. While it is noted that no margin was pre-specified for this endpoint, the extension of the confidence intervals for the difference in LSMeans is small in relation to the change from baseline, indicating good quantification of the differences and supporting similarity of the two treatments across the analysis. Though in the lack of pre-specified equivalence margins this result cannot be used as a sole confirmatory result, it can be considered sensitive to detect differences between the treatments arms and adds supporting evidence of similarity. Therefore, tumour burden strengthens the notion of similarity between MB02 and Avastin in the clinical assessment.

Other secondary efficacy endpoints were in consistency with the primary endpoint, with point estimates favouring EU Avastin. The slightly higher efficacy estimated for Avastin vs MB02 on the primary and secondary endpoints could be partly explained by the slightly lower exposure and number of cycles of IMP and chemotherapy in the MB02 arm than in the Avastin arm. Similar differences in exposure were also seen in the SAF set, where this imbalance did not lead to a crossing of the acceptance range in the ITT analysis for the ORR RD.

Nonetheless, the comparability exercise at the quality and functional level forms the basis of the biosimilarity demonstration, and similarity was demonstrated in the relevant characteristics. Similarity in PK was also concluded in a well conducted study in healthy volunteers. These are the most sensitive parts of the comparability exercise. In the efficacy and safety trial, the primary analysis in the ITT population met the predefined equivalence margins, and while the initial PPS analysis on the ORR

extended wider, several requested post-hoc results including sensitive models support similarity with respect to the primary endpoint ORR. The safety seems broadly comparable.

In summary, the initial ITT efficacy data and the requested additional results in sensitive analyses sets together with the evidence provided by analytical/ quality parameters, clinical PK, safety and immunogenicity support a conclusion of demonstration of biosimilarity based on the entire data package.

3.5. Extrapolation of safety and efficacy

The indications approved for the reference product Avastin were applied for Alymsys except for one concerning platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. The primary mechanism of action of bevacizumab is the inhibition of tumour vessel growth by blocking VEGF. The mode of action of bevacizumab is considered to be the same across all approved cancer indications of Avastin. The biological activities related to the mode of action have been comprehensively evaluated in the analytical similarity exercise. Extrapolation to all other approved indications of the reference product is considered acceptable.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Alymsys 25 mg/mL concentrate for solution for infusion is considered approvable.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Alymsys 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 Alymsys is favourable in the following indication:

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

Alymsys 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 of the SmPC.

Alymsys 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 of the SmPC.

Alymsys, 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.

Alymsys, 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.

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

Alymsys, 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 III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Alymsys, 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.

Alymsys, in combination with topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

Alymsys, 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.