CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761231Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	BLA
Application Number	761231
Submit Date	April 13, 2021
Received Date	April 13, 2021
BsUFA Goal Date	April 13, 2022
Division/Office	Division of Oncology 3
Review Completion Date	See review stamp date
Product Code Name	MB02
Proposed Non-Proprietary Name[1]	Bevacizumab-maly
Proposed Proprietary Name[1]	ALYMSYS
Pharmacologic Class	Vascular Endothelial Growth Factor (VEGF) inhibitor
Applicant	Amneal Pharmaceutical LLC (Amneal)
Applicant Proposed Indication(s)	1. Metastatic colorectal cancer • In combination with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment • In combination with fluoropyrimidine-, irinotecan- or fluoropyrimidine-oxaliplatin based chemotherapy for second line treatment in patients who have progressed on a first-line bevacizumab product containing regimen. Limitation of Use: not indicated for adjuvant treatment of colon cancer 2. Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer in combination with carboplatin and paclitaxel. 3. Recurrent glioblastoma in adults. 4. Metastatic renal cell carcinoma in combination with interferon alfa 5. Persistent, recurrent, or metastatic cervical cancer in combination with paclitaxel and cisplatin or paclitaxel and topotecan 6. Epithelial ovarian, fallopian tube or primary peritoneal cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemogherapy regimens.
Recommendation on Regulatory Action	Approval

[1] Section 8 of the Biosimilar Mutli-Disciplinary Evaluation and Review discusses the acceptability of the proposed proper and proprietary names, which are conditionally accepted until such time that the application is approved.

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management

Glossary

ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under the Curve
ATE	Arterial Thromboembolism
BIA	Biosimilar Initial Advisory
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BOR	Best Overall Response
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CCA	Comparative Analytical Assessment
CCS	Clinical Comparative Study
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CN-Avastin	China-approved Avastin
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CMO	Contract Manufacturing Organization
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficient of Variation
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DOR	Duration of Response
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRC	Independent Review Committee
iPSP	Initial Pediatric Study Plan
IQA	Integrated Quality Assessment
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NSCLC	Non-Small Cell Lung Cancer
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Phamaceutical Quality
ORR	Overall Response Rate
OS	Overall Survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PFS	Progression-Free Survival
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPc	Summary of Product Characteristics
SMQ	STnadard MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
US-Avastin	U.S.-licensed Avastin
USPI	United States Prescribing Information
VTE	Venous Thromboembolism

Signatures

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1. Executive Summary

1.1. Product Introduction

Amneal Pharmaceuticals (Amneal; also referred to as "Applicant" in this review) submitted this biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for MB02 as a proposed biosimilar to US-licensed Avastin (bevacizumab). On July 12, 2021, FDA issued a letter informing Amneal of the conditional acceptance of the proposed proprietary name Alymsys, and the proposed nonproprietary name bevacizumab-maly was determined to be conditionally acceptable on February 1, 2022.

Like US-licensed Avastin (US-Avastin), MB02 is a is recombinant humanized monoclonal IgG1 antibody that binds vascular endothelial growth factor-A (VEGF).

The following are the indications for which Amneal is seeking licensure and for which US-Avastin has been previously approved:

- Metastatic colorectal cancer (CRC), in combination with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment.
- Metastatic colorectal cancer (CRC), in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second- line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen.
  Limitation of Use: not indicated for adjuvant treatment of colon cancer
- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel for the first-line treatment,.
- Recurrent glioblastoma (GBM) in adults.
- Metastatic renal cell carcinoma (RCC) in combination with interferon alfa .
- Persistent, recurrent, or metastatic cervical cancer in combination with paclitaxel and cisplatin or paclitaxel and topotecan .
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens

US-Avastin is also approved for the treatment of Stage 3 or 4 epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection; platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer; and in combination with atezolizumab, for the treatment of unresectable or metastatic hepatocellular carcinoma. These indications are currently protected by orphan drug exclusivity. Amneal is not seeking licensure for these indications at this time.

MB02 is administered as an intravenous infusion. The proposed dosing regimens for each indication that Amneal is seeking licensure for, and for which US-Avastin has been previously approved[2] are listed below.

- Metastatic colorectal cancer
  - 5 mg/kg every 2 weeks intravenously in combination with bolus-IFL.
  - 10 mg/kg every 2 weeks intravenously in combination with FOLFOX4.
  - 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a first-line bevacizumab product-containing regimen.
- First line non-squamous non-small cell lung cancer (NSCLC)
  - 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel
- Recurrent glioblastoma (GBM)
  - 10 mg/kg intravenously every 2 weeks
- Metastatic renal cell carcinoma (RCC)
  - 10 mg/kg intravenously every 2 weeks in combination with interferon alpha

[2] FDA-approved Avastin labeling

- Persistent, recurrent, or metastatic cervical cancer
  - 15mg/kg intravenously in combination with paclitaxel and cisplatin, paclitaxel, or topotecan
- Platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.
  - 10 mg/kg intravenously every 2 weeks in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week
  - 15 mg/kg intravenously every 3 weeks in combination with topotecan every 3 weeks.

MB02 is a clear to slightly opalescent, colorless to pale brown solution that will be supplied in cartons containing one single-dose vial in 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) strengths.

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

The mechanism of action for US-Avastin (for all approved indications) is through binding to VEGF which prevents the interaction of VEGF with its receptors on the surface of endothelial cells. Like US-Avastin, MB02 is a recombinant humanized IgG1 kappa monoclonal antibody directed against VEGF. Amneal provided data (please refer to the Office of Product Quality Integrated Quality Assessment) that supports the conclusion that MB02 and US-Avastin utilize the same mechanism of action based on results from the following assays: in vitro inhibition of VEGF-induced human umbilical vein endothelial cell (HUVEC) proliferation; and binding to human VEGF165/VEGF121/VEGF189, C1q, FcγR receptors, and FcRn. MB02 also exhibited a lack of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) activity, as expected based on a similar lack of activity with US-Avastin.

US-Avastin and MB02 are injections, for intravenous use. Both US-Avastin and MB02 are supplied in single-dose vials of 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL).

The conditions of use for which Amneal is seeking licensure for MB02 have been previously approved for the reference product, US-Avastin.

1.4. Inspection of Manufacturing Facilities

An inspection of drug substance manufacturing site, (b) (4) , occurred during (b) (4) . A 9-item Form FDA 483 was issued to the firm at the end of the inspection. The firm was initially classified as VAI with an approval recommendation given for the submission, based on the inspectional findings. The firm's responses and corrective actions to the FDA Form 483 observations were considered adequate as they have corrected or committed to correct the observed deficiencies.

In lieu of an on-site pre-license inspection for the drug product manufacturing facility, (b) (4) a review of requested manufacturing site records under Section 704(a)(4) was conducted and found satisfactory. The proposed drug product manufacturing facility is found to be acceptable to support the approval of BLA 761231.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Ameal provided adequate data to establish the scientific bridge to justify the relevance of data generated from the Study MB02-C-02-17, which used EU-Avastin as the non-U.S.-licensed comparator product, to the assessment of biosimilarity:

- The Office of Pharmaceutical Products (OPQ), CDER has determined that based on the data provided by the Applicant, the analytical component of the scientific bridge between MB02, US-Avastin and EU-Avastin was established. The comparative analytical assessment was comprised of extensive comparative physicochemical and functional assessment of the quality attributes of MB02 and US-Avastin. Amneal used a comprehensive selection of analytical methods that were suitable to evaluate the critical quality attributes of MB02 and US-Avastin to support the demonstration that the products are highly similar. Numbers of lots tested and statistical analyses were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. Based on FDA's assessment of the data, the review team also concludes that Amneal established the analytical component of the scientific bridge between MB02, US-Avastin, and EU-Avastin, using the same methods and statistical approaches used to evaluate similarity between MB02 and US-Avastin.

- The Office of Clinical Pharmacology (OCP) has determined that based on the data provided by the Applicant, the PK data establish the PK component of the scientific bridge. In Study MB02-A-05-18, a PK similarity study in healthy male subjects, following a single intravenous infusion 3 mg/kg of MB02, US-Avastin or EU-Avastin, the 90% CIs for the GMRs of MB-02 to US-Avastin; MB02 to EU-Avastin; EU-Avastin to US-Avastin for the tested PK parameters (i.e. $AUC_{0\text{-}inf}$ and

C_{max}) were all within the PK similarity acceptance interval of 80-125%. These pairwise comparisons met the pre-specified criteria for PK similarity; thus, the PK portion of the scientific bridge was established to support the relevance of the data generated using EU-Avastin as the comparator in the comparative clinical study (MB02-C-02-17).

1.6. Biosimilarity Assessment

Comparative Analytical Studies[3]	
Summary of Evidence	• MB02 has the same dosage form and route of administration as US-Avastin. Amneal seeks approval for 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL) strengths in a single-dose vial presentation; US-Avastin is available at these strengths and in this presentation. The quality attributes analyzed in the comparative analytical assessment support a demonstration that MB02 is highly similar to US-Avastin, notwithstanding minor differences in clinically inactive components. Each strength of MB02 in a vial is the same strength as US-Avastin. • The analytical component of the scientific bridge between MB02, US-Avastin and EU-Avastin was established to justify the relevance of the data generated from studies using EU-Avastin as a comparator to the assessment of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	

[3]Refer to the Comparative Analytical Assessment (CAA) Chapter of the IQA for additional information regarding comparative analytical data.

Summary of Evidence	• The Applicant compared the toxicity profile of MB02 and EU-Avastin in cynomolgus monkeys. The observed toxicities and the toxicokinetic data were similar between MB02 and EU-Avastin. Given the scientific bridge was established between MB02, US-Avastin and EU-Avastin, the information in the pharmacology/toxicology assessment support the demonstration of biosimilarity.
Assessment of Residual Uncertainties	• From the pharmacology/toxicology perspective, there are no residual uncertainties.
Clinical Studies	
Clinical Pharmacology Studies	

Summary of Evidence	• Amneal submitted pharmacokinetic (PK) data and immunogenicity data from two clinical studies to support the demonstration of no clinically meaningful differences between MB02 and US-Avastin and to establish the PK component of the bridge to justify the relevance of data generated with EU-Avastin to the assessment of biosimilarity. • Study MB02-A-05-18 is a randomized, double-blind, single-dose, parallel, 3-arm PK similarity study between MB02 (n = 38), EU-Avastin (n = 38), and US-Avastin (n = 38) in healthy male subjects at a dose of 3 mg/kg. The geometric mean ratio (GMR) of the primary PK parameter (AUC0-inf) along with the 90% confidence interval (CI) for all pairwise comparisons were within the prespecified margin of 80% to 125%. The results of the study establish PK similarity between MB02 and US-Avastin and the PK portion of the scientific bridge between MB02, US-Avastin and EU-Avastin. • In Study MB02-C-02-17, the incidence of immunogenicity was comparable between MB02 and EU-Avastin. The reported incidence of anti-drug antibodies (ADA) was 17% in the MB02 arm versus 16.1% in the EU-Avastin arm over the course of the study. The reported incidence of neutralizing anti-drug antibodies (NAbs) was 3.2% in the MB02 arm versus 4.2% in the EU-Avastin arm over the course of the study. There was no apparent impact of ADA or NAbs on safety, or efficacy.
Assessment of Residual Uncertainties	• From the clinical pharmacology perspective, there are no residual uncertainties.
Additional Clinical Studies	

Summary of Evidence	• In the MB02-C-02-17 comparative clinical study, 627 patients with metastatic NSCLC and no prior chemotherapy for metastatic disease were randomized (1:1) to receive chemotherapy in combination with MB02 or EU-Avastin 15 mg/kg every 3 weeks for up to 6 cycles, followed by MB02 or EU-Avastin as single agents. Of the 627 patients, 315 and 312 patients were randomized to the MB02 and EU-Avastin arms respectively. Overall response rate (ORR) at Week 18 was 40% (95% CI: 35%,46%) in the MB02 arm and 45% (95% CI: 39%, 50%) in the EU-Avastin arm. The estimated ratio of ORR is 0.91 and its 90% CI is (0.78, 1.06) which is within the pre-specified and FDA recommended similarity margin of (0.73; 1.36). Secondary and sensitivity analyses of the primary endpoint produced similar results. Median duration of response, a secondary endpoint, was 30.3 weeks (95% CI: 28.3, 38.4) and 37.1 weeks (95% CI: 30.4, 39.6) in the MB02 and EU-Avastin arms, respectively. There were no meaningful differences in safety outcomes. • Given the analytical and PK components of the scientific bridge were established between MB02, US-Avastin and EU-Avastin to justify the relevance of clinical data generated with EU-Avastin, the results from comparative clinical study MB02-C-02-17 support a demonstration of no clinically meaningful differences between MB02 and US-Avastin in the studied indication (NSCLC).
Assessment of Residual Uncertainties	• From the clinical and statistical perspective, there are no residual uncertainties.
Extrapolation	

Summary of Evidence	• Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors, inhibiting the formation of new tumor vasculature. In each approved indication, the mechanism of action (MOA) of bevacizumab is to inhibit VEGF-induced angiogenesis. The Applicant provided adequate justification to support that MB02 has the same known and potential mechanisms of action as U.S.-Avastin for all the indications for which they are seeking approval. • As summarized in the Avastin USPI, bevacizumab exhibits a dose proportional and linear PK profile over the studied dose range (1–20 mg/kg) and similar PK characteristics across CRC, NSCLC, breast cancer, RCC, GBM, and cervical cancer (Avastin USPI; EMA Avastin SmPC; Lu JF, 2008; Han K., 2016). In Study MB02-A-05-18, the GMR of the primary PK parameter (AUC0-inf) along with the 90% confidence interval (CI) for all pairwise comparisons (MB02 vs. US-Avastin, MB02 vs. EU-Avastin, and US-Avastin vs. EU-Avastin) were within the prespecified margin of 80% to 125%, establishing the PK similarity between MB02 and US-Avastin and the PK portion of the scientific bridge between MB02, US-Avastin and EU-Avastin to justify the relevance of data used f EU-Avastin in the comparative clinical study (CCS). Since similar PK was demonstrated between MB02 and US-Avastin, a similar PK profile would be expected for MB02 in patients across the indications being sought for licensure. • The analysis of studies MB02-A-05-18 and MB02-C-02-17 indicate that immunogenicity was similar and that treatment of subjects with NSCLC with either MB02 or EU-Avastin or US-Avastin results in similar rates of ADAs and neutralizing antibodies. Based on results from study MB02-A-05-18 in healthy subjects, after single dose, there was no meaningful effect of immunogenicity on the PK of MB02. The Applicant provided adequate justification that similar immunogenicity is expected between MB02 and US-Avastin for all indications being sought for licensure.

	• The expected toxicities of bevacizumab are well characterized and are summarized in the Avastin USPI. While the incidence of specific toxicities may differ across the indications (e.g., fistula occurs more frequently in patients with cervical cancer while hemoptysis occurs more frequently in patients with NSCLC), due to the common MOA, the differing toxicities are predictable in each indication for which licensure is sought for MB02 in this application. Data from Study MB02-C-02-17 demonstrated that the type and incidence of treatment-emergent adverse events of special interest were similar between MB02 and EU-Avastin and that there were no meaningful differences between arms.
Assessment of Residual Uncertainties	• There are no residual uncertainties regardingextrapolation of data and information to support licensure of MB02 as a biosimilar to US-Avastin for the indications being sought.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that MB02 is highly similar to U.S.-Avastin, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between MB02 and U.S.-Avastin in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that MB02 is biosimilar to U.S.-Avastin for each of the following indications for which U.S.-Avastin has been previously approved and for which the Applicant is seeking licensure of MB02[4]:

- Metastatic colorectal cancer, in combination with intravenous 5-fluorouracil– based chemotherapy for first- or second-line treatment.
- Metastatic colorectal cancer, in combination with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second- line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen.
  Limitation of Use: not indicated for adjuvant treatment of colon cancer

[4]The proposed PRODUCT CODE NAME labeling states: BIOSIMILARITY STATEMENT IN DRAFT LABELING.

- In combination with carboplatin and paclitaxel for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer,.
- Recurrent glioblastoma in adults.
- In combination with interferon alfa for the treatment of metastatic renal cell carcinoma,.
- In combination with paclitaxel and cisplatin or paclitaxel and topotecan for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens

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2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

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

This summary of presumbission regulatory history (all meetings were conducted under IND 135128) will only describe interactions and comments regarding the clinical development of MB02. For further details on agreements and advice given regarding product quality, please refer to the respective reviews.

- **June 30, 2017:** A Biosimilar Biological Product Development Type 2 (BPD Type 2) meeting was held to discuss the development plan for MB02. Key clinical highlights from the meeting include:
  - mAbxience (the original IND sponsor) conducted the initial development of MB02 with material manufactured by a contract manufacturing organization (CMO), referred to as MB02-DK. FDA did not agree with the use of data generated with MB02-DK to support the assessment of no clinically meaningful differences. FDA advised that clinical studies should not be initiated until the results of planned studies assessing the analytical similarity between MB02, US- Avastin, and EU-Avastin are available for review to FDA.
  - FDA agreed with inclusion of the E4599, JO19907, aVF0757, AVAiL, and BEYOND trials in the meta-analysis to characterize the historical treatment effects of bevacizumab on overall response rate (ORR) in patients with NSCLC.
  - FDA did not agree with pooling the immunogenicity and safety data from Study

BEVZ-A-02-13 conducted with the MB02-DK product with the immunogenicity and safety data obtained in the 2 proposed clinical studies to be conducted with MB02. FDA did agree with mAbxience's plan to use a single-assay approach in the proposed PK similarity study, BEVZ92-A-02-18 and in the proposed comparative clinical study (CCS), MB02-C-02-17.

- **July 31, 2017:** Based on the BPD Type 2 meeting, FDA provided additional comments to address the Sonsor's proposed primary endpoint of ORR, in alignment with EMA guidelines recommendations. Instead, FDA recommended best overall response (BOR) as the primary endpoint instead of ORR at Week 18..
- **December 1, 2017:** FDA provided additional advice in the context of the development plan described in the BPD Type 2 meeting package and meeting minutes. FDA recommended using an equivalence margin of (0.73, 1.36) for the primary ORR endpoint for the proposed comparative clinical study, Study MB02-C-02-17 in patients with NSCLC.
- **October 4, 2018:** A Biosimilar Biological Product Development (BPD) Type 2 meeting was held to discuss the clinical development plan.
  - FDA agreed to ORR at Week 18 as the primary endpoint and to the timing of the primary analysis for Study MB02-C-02-17, proposed to occur when the last randomized patient was assessed for ORR at Week 18.
  - FDA recommended that the total sample size be increased to 600 patients to ensure adequate power and allow assessments of secondary endpoints.
  - For the secondary endpoints of progression free survival (PFS) and overall survival (OS), FDA recommended against evaluating these time-to-event endpoints using landmark rates. FDA also recommendeduse of the log-rank test and the Cox model to analyze PFS and OS. In a subsequent protocol revision (Amendment 1, dated December 3, 2018), the sponsor changed margin and sample size and stated that all subject data on PFS and OS will be included accrued up to the cut-off time point for the time-to-event analysis.
  - FDA did not agree with inclusion of Study 20120265 in mAbxience's metanalysis to the previously proposed 5 trials for the purpose of conducting a metanalysis for margin determination because the study was not designed to demonstrate the effect of the addition of bevacizumab to a backbone therapy; instead, FDA stated that the study was designed to support a demonstration of no clinically meaningful differences between ABP215 (MVASI) and US-Avastin and therefore could not be used to estimate the magnitude of the bevacizumab treatment effect.
  - FDA agreed that the design of the ongoing PK similarity study MB02-A-05-18, appeared acceptable; however, FDA recommended increasing the sample size to ensure sufficient power (e.g., 90% rather than 85%). During the meeting, FDA agreed to the proposed sample size but clarified that the drop-out rate should be pre-specified in the sample size calculation and that drop-outs should not be replaced. A drop-out rate of ≤ 10% would be acceptable for the proposed PK similarity study.
- **October 14, 2020:** BPD Type 2 meeting held to discuss and obtain feedback on the adequacy of the CMC and clinical development programs. mAbxience requested FDA agreement that no additional clinical evidence would be needed to support a

demonstration of biosimilarity that is based on the in-vitro analytical comparability between pre-post changes batches, and considering that the proposed clinical program addressed residual uncertainties, if any existed, from the analytical similarity/comparability data. FDA stated that while the proposed approach appeared reasonable, the need for additional clinical studies would be a review issue.

- **February 1, 2021:** BPD Type 4 meeting held to discuss the content and format of the proposed BLA. Based upon the information provided in the meeting package, the overall content and structure of the proposed BLA appeared acceptable, while noting a final determination will be made during filing review.

  FDA requested that mAxbience include the following in the original BLA submission:
  - A stand-alone document in Module 2 that provides the justification for extrapolation to other indications.
  - A flag in the ADAM datasets ADAE, ADLP, and ADVS that identifies events occurring during the combination chemotherapy/MB02-EU-Avastin period. FDA did not agree that the variables currently included (b) (4) which identify the monotherapy period) adequately identified adverse events or laboratory data in patients who received less than 6 cycles of combination therapy before switching to the monotherapy portion. FDA stated the datasets should contain a flag identifying events occurring during the combination chemotherapy/MB02-EU-Avastin period. mAbxience agreed to provide the information in the BLA submission.
  - An.xpt or .xlxs file with the financial disclosure information (in addition to the pdf file);
  - SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis.

  FDA agreed to mAbxience's proposal to submit studies MB02-A-05-18 and MB02-C-02-17 (STELLA) to support the comparative clinical and PK assessments in the proposed original BLA. Regarding the proposed comparative analytical assessment studies, FDA stated that the overall testing strategy provided in the meeting package and the general comparability approach of the selected product quality attributes appeared appropriate.

  FDA reiterated that mAbxience should not submit a marketing application before FDA has confirmed agreement on the iPSP. FDA noted that the agreed iPSP can be amended to the application during the review process.

2.2. Studies Submitted by the Applicant

Refer to the Comparative Analytical Assessment (CAA) Chapter of the IQA for additional information regarding comparative analytical data.

Table 1. Relevant Nonclinical Studies Submitted

Study Title	Study Number	Species	Number Per Treatment Arm	Study Duration	Route of administration/Dose
Animal Studies					
BEVZ92 (Biosimilar) and EU Avastin: 28 Day Intravenous (Infusion) Administration Toxicity Study in the Monkey	8255467 (BEVZ92-NC-01)	Cynomolgus Monkey	3/sex/group	1 month	Intravenous; 50 mg/kg

Table 2. MB02 Relevant Clinical Studies Submitted

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Studies					
MB02-A-05-18		Comparative pharmacokinetics and safety of MB02, US-Avastin, and EU-Avastin Primary: To investigate and compare the PK profiles of MB02, US-Avastin, and EU-Avastin Secondary: To compare other PK parameters and the safety profiles and immunogenicity of MB02, US- Avastin and EU-Avastin	Randomized, double blind, three arm, single dose, PK similarity study Subjects received a single 3 mg/kg dose of either MB02, US-Avastin, or EU-Avastin by IV infusion over 90 minutes. Patients were stratified into 2 groups based on weight (stratum 1: ≥ 60 to < 77.5 kg and stratum 2: > 77.5 to ≤ 95.0 kg	Healthy adult male	*MB02: 38* *US-Avastin: 38* *EU-Avastin: 38*
MB02-A-06-20		PK comparison between MB02-SP (the product used during clinical development), MB02-DM (the to-be-marketed product), and US-Avastin	Randomized, double blind, single dose, PK comparability study Subjects received a single 1 mg/kg dose of either MB02-SP, MP02-DM, or US-Avastin, by IV infusion over 90 minutes.	Healthy adult male	MB02-SP: 37 MB02-DM: 39 US-Avastin: 38

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
Comparative Clinical Study					
MB02-C-02-17		Primary: To compare ORR of MB02 and EU-Avastin in patients with NSCLC receiving concomitant carboplatin and paclitaxel Secondary: To evaluate safety profile, immunogenicity and other efficacy parameters (PFS and OS) of MB02 compared to EU-Avastin	Randomized, double-blind, parallel group, multicenter study. Patients randomized 1:1 to receive MB02 or EU-Avastin (15 mg/kg IV on Day 1 of every 21-day cycle) concurrently with chemotherapy (paclitaxel 200 mg/m2 and carboplatin AUC 6 on Day 1 of every 21-day cycle) up to cycle 6 and then continuation of MB02 or EU-Avastin alone.	Patients with Stage IIIB/IV non-squamous NSCLC	MB02:315 EU-Avastin: 312

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3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

To support a demonstration that MB02 is highly similar to US-Avastin, a comparative analytical assessment was conducted. The analytical component of the scientific bridge was also established, which consisted of three pairwise comparisons between MB02 to US-Avastin, MB02 to EU-Avastin and EU-Avastin to US-Avastin. There are more than 15 lots of MB02, 19 lots of US-Avastin and 17 lots of EU-Avastin with expiration dates ranging from October 2017 through September 2021, was provided. The ages at the time of testing of US- and EU-Avastin were adequate to capture potential reference product analytical differences over time.

There were two process iterations during the commercial development stage of MB02: the SP (used in comparative clinical studies) and DM processes. These process

iterations had the goal of enhancing process consistency and further improving the analytical similarity between MB02 and US-Avastin. Improvements were made in the MB02-SP proces (b) (4)

Although the data from the proposed commercial (MB02-DM) process better aligns with US-Avastin, which strengthens the support for a demonstration that MB02 is highly similar to US-Avastin, these changes would not preclude the ability to leverage the clinical studies that were performed with MB02-SP lots as they were found to be comparable with lots manufactured by the proposed commercial process (MB02-DM).

The comparative analytical assessment was comprised of extensive comparative physicochemical and functional assessment of the quality attributes of MB02, EU-Avastin, and US-Avastin. Amneal assessed quality attributes using an approach based on risk and criticality for statistical evaluation of analytical results. The highest-ranking attributes that were tested using quantitative assays were evaluated using equivalence testing. Attributes that were considered moderate for criticality that were tested using quantitative assays were evaluated using quality ranges that took both manufacturing variability of US-Avastin as well as assay variability into account. The least critical attributes, and those attributes that were tested using qualitative assays, were evaluated using a comparison of visual displays of the data. Results from method validation or qualification studies support the suitability of the methods used in the comparative analytical assessment.

Amneal is seeking licensure of two strengths of MB02, 100 mg/4 mL and 400 mg/16 mL per vial. US-Avastin is available in the same two strengths, 100 mg/4 mL and 400 mg/16 mL, single-dose vials for intravenous infusion. OPQ's assessment of the MB02 and US-Avastin data supports that MB02 has been demonstrated to be highly similar to US-Avastin, notwithstanding minor differences in clinically inactive components. MB02 has the same strength, dosage form, and route of administration as US-Avastin. Amneal used a comprehensive selection of analytical methods that were suitable to evaluate the critical quality attributes of MB02 and US-Avastin to support the demonstration that the products are highly similar. Numbers of lots tested and statistical analyses were appropriate to allow for a meaningful evaluation of the results of the comparative analytical studies. While some minor differences were observed in a subset of quality attributes, these differences were determined not to preclude a demonstration that MB02 and US-Avastin are highly similar.

Based on the assessment of the data, OPQ also concludes that Amneal established the analytical component of the scientific bridge between MB02, US-Avastin, and EU-Avastin, using the same methods and statistical approaches used to support a demonstration that MB02 is highly similarity to US-Avastin. The analytical component of the scientific bridge was established to justify the relevance of the data generated from studies using EU-Avastin as a comparator to the assessment of biosimilarity. Although minor differences were observed in certain attributes for comparisons between MB02, US-Avastin, and EU-Avastin, the Applicant provided adequate data and information to

resolve the residual uncertainty raised by these differences. The observed differences do not preclude a demonstration that MB02 is highly similar to US-Avastin or the establishment of the analytical component of the scientific bridge.

3.2. Devices

Not applicable.

3.2.1. Center for Devices and Radiological Health (CDRH)

Not applicable.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

Not applicable.

3.3. Office of Study Integrity and Surveillance (OSIS)

OSIS conducted a review of the clinical portion of Study MB02-A-05-18 conducted at PAREXEL International GmbH, Berlin, Germany. No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI). OSIS (see review in darrts uploaded February 11, 2022) concluded that the clinical data from the audited study are reliable.

OSIS conducted a remote record review (RRR) of the analytical portion of Studies MB02-A-05-18 and MB02-C-02-17 (b) (4) . An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic. Based on the review of the inspectional findings and the study records during the RRR, OSIS concluded that the clinical and analytical data from Studies MB02-A-05-18 and MB02-C-02-17 are reliable (see review in darrts uploaded February 11, 2022).

3.4. Office of Scientific Investigations (OSI)

The clinical and statistical review teams conducted an analysis of enrollment, efficacy, safety results, and protocol deviations at the clinical sites enrolling patients in Study MB02-C-02-17. There were no clear outliers in efficacy or safety outcomes. The highest enrolling site, Site 2804 (Dr. Trukhin), was not chosen because it was recently inspected in March 2020 with a finding of No Action Indicated. The Division initially requested inspections at two clinical sites, noting that only foreign data were submitted to support the application. The two clinical sites, Site 2807 (Dr. Levenko) and Site 2801 (Dr. Bondarenko) were selected as they were high enrolling sites. Both selected sites are in the Ukraine. In December 2021, the US Department of State issued level 4 travel

advisory for Ukraine (Do Not Travel) due to COVID-19 and increased threats from Russia[5]. Thus, inspection of both selected clinical sites was unable to be conducted due to the inability to obtain clearance to travel to Ukraine. However, Dr. Bondarenko has had 3 previous inspections (2013, 2017 and 2018), all with an inspectional finding of No Action Indicated. Dr. Levenko has not previously been inspected. Given that the two high enrollment sites were recently inspected by FDA and there were no significant findings, and the finding of no significant outliers in terms of results, safety, or protocol violations, no other site inspections were requested.

The study sponsor, mAbxience Research SL (former IND Sponsor), and the clinical research organization, (b) (4) were also chosen for inspection, as neither had been inspected previously. The inspections were onsite. The inspections revealed no significant findings. Based on the results of these inspections and a remote regulatory assessment, the study appears to have been conducted adequately and the data generated by the inspected entities appear to be acceptable in support of the BLA.

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4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

The Applicant compared the activity and safety of MB02 and EU-Avastin in cynomolgus monkeys. A review of these studies is included in the Nonclinical Appendix, Section 14.3. MB02 (BEVZ92) 50 mg/kg and EU-Avastin 50 mg/kg were administered to cynomolgus monkeys by intravenous infusion once every 3 days for 28 days for a total of 8 doses. There were no toxicologically significant differences between MB02 and EU-Avastin noted in this study. Given the scientific bridge was established between MB02, US-Avastin and EU-Avastin, the information in the pharmacology/toxicology assessment support the demonstration of biosimilarity.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

[5] https://travel.state.gov/content/travel/en/traveladvisories/traveladvisories/ukraine-travel-advisory.html

4.2. Product Information

Product Formulation

Table 3.2.P.1 - 1 Quantitative and Qualitative Composition of MB02 DP

Component	Amount per mL	Amount per 4 mL vial	Amount per 16 mL vial	Function	Quality Standard
Bevacizumab	25 mg	100 mg	400 mg	Active Substance	*In-house* [a]
Trehalose, dihydrate	60.0 mg	240.0 mg	960.0 mg	(b) (4)	*Ph. Eur., USP, JP*
Monobasic Sodium Phosphate, monohydrate	5.8 mg	23.2 mg	92.8 mg		*USP*
Dibasic Sodium Phosphate, anhydrous	1.2 mg	4.8 mg	19.2 mg		*Ph. Eur., USP, JPE*
Polysorbate 20	0.4 mg	1.6 mg	6.4 mg		*Ph. Eur., USP, JPE*
Water for injection	q.s.	(q.s. to 4 mL)	(q.s. to 16 mL)		*Ph. Eur., USP*

q.s. = quantum sufficit (sufficient quantity).

[a] Tested according to the internal specification (refer to 3.2.S.4.1 Specification).

[b] Buffer is used to adjust pH to 6.2.

(Excerpted from Applicant's submission)

Comments on Excipients

There are no novel excipients. The formulations for MB02 and US-Avastin are different; however, the excipients in MB02 are below the levels in US-Avastin and are not of toxicological concern.

Comments on Impurities of Concern

There are no impurities/degradants of concern.

Authors:

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Nonclinical Reviewer

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Nonclinical Team Lead

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

The applicant submitted pharmacokinetic, immunogencity, safety, and efficacy data to support a demonstration of no clinically meaningful differences between MB02 and US-Avastin.

Study MB02-A-05-18 is a single-dose, parallel, randomized, 3-arm, double-blind, PK similarity study in healthy male subjects comparing a 3 mg/kg dose of MB02, US-Avastin and EU-Avastin. The 90% confidence intervals (CI) of the geometric mean

ratios (GMRs) of the primary endpoint $AUC_{0\text{-}inf}$ for all pairwise comparisons were within the pre-specified PK similarity acceptance criterion of 80 - 125%. The results of the study established PK similarity between MB02 and US-Avastin and the PK protion of the scientific bridge between US-Avastin and EU-Avastin.

Study MB02-A-06-20 was conducted to compare PK between MB02-SP (the product used during clinical development), MB02-DM (the to-be-marketed product), and US-Avastin. The 90% CI for GMRs of AUC0-inf, AUC0-t, and Cmax were within 80 - 125% for comparisons between MB02-SP to MB02-DM; MB02-SP to US-Avastin; MB02-DM to US- Avastin. These results support comparability between MB02-SP and MB02-DM and confirm that the changes in the manufacturing process do not preclude the ability to leverage the clinical studies that were performed with MB02-SP lots.

Study MB02-C-02-17 is a randomized, double-blind, parallel, 2-arm, comparative clinical study comparing efficacy, safety and immunogenicity of MB02 to EU-Avastin, both in combination with paclitaxel and carboplatin in patients with Stage IIIB/IV nonsquamous NSCLC.In the study population, the immunogenicity of MB02 was comparable to that of EU-Avastin. The ADA incidence was 17% and 16.1% in the MB02 and EU-Avastin arms respectively after the administration of multiple doses.

Overall, the PK results from Study MB02-A-05-18 and Study MB02-C-02-17 support the demonstration of no clinically meaningful differences between MB02 and US-Avastin and add to the totality of evidence to support a demonstration of biosimilarity between MB02 and US-Avastin.

Table 3. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics Similarity	• PK similarity has been demonstrated between MB02 and US-Avastin, and supports a demonstration of no clinically meaningful differences between MB02 and US-Avastin. • PK similarity between MB02, EU-Avastin and US-Avastin provides the PK component of the scientific bridge to support the relevance of comparative data generated using EU-Avastin in Study MB02-C-02-17 to the assessment of biosimilarity.
Pharmacodynamics Similarity	• Not applicable
Immunogenicity	• There was a comparable incidence of ADA and NAbs formation between between MB02 and EU-Avastin in patients with Stage IIIB/IV nonsquamous NSCLC in Study MB02-C-02-17. Because the scientific bridge was established to justify the relevance of data

	generated with EU-Avastin, these data support a desmonstration of no clinical meaningful differences between MB02 and US-Avastin.
Other (PK Comparability)	• PK of MB02-SP (the product used during clinical development), MB02-DM (the to-be-marketed product) and US-Avastin was shown to be comparable in Study MB02-A-06-20.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

Clinical study MB02-A-05-18 demonstrated PK similarity of MB02, US-Avastin, and EU-Avastin and showed no increase in immunogenicity risk for MB02. There was comparable immunogenicity incidence between between MB02 and EU-Avastin in patients with NSCLC in Study MB02-C-02-17. The PK portion of the scientific bridge was established to support the relevance of the data generated using EU-Avastin as the comparator in the comparative clinical study (MB02-C-02-17).There are no residual uncertainties from the clinical pharmacology assessment.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

In Study MB02-A-05-18, a PK similarity study in healthy male subjects, following a single intravenous infusion 3 mg/kg of MB02, US-Avastin or EU-Avastin, the 90% CIs for the GMRs of MB-02 to US-Avastin; MB02 to EU-Avastin; EU-Avastin to US-Avastin for the tested PK parameters (i.e. $AUC_{0\text{-}inf}$ and C_{max}) were all within the PK similarity acceptance interval of 80-125%. These pairwise comparisons met the pre-specified criteria for PK similarity; thus, the PK portion of the scientific bridge was established to support the relevance of the data generated using EU-Avastin as the comparator in the comparative clinical study (MB02-C-02-17).

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

Clinical Pharmacology Study Design Features

The applicant conducted one PK similarity study (i.e., Study MB02-A-05-18) with MB-02, US-Avastin, and EU-Avastin in healthy male subjects as described in Table 2 in Section **Error! Reference source not found.**. The design of Study MB02-A-05-18 is considered adequate to demonstrate PK similarity for the following reasons:

- A single-dose study in healthy subjects is considered safe and an appropriately sensitive population.
- US-Avastin PK is linear in the dose range of 1 to 10 mg/kg and a single dose of 3 mg/kg was selected to minimize any safety concerns while providing

interpretable data to detect and evaluate any potential differences in the PK profiles of MB02, US-Avastin and EU-Avastin. .

- A parallel design was used to assess the PK similarity of MB-02, US-Avastin, and EU-Avastin because of the long half-life (approximately 20 days) of bevacizumab.

in Study MB02-A-06-20, PK of MB02-SP (the product used during clinical development), MB02-DM (the to-be-marketed product) and US-Avastin was compared.

In Study MB02-C-02-17, immunogenicity was compared between MB-02 and EU-Avastin after multiple doses to characterize the onset and persistence of ADA and NAb response in both arms.

Refer to Table 2 in Section **Error! Reference source not found.**. for a summary of the studies listed above. This clinical pharmacology review primarily focused on the PK similarity Study MB02-A-05-18. We also evaluated the immunogenicity in Study MB02-C-02-17.

Clinical Pharmacology Study Endpoints

In Study MB02-A-05-18, the prespecified endpoint was $AUC_{0\text{-}inf}$, and PK similarity would be established if the 90% CI of the GMR of $AUC_{0\text{-}inf}$ for all pairwise comparisons were within 80% to 125%. The endpoints are acceptable. The study design elements and the PK similarity assessments were aligned with the FDA guidance for industry Clinical Pharmacology Data To Support A Demonstration Of Biosimilarity To A Reference Product", (December 2016).

PK blood samples were collected at pre-dose, on Day 1 (end of infusion, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h post-dose), Day 2, 3, 4, 5, 6, 7, 8, 10, 14, 21, 28, 42, 56, 78, 100 (2376 hr) post-dose.

Bioanalytical PK Method and Performance

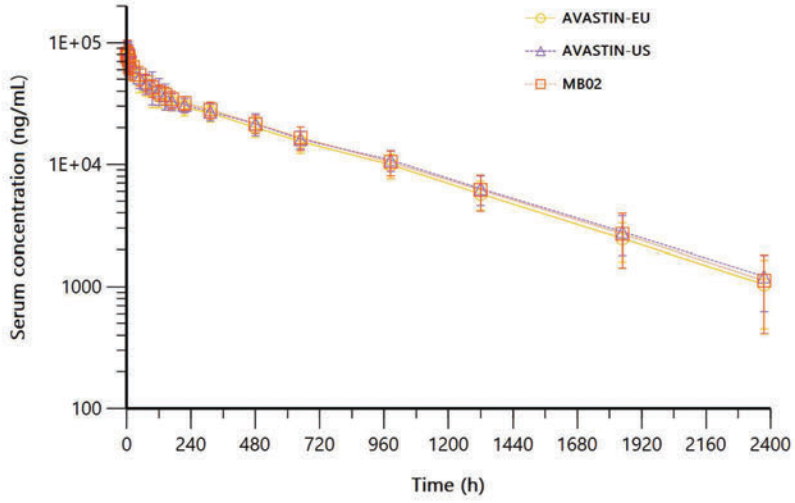
The serum concentrations of MB02, EU-Avastin and US-Avastin were appropriately quantified using validated enzyme-linked immunosorbent assay (ELISA) in Study MB02-A-05-18 (validation report 8370499 and analysis report 8412385). The LLOQ and ULOQ were 400 and 4000 ng/mL, respectively. For the method validation, the selectivity and matrix effect (including lipemic and hemolysed matrix), dilutional linearity and hook effect, accuracy, precision, stability (benchtop, refrigerator and freeze-thaw) and long-term storage were all acceptable. Bioanalytical similarity was demonstrated to support the use of a single bioanalytical method in sample analysis. The accuracy and precision during the sample analysis were within the acceptable margin (+/- 20%). There is no interference by VEGF at LLOQ with up to 15 ng/mL of $VEGF_{165}$ present and no interference at ULOQ with up to 100 ng/mL of $VEGF_{165}$ present.

See detailed information about the assay validation in Appendix **Error! Reference source not found.**

PK Similarity Assessment

PK similarity between MB02, US-Avastin and EU-Avastin was demonstrated in the single-dose parallel Study MB02-A-05-18. The 90% CIs of the GMR for PK endpoint ($AUC_{0\text{-}inf}$) was within 80-125% (Table 4).

Figure 1. MB02-A-05-18: PK Profiles Following a Single IV Infusion of MB02, EU-Avastin and US-Avastin in Healthy Subjects



Source: FDA analysis, dataset ADPC

The PK similarity analysis showed that the 90% CI for GMRs of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} were within 80 - 125% for comparisons between MB02 to US-Avastin; MB02 to EU-Avastin; EU- Avastin to US- Avastin (Table 4).

Table 4. MB02-A-05-18: Summary of Statistical Analyses for Assessment of PK Similarity

Parameter	Statistic	MB02 (n=38)	EU-Avastin (n=38)	US-Avastin (n=38)	Geometric Mean Ratio* (90% CI)		
					MB02 vs EU-Avastin	MB02 vs US-Avastin	EU vs US-Avastin
Primary							
$AUC_{0\text{-}inf}$ (ng•h/mL)	Geometric Mean (Geometric CV%)	31137238 (16.0)	29189811 (16.5)	31145846 (12.8)	106.67 (100.71, 112.99)	99.97 (94.38, 105.89)	93.72 (88.48, 99.27)
Secondary							

AUC_{0-t} (ng•h/mL)	Geometric Mean (Geometric CV%)	30343175 (15.5)	28185267 (15.9)	30315775 (12.4)	107.66 (101.83, 113.81)	100.09 (94.68, 105.81)	92.97 (87.94, 98.29)
C_{max} (ng/mL)	Geometric Mean (Geometric CV%)	86147 (24.8)	81059 (20.0)	87465 (24.9)	106.28 (97.36, 116.01)	98.49 (90.23, 107.51)	92.68 (84.90, 101.17)

*Presented as percent. Source: FDA analysis dataset ADPC

Overall, from a clinical pharmacology perspective, the submitted clinical pharmacology study (1) supports a demonstration that there are no clinically meaningful differences between MB02 and US-Avastin and (2) established the PK component of the scientific bridge that justifies the relevance of comparative data generated using EU-Avastin to the assessment of biosimilarity.

PK Comparability (Study MB02-A-06-20)

PK of MB02-SP (the product used during clinical development), MB02-DM (the to-be-marketed product), and US-Avastin was compared in study MB02-06-20. The 90% CI for GMRs of AUC0-inf, AUC0-t, and Cmax were within 80 - 125% for comparisons between MB02-SP to MB02-DM; MB02-SP to US-Avastin; MB02-DM to US- Avastin. These results support comparability between MB02-SP and MB02-DM and confirms that the changes in the manufacturing process do not preclude the ability to leverage the clinical studies that were performed with MB02-SP lots.

PK of MB02 and EU-Avastin in NS-NSCLC patients (Study MB02-C-02-17)

No PK data were collected in patients with Stage IIIB/IV non-squamous non-small cell lung cancer (NSCLC) in Study MB02-C-02-17.

PD Similarity Assessment

Not applicable.

5.4. Clinical Immunogenicity Studies

Design features of the clinical immunogenicity assessment

Immunogenicity was evaluated in patients with NSCLC after multiple doses of MB02 or EU-Avastin in Study MB02-C-02-17. In total, 311 and 310 patients were randomized to MB02 and EU-Avastin arm, respectively. Samples for ADA assessment were collected over 52 weeks, as well as study treatment discontinuation, at trough PK levels to minimize interference.

ADA was also assessed in healthy subjects after a single dose of MB02, US-Avastin, or EU-Avastin in Study MB02-A-05-18.

Immunogenicity endpoints

Serum samples collected for immunogenicity assessment were first tested for ADA. Samples confirmed as positive for ADA were further tested for neutralizing antibodies (NAb).The ADA and NAb results were listed and summarized by treatment arm and time point using descriptive statistics based on ADA evaluable population. There were no pre-specified hypothesis for immunogenicity.

Immunogenicity assay's capability of detecting the antidrug antibodies (ADA) in the presence of proposed product, reference product, and any other comparator product (as applicable) in the study samples

The Applicant developed binding and neutralizing antibody assays that are suitable for detecting ADA and NAb in the presence of expected levels of MB02, US-Avastin and EU-Avastin. The sensitivity of the ADA assay was 20 ng/mL for anti-bevacizumab antibodies. For normal human serum, the ADA assay demonstrated a relative sensitivity of 100 ng/mL anti-MB02 antibodies in the presence of 100 µg/mL and 200 µg/mL of MB02, EU-Avastin or US-Avastin. In NSCLC matrix, drug tolerance of the assay showed a slightly reduced relative sensitivity of 100 ng/mL of anti-MB02 antibodies in the presence of 50 µg/mL of MB02 or US-Avastin and 100 µg/mL in the presence EU-Avastin.

The sensitivity of the NAb assay was 94.03 ng/mL. The concentration of drug (MB02, EU-Avastin and US-Avastin) which could interfere with detection of anti-MB02 antibodies differed. The NAb assay had the following sensitivity and drug tolerance in normal human serum:

- MB02: 100 ng/mL anti-bevacizumab antibodies in the presence of 30 µg/mL.
- EU-Avastin: 100 ng/mL anti-bevacizumab antibodies in the presence of 30 µg/mL.
- US-Avastin: 100 ng/mL anti-bevacizumab antibodies in the presence of 50 µg/mL.

Refer to the OBP Immunogenicity review for more details.

Adequacy of the sampling plan to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation

The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation.

- **Study MB02-C-02-17:** Blood samples for ADA assessment were collected at pre-dose on Weeks 1, 4, 10, 19, 34, end of treatment (within 3 weeks of last cycle), and 52 (end of study).
- **Study MB02-A-05-18:** Blood samples for ADA assessment were collected on Day -1 (baseline), and pre-dose on Day 14, 28, 56 and 78.

Immunogenicity in NSCLC patients after multiple doses

In Study MB02-C-02-17, after multiple doses in patients with NSCLC, a total of 38 subjects (6.1%) with baseline ADA assessments tested positive for ADAs: 16 (5.1%) subjects in the MB02 group and 22 (7.1%) subjects in the EU-Avastin group. Treatment-induced ADAs over the course of the study were observed in a total of 103 patients (16.6%)- 53 patients (17%) in the MB02 group and 50 patients (16.1%) in the EU-Avastin group. NAb responses were showed to be also similar between both groups occurring in 10 patients (3.2%) in the MB02 group and in 13 patients (4.2%) in the EU-Avastin group over the course of the study (Table 5).

The ADA and NAb incidence rates were comparable between MB02 and EU-Avastin arms.

Table 5. MB02-C-02-17: Summary of ADA and NAb Incidence

Category		MB02 N=311	EU-Avastin N=310
ADA	Baseline Cycle 1 pre-dose (n, % positive)	16 (5.1%)	22 (7.1%)
	TI-ADA (n, % positive)	53 (17.0 %)	50 (16.1%)
	Pesistent TI-ADA (n, % positive)	3 (1.0 %)	10 (3.2 %)
	Transient TI-ADA (n, % positive)	50 (16.0 %)	40 (12.9 %)
NAb	Baseline Cycle 1 pre-dose (n, % positive)	0 (0 %)	4 (1.3%)
	TI-Nab (n, % positive)	10 (3.2%)	13 (4.2%)
	Pesistent TI- Nab (n, % positive)	0 (0 %)	0 (0 %)
	Transient TI- Nab (n, % positive)	10 (3.2%)	13 (4.2%)

Source: Reviewer generated based on table 2.7.2-10 in summary of clinical pharmacology and CSR MB02-C-02-17 Table 61-62.
Note: TI, treatment induced.

Immunogenicity in healthy subjects after single dose

In Study MB02-A-05-18, after a single 3 mg/kg intravenous infusion dose in healthy subjects, ADA were present in 12 (31.5%), 9 (23.6%) and 14 (36.8%) subjects in the MB02, US-Avastin and EU-Avastin arms respectively.

Table 6 summarizes the incidence of ADA and NAb by treatment group in study MB02-A-05-18 in healthy subjects.

Table 6. MB02-A-05-18: Immunogenicity Results

Treatment	Category	Day -1	Day 14	Day 28	Day 56	Day 78
3 mg/kg MB02 IV (N = 38)	Anti-drug Antibody MB02	2 (5.3%)	4 (10.5%)	5 (13.2%)	4 (10.5%)	5 (13.2%)
	Neutralising Anti-drug Antibody MB02	---	---	---	---	2 (5.3%)
	Non-Neutralising Anti-drug Antibody MB02	2 (5.3%)	4 (10.5%)	5 (13.2%)	4 (10.5%)	3 (7.9%)
3 mg/kg US Avastin IV (N = 38)	Anti-drug Antibody MB02	---	1 (2.6%)	4 (10.5%)	1 (2.6%)	3 (7.9%)
	Neutralising Anti-drug Antibody MB02	---	---	1 (2.6%)	---	1 (2.6%)
	Non-Neutralising Anti-drug Antibody MB02	---	1 (2.6%)	3 (7.9%)	1 (2.6%)	2 (5.3%)
3 mg/kg EU Avastin IV (N = 38)	Anti-drug Antibody MB02	1 (2.6%)	4 (10.5%)	6 (15.8%)	7 (18.4%)	4 (10.5%)
	Neutralising Anti-drug Antibody MB02	---	---	---	---	---
	Non-Neutralising Anti-drug Antibody MB02	1 (2.6%)	4 (10.5%)	6 (15.8%)	7 (18.4%)	4 (10.5%)

Source: CSR MB02-A-05-18 Table 12-7

Impact of ADA on the PK, safety, and clinical outcomes of the proposed biosimilar product

The immunogenicity of MB02 was comparable to that of US-Avastin and EU-Avastin in healthy subjects (Study MB02-A-05-18) and to that of EU-Avastin in patients with NSCLC (Study MB02-C-02-17).

Based on results from Study MB02-A-05-18 in healthy subjects, after single dose, there was no meaningful effect of immunogenicity on the PK of MB02. Due of the lack of PK sample collections in patients in Study MB02-C-02-17, the effect of immunogenicity on the PK of MB02 after multiple doses in patients with NSCLC is unknown.

Based on results from Study MB02-C-02-17, the occurrence of ADA against MB02 or EU-Avastin did not appear to impact the efficacy results or correlate with safety.

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

The totality of the efficacy and safety data from Study MB02-C-02-17 supports the

conclusion that there are no clinically meaningful differences between MB02 and EU-Avastin. As summarized above, Amneal provided data demonstrating that MB02, EU-Avastin, and US-Avastin are highly similar and established the analytical and PK components of the scientific bridge to justify the relevance of data generated from the comparative clinical study using EU-Avastin in the assessment of biosimilarity. Therefore, Study MB02-C-02-17 supports, in the context of the totality of the evidence, the conclusion that MB02 is a biosimilar to US-Avastin notwithstanding minor differences.

The clinical and statistical review teams recommend approval of MB02 for the same indications as US-Avastin for which the Applicant is seeking licensure.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

The primary efficacy endpoint of Study MB02-C-02-17 was overall response rate (ORR) at Week 18 by independent review committee (IRC) assessment. The relative risk (RR) of ORR at Week 18 was 0.91 with a two-sided 90% CI of (0.78, 1.06), which fell within the predefined margin of (0.73, 1.36). These results support the conclusion that there were no clinically meaningful differences between MB02 and EU-Avastin with respect to ORR.

Secondary endpoints were PFS and OS as assessed by investigators at Week 18 and Week 52. There were imbalances between the study arms observed for PFS and OS. While the point estimates of the HRs for PFS and OS were close to 1, the median PFS of the MB02 arm was 7 weeks shorter than the EU-Avastin arm, which corresponded to a median DOR of the MB02 arm approximately 7 weeks shorter than the EU-Avastin arm.

To address the uncertainty raised by the imbalance in median PFS and median DOR between arms, the Applicant conducted several sensitivity analyses for PFS assessed by investigator, taking into consideration clinical progression (i.e., treatment discontinuation due to disease progression) and use of subsequent therapy. The results were similar to those of the primary PFS analysis**Error! Reference source not found.**. A sensitivity analysis for OS was conducted by censoring patients at the end of study (Week 52). The median OS was not reached for patients in the Avastin arm while HR remained similar. The Applicant's analyses may not provide an adequate explanation of the longer median DOR, PFS and OS in the EU-Avastin arm. Even though the median follow-up times appear comparable between arms, 71% patients in the MB02 and EU-Avastin arms are still under study follow-up and the results may not be stable.Given the study may not be adequately powered on the secondary endpoints, the results of these endpoints are considered exploratory and should be interpreted with caution.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. MB02-C-02-17: STELLA

MB02-C-02-17: 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)

Data and Analysis Quality

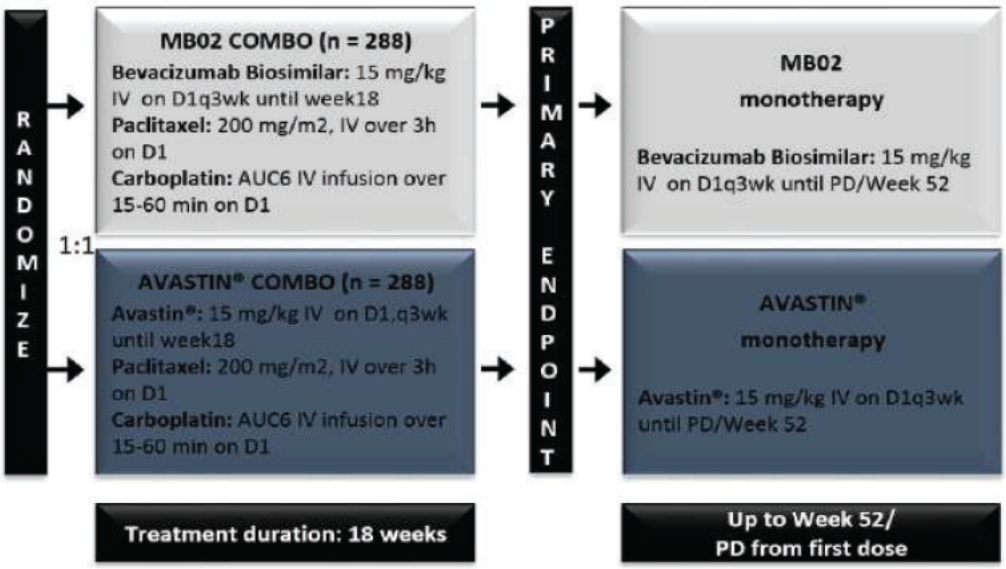
There are no concerns regarding data quality and integrity.

The BLA submission was in electronic common technical document (eCTD) format and was adequately organized. For study MB02-C-02-17, data quality assurance procedures were documented in Section 9.6 of the clinical study report; statistical methodologies and blinding/unblinding procedures were documented in the protocol and Statistical Analysis Plan

Study Design and Endpoints

Study MB02-C-02-17 is a randomized (1:1), double-blind, multicenter, clinical comparative study of MB02 plus chemotherapy versus EU-approved Avastin plus chemotherapy in patients with Stage IIIB/IV non-squamous NSCLC who have not received prior systemic therapy outside of the adjuvant or neo-adjuvant setting. The study design is depicted in Figure 2. Randomization was stratified by sex (male, female), smoking status (smoker, non-smoker), disease diagnosis (newly diagnosed, recurrent disease), and disease stage (Stage IIIB, Stage IV).

Figure 2. Study Schema MB02-C-02-17



During the combination period, patients were treated with MB02 or EU-Avastin at 15 mg/kg IV every 3 weeks in combination with carboplatin AUC 6 and paclitaxel 200 mg/m^2 administered IV every 3 weeks for up to 6 cycles. Patients who completed 6 cycles of the combination treatment could continue to receive monotherapy treatment with MB02 or EU-Avastin every 3 weeks until death, progressive disease, unacceptable toxicity, study closure, or other discontinuation criteria was met, for up to 52 weeks.

Tumor assessments were performed every 6 weeks from Cycle 1 Day 1 until the end of Cycle 6 (i.e., 18 weeks after the first study drug administration); after Cycle 6, tumor assessments were performed at intervals of 9 weeks until disease progression and/or the start of new antitumor treatment, death, or week 52, whichever occurred first
The primary objective of the study was to compare the objective response rate (ORR) between arms; the primary endpoint was ORR at Week 18, according to RECIST1.1, as assessed by an independent review committee (IRC).

The secondary objectives were to evaluate safety, immunogenicity, as well as PFS and OS at Weeks 18 and 52. Tumor assessments for ORR were confirmed by IRC per RECIST v1.1. Disease status and PFS were assessed by investigators per RECIST v1.1. Per the statistical analysis plan (SAP), PFS was assessed by IRC up to Week 18 and by local review after Week 18.

Secondary endpoints were defined as follows:

- PFS is defined as the time from randomization to subsequent confirmed progression per RECIST1.1, or death, whichever comes first. Per SAP, PFS will be censored in the following scenarios:
    - No baseline radiological assessments -- censor at the date of randomization.

- No death or PD – censored at the date of last adequate radiological assessment.
- Treatment discontinuation for clinical progression (no formal tumor assessment)– censored at the date of last adequate radiological assessment.
- Treatment discontinuation for toxicity or reason other than PD, clinical progression, or death – censored at the date of last adequate radiological assessment.
- New anticancer treatment started with PD occurring beforehand – censored at the date of last adequate radiological assessment before start of new anticancer treatment.
- Treatment discontinuation for any reason other than confirmed PD or death, and no post-baseline radiological assessments – censored at the date of randomization.

Key inclusion criteria include:

- Age ≥ 18 years to ≤ 80 years.
- Newly diagnosed or recurrent Stage IIIB/IV (non-squamous NSCLC not amenable to curative intent surgery. Patient may not have received any systemic therapy for advanced disease. For patients with recurrent disease, at least 6 months must have elapsed before randomization from previous adjuvant treatment.
- Prior radiation therapy must be completed > 4 weeks before randomization. Palliative radiation to bone lesion must be completed > 2 weeks prior to randomization.
- At least 1 unidimensional measurable lesion per RECIST v1.1.
- ECOG performance status ≤ 1.
- Adequate hepatic, renal, and hematologic function defined as:
  - Bilirubin < 1.5 X ULN, ALT and AST < 2.5 X ULN.
  - Serum creatinine < 1.5 X ULN, calculated creatinine clearance (CrCl) > 50 mL/min (Cockcroft-Gault formula), urine protein to creatinine ratio < 1 g of protein in 24 hour urine collection.
  - Absolute neutrophil count > 1.5 X 10^9 /L, platelets > 100 X 10^9 /L, and hemoglobin (Hb) > 9g/dL

Key exclusion criteria include:

- Prior treatment with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including Avastin.
- Known malignant central nervous system disease. Patients with treated brain metastases (radiation, surgery, stereotactic surgery) and off steroids for at least 4 weeks prior to randomization may be eligible.
- Current or recent (within 10 days of first dose of study treatment) use of aspirin or other nonsteroidal anti-inflammatory drugs with antiplatelet activity of treatment with dipyridamole, ticlopidine, clopidogrel, or cilostazol.
- Current or recent (within 5 days) use of therapeutic anticoagulation or use of thrombotic agent.

- INR > 2, unless receiving active anticoagulation treatment.
- A diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung.
- A diagnosis of a tumor that harbors activating epidermal growth factor receptor mutation or ALK rearrangement
- Known active viral infection, including but not limited to: hepatitis B, hepatitis, or HIV.
- Known history of abdominal fistula, GI perforation, intra-abdominal abscess within 6 months of randomization.
- Presence of nonhealing wound, active ulcer, or untreated bone fracture.
- History of hypertensive crisis or hypertensive encephalopathy.
- NYHA Grade ≥ II congestive heart failure or angina, myocardial infarction within 6 months before randomization; symptomatic arrhythmia or serious cardiac arrhythmia requiring medication; abnormal left ventricular ejection fraction < 50% assessed by ultrasound or mitigated acquisition scan.
- History of significant vascular event within 6 months before randomization (including MI, stroke, or TIA).
- Known bleeding diathesis or significant coagulopathy defined as a bleeding event Grade ≥2 within 3 months before randomization.
- History of Grade ≥ 2 hemoptysis within 6 months before randomization.
- Tumor invading or compressing major blood vessels.

Statistical Methodologies

The primary endpoint of ORR at Week 18 was calculated as the proportion of patients who experienced either complete response (CR) or partial response (PR) per RECIST v1.1 at Week 18 as assessed by IRC. Patients who discontinued treatment before Week 18 were considered as non-responders. Based on the definition of primary endpoint, patients who had changes in their CR/PR status before Week 18 were not considered as responders. No imputation was specified for handling missing data in statistical analyses. The primary analysis was performed in the ITT population using the Cochran-Mantel-Haenszel (CMH) method to estimate the risk ratio (RR) of ORRs (MB02 versus Avastin) and its two-sided 90% CI, adjusting for the randomization stratification factors.

The equivalence with respect to efficacy will be demonstrated if the 90% CI of RR lies within an equivalence margin of (0.73, 1.36). This margin was determined based on a

meta-analysis of relevant randomized clinical trials[6,7,8,9] following FDA advice and guidelines. If the two-sided 90% confidence interval (CI) of the RR lies entirely within this margin, the study would be considered to have demonstrated that MB02 has no clinically meaningful differences compared to Avastin with respect to ORR.

The primary analysis was also performed in the modified ITT (mITT) and per protocol (PP) populations. The mITT population was defined as all randomized patients (i.e., ITT population) who were treated with study drug and had measurable disease at screening as determined by IRC. The PP population was defined as all patients in the mITT population who completed at least the first 6 cycles of study drug and chemotherapy, or who discontinued study drug or chemotherapy after completing at least 4 cycles of study drug and chemotherapy, and for whom no major protocol deviations affecting efficacy occurred up to and including Week 18.

The secondary endpoints of PFS and OS were analyzed using the Kaplan-Meier method and Cox proportional hazards model including treatment and randomization stratification factors as covariates. DOR was estimated using the Kaplan-Meier method. No multiplicity control was planned for secondary endpoints.

Protocol Amendments

The original protocol was dated 4 August 2017 and was amended on December 3, 2018 (Amendment 1) and May 25, 2019 (Amendment 2)

Amendment 1: The primary purpose of this amendment was to implement FDA recommendations received after meeting with FDA. Main changes include:

- Allow a 1-week window for primary endpoint assessments (ORR at Week 18).
- Clarified that a patient will be discontinued from treatment if he/she discontinues MB02/EU-Avastin before completing 6 cycles of therapy and before the primary endpoint at Week 18. Also clarified that for a subject who discontinued chemotherapy before completing 6 cycles and before the primary endpoint at Week 18, it is possible to continue bevacizumab monotherapy per Sponsor decision.

[6] Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542-50.
[7] Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2004;22:2184-91.
[8] Niho S, Kunitoh H, Nokihara H, et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer. 2012;76:362-267.
[9] Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for non-squamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol. 2010;21:1804-9.

- Clarified secondary endpoints of PFS and OS will be analyzed for all patient data at cutoff points at Week 18 and Week 52.
- Clarified tumor assessment schedule will remain the same even if treatment is delayed.
- Updated sample size from 576 to 600 (300 per arm)/ Sample size calculations were conducted using PASS13 software.
- Updated number of study centers from 142 to 150, number of countries participating from 21 to 19.
- Defined "inadequately controlled hypertension" as systolic blood pressure > 140 mm Hg and diastolic blood pressure > 90 mm Hg.
- Clarified 12-lead ECG collection time points.

Amendment 2: The primary purpose of this amendment is to clarify the procedures applicable to patients who are responding to treatment at Week 52 and are offered the opportunity to be treated with biosimilar MB02 monotherapy until disease progression, unacceptable toxicity, or death. Changes include:

- Removed throughout the protocol wording that no further study assessments will be performed beyond Week 52 and the opportunity to continue treatment beyond Week 52 is only for patients that are responding to study treatment.
- Addition of section to clarify specific procedures applicable beyond week 52 and updated schedule of assessment.

The modifications did not have an impact on the integrity of the study.

Subject Disposition

A total of 627 patients were randomized in Study MB02-C-02-17, 315 patients to the MB02 arm and 312 patients to the EU-Avastin arm. All patients were included in the intent-to-treat (ITT) population and used for efficacy analyses. The mITT and PP populations included 598 patients (303 in the MB02 arm and 295 in the EU-Avastin arm) and 511 patients (256 in the MB02 arm and 255 in the EU-Avastin arm), respectively.

Of the 627 patients randomized, 4 patients in the MB02 arm and 2 patients in the EU-Avastin arm did not receive treatment due to investigator decision or other reasons. Therefore, the safety analysis set (SAS) contains a total of 621 patients (311 in the MB02 arm and 310 in the EU-Avastin arm).

Table 7 summarizes the disposition of patients in the ITT population at Week 18.

Table 7. MB02-C-02-17: Disposition at week 18 (ITT population)

	MB02 N=315 n (%)	**EU-Avastin N= 312 n (%)**
Treated	311 (99)	310 (99)
Completed treatment up to Week 18	207 (65)	220 (71)

Discontinued in first 18 weeks	104 (33)	90 (29)
- Disease progression	27 (9)	38 (12)
- Unacceptable toxicity	29 (9)	20 (6)
- Death	14 (4.4)	12 (3.8)
- Consent withdrawn	17 (5)	12 (3.8)
- Investigator Decision	7 (2.2)	5 (1.6)
- Patient decision	2 (0.6)	1 (0.3)
- Protocol deviation	2 (0.6)	0
- Lost to follow-up	6 (1.9)	2 (0.6)

Source: Reviewer table based on Figure 2: mb02-c-02-17 Final CSR

Reviewer Comment: Patient disposition at the end of week 18 is generally well balanced between arms. Although there is a slightly higher percentage of patients in the EU-Avastin completed treatment up to week 18 compared to the MB02 arm (71% versus 65%), when analyzing the cause for treatment discontinuations, there are no pattern or cause that may indicate a difference in efficacy or toxicity between treatment arms.

Demographics and Baseline Characteristics

A total of 627 patients were enrolled and randomized, 312 to the MB02 arm and 315 to the EU-Avastin arm. The first patient was randomized February 6, 2018 and the last patient completed Week 18 on July 3, 2019. Patients were enrolled in 93 centers in 16 countries. Of centers where patients were enrolled, 86 centers (92%) enrolled ≤20 patients while 7 centers (8%) enrolled more than 20 patients. One site in Ukraine (#2804) enrolled 57 patients (9% of patients). Of all randomized patients, 189 were enrolled at centers in Ukraine (30%) and 107 (17%) were enrolled at centers in Russia.

Table 8 summarizes the demographics and baseline characteristics in the ITT population.

Table 8. MB02-C-02-17: Demographics and Baseline Characteristics (ITT Population)

	MB02 N=315 n (%)	Avastin N=312 n (%)
Male	193 (61)	190 (61)
Age, median (range)	61 (26 – 78)	61 (25 – 79)
<65 years	206 (65)	202 (65)
≥65 years	109 (35)	110 (35)
BMI (kg/m²), median	24.5	24.5
Race		
White	228 (72)	241 (77)
Asian	71 (23)	54 (17)
Other	16 (5)	16 (5)
Not collected	0	1 (0.3)
Region		
Europe	223 (71)	235 (75)
Asia	72 (23)	55 (18)
South/Latin America	18 (6)	21 (7)
Middle East	2 (0.6)	1 (0.3)
ECOG		
0	92 (30)	94 (30)
1	219 (70)	216 (70)
Diagnosis Type		
Newly Diagnosed	289 (92)	287 (92)
Recurrent Disease	26 (8)	25 (8)
Smoking Status		
Smoker	157 (50)	157 (50)
Non-smoker	158 (50)	160 (51)
Stage at Enrollment		
Stage II	0	2 (0.6)
Stage IIIA	1 (0.3)	1 (0.3)
Stage IIIB	31 (10)	37 (12)
Stage IV	283 (90)	272 (87)
Prior NSCLC Systemic Therapy	7 (2.2)	11 (3.5)
Prior NSCLC Surgery (≥1)	222 (71)	218 (70)
Primary tumor surgery	25 (8)	34 (11)
Metastasis surgery	6 (1.9)	7 (2.2)
Prior NSCLC Radiotherapy	28 (9)	28 (9)

Reviewer Comment: Baseline demographics and disease characteristics were well balanced between arms. With the exception of geography, the study population is similar to the studies used to calculate the historical bevacizumab effect.

Analysis of Primary Clinical Endpoint(s)

The primary analysis of IRC-assessed ORR at Week 18 in the ITT population (N=627) is summarized in Table 9. Of the 315 patients in the MB02 arm, there were 127 (40%) responders, with 6 (1.9%) CRs and 121 (38%) PRs. Of the 312 patients in the EU-Avastin arm, there were 139 (45%) responders, with 3 (1.4%) CRs and 136 (44%) PRs. The RR of ORR at Week 18 was 0.91 with a two-sided 90% CI of (0.78, 1.06), which fell within the predefined margin of (0.73, 1.36). The RRs in the mITT and PP populations were consistent to that in the ITT population. The results support the conclusion that there were no clinically meaningful differences between MB02 and EU-Avastin with respect to ORR per IRC.

Table 9. MB02-C-02-17: Primary Analysis of IRC-Assessed ORR at Week 18

	MB02 N = 315 n (%)	Avastin N = 312 n (%)
Overall Response at Week 18		
Responses	127 (40)	139 (45)
Complete Response	6 (2)	3 (1)
Partial Response	121 (38)	136 (44)
ORR at Week 18 (95% CI)[1]	(35, 46)	(39, 50)
RR ($ORR_{MB02}/ORR_{Avastin}$)[2]	**0.91**	
90% CI	**(0.78, 1.06)**	

RR: risk ratio
[1] Estimated using the Clopper-Pearson exact method.
[2] Adjusted for the randomization stratification factors sex, smoking status, disease diagnosis and stage using the Cochran-Mantel-Haenszel test.
Source: Reviewer

We performed an exploratory analysis by analyzing BOR by Week 18 as assessed by IRC in the ITT population. The results (Table 10) supported the conclusion that there are no clinically meaningful differences between MB02 and EU-Avastin. The RR of IRC-assessed BOR by Week 18 (and endpoint that would include patients with unconfirmed responses) was 0.93 with a 90% CI of (0.78, 1.06) falling within the predefined margin, supporting this conclusion.

Table 10. MB02-C-02-17: Analysis of IRC-Assessed BOR by Week 18

	MB02 N = 315 n (%)	Avastin N = 312 n (%)
Best Overall Response (BOR) by Week 18		
Responses	160 (51)	172 (55)
Complete Response	6 (2)	3 (1)
Partial Response	154 (49)	169 (54)
ORR (95% CI)[1]	(45, 56)	(49, 61)
RR ($ORR_{MB02}/ORR_{Avastin}$)[2]	**0.93**	
90% CI	**(0.82, 1.05)**	

[1] Estimated using the Clopper-Pearson exact method.
[2] Adjusted for the randomization stratification factors sex, smoking status, disease diagnosis and stage using the Cochran-Mantel-Haenszel test.
Source: Reviewer Analysis

Potential Effects of Missing Data

Per SAP, missing data was not replaced (i.e., handled as missing) in the efficacy analysis. To evaluate the potential effects of missing data, a multiple imputation method was used as a sensitivity analysis of the primary endpoint in the ITT, mITT, and PP populations. Specifically, missing data in the sum of diameters for target lesions was imputed first and then the missing overall response was derived based on the imputed data. The IRC-assessed ORRs at Week 18 based on imputed data increased in both arms across all populations compared to the IRC-assessed ORRs in the primary analysis. The RRs and 90% CIs (Table 11**Error! Reference source not found.**) were supportive of the results of the primary analysis. We note that all the sensitivity analyses were post-hoc and therefore considered exploratory.

Table 11. MB02-C-02-17 Sensitivity Analysis of IRC-Assessed ORR at Week 18

	MB02 N = 315 n (%)	Avastin N = 312 n (%)
ITT		
Overall Response at Week 18	148 (47)	153 (49)
ORR at Week 18 (95% CI)	(41, 53)	(43, 55)
RR (90% CI)	0.96 (0.84, 1.09)	
mITT	n = 303	n = 295
Overall Response at Week 18	147 (49)	152 (52)
ORR at Week 18 (95% CI)	(43, 54)	(46, 57)
RR (90% CI)	0.95 (0.83, 1.07)	
PPS	n = 256	n = 255
Overall Response at Week 18	120 (47)	131 (51)
ORR at Week 18 (95% CI)	(41, 53)	(45, 58)
RR (90% CI)	0.90 (0.78, 1.03)	

Source: Tables 14.2.1.1.10 – 14.2.1.1.12- Final CSR

Analysis of Secondary Clinical Endpoint(s):The analyses of secondary endpoints were summarized in Table 12 and Figure 3 and Figure 4. Per protocol, disease status and PFS were assessed by investigators through the end of study (Week 52). Instead of adjusting for hazard ratio (HR) by including stratification factors as covariates, we estimated HR using a stratified Cox model by those factors. The Applicant's HRs were similar to FDA's analysis using stratified HRs. We noted that the point estimates of HR for PFS and OS were close to 1, and the median PFS of the MB02 arm was 7 weeks shorter than the EU-Avastin arm. Therefore, the potential decrement in PFS and OS is of concern to the review team. In addition, the median DOR of the MB02 arm was approximately 7 weeks shorter than the EU-Avastin arm. An information request was sent on 15 September 2021 to address these issues. The Applicant conducted several sensitivity analyses for PFS assessed by investigator taking into consideration clinical progression (i.e., treatment discontinuation due to disease progression without radiological confirmation) and use of subsequent therapy. The results were similar to those of the primary PFS analysis in Table 12**Error! Reference source not found.**. A sensitivity analysis for OS was conducted by censoring patients at the end of study (Week 52). The median OS became not reached for patients in the EU-Avastin arm while HR remained similar. The sponsor's responses to FDA's information request may not provide good explanation of the longer median DOR, PFS and OS in the Avastin arm. FDA noted that the median follow-up times appear comparable between arms (median 52.3 weeks [95% CI: 52.1, 52.4]) and may indicate data maturity. However, 71% patients in the MB02 and EU-Avastin arms are still under study follow-up and the results may not be stable.

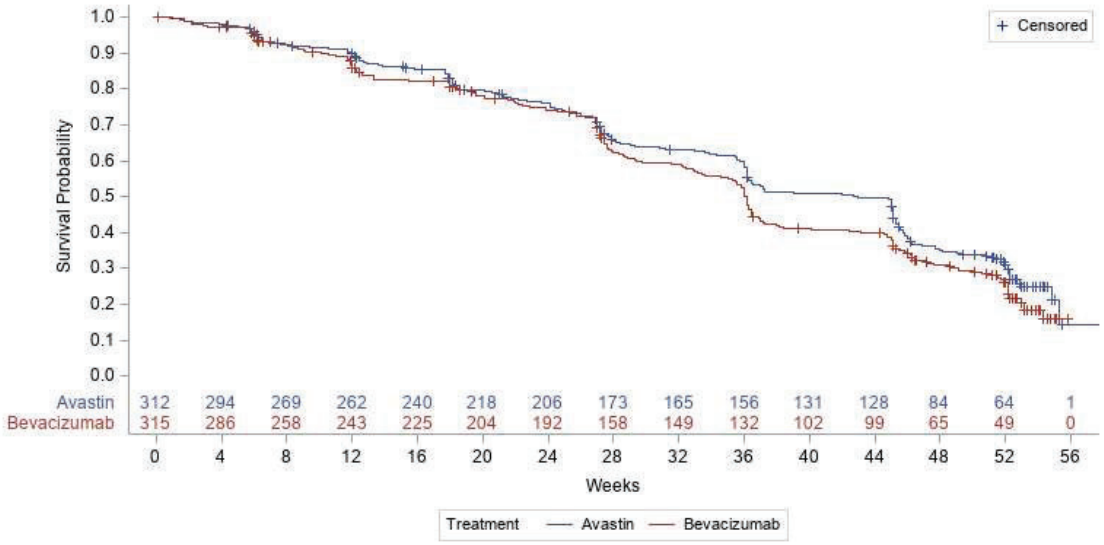
The Applicant demonstrated analytical and PK similarity between MB02, US- and EU-Avastin and established the scientific bridge between US-Avastin and EU-Avastin supporting the use of EU-Avastin in the CCS. In the context of the totality of data, the results of Study MB02-C-02-17 support the conclusion of similarity between MB02 and US-Avastin. MB02-C-02-17 was not adequately powered for assessment of the secondary endpoints and therefore the results of these endpoints are considered exploratory and should be interpreted with caution.

Table 12. MB02-C-02-17: Analysis of Secondary Endpoints

	MB02 N = 315	Avastin N = 312
PFS		
Number of Events (%)	201 (64)	195 (63)
Median in Weeks (95% CI)[1]	36.0 (33.6, 36.9)	43.0 (36.1, 45.1)
Hazard Ratio (95% CI)[2]	1.20 (0.99, 1.46)	
Stratified Hazard Ratio (95% CI)[3]	1.22 (1.00, 1.49)	
OS		
Number of Events (%)	91 (29)	90 (29)
Median in Weeks (95% CI)[1]	NR (NE, NE)	63.6 (63.6, NE)
Hazard Ratio (95% CI)[2]	1.11 (0.83, 1.48)	
Stratified Hazard Ratio (95% CI)[3]	1.12 (0.83, 1.50)	
DOR, n	165	183
DOR ≥ 6 months, n (%)	88 (53)	116 (63)
DOR ≥ 12 months, n (%)	0	1 (1)
Median in Weeks (95% CI)	30.3 (28.3, 38.4)	37.1 (30.4, 39.6)
Range in Weeks	(0.1+, 48.0+)	(0.1+, 54.6+)

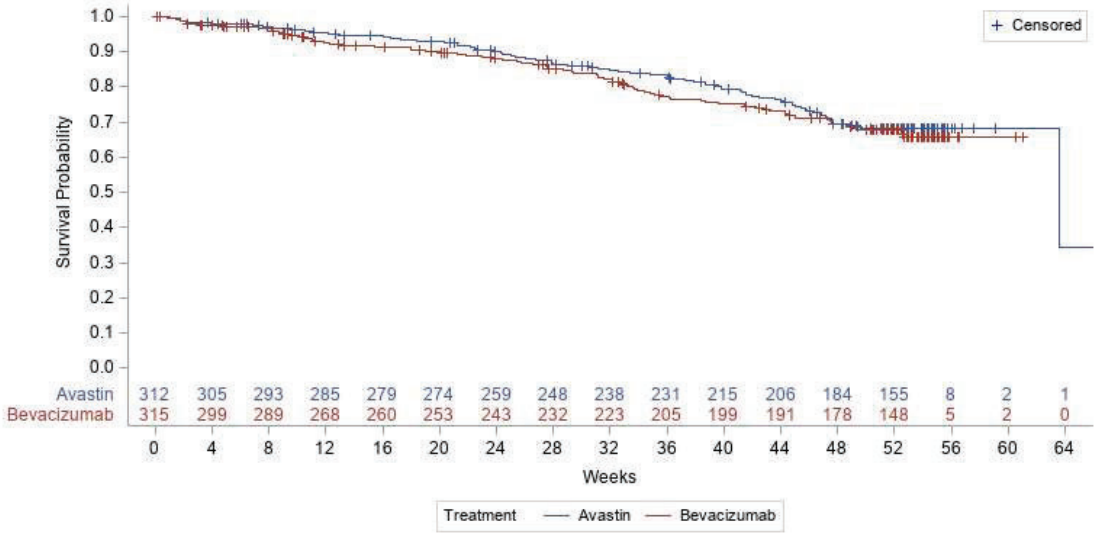
NR: not reached; NE: not estimable
[1] Estimated using Kaplan-Meier method.
[2] Estimated using Cox proportional hazards model including treatment and randomization stratification factors as covariates.
[3] Estimated using Cox proportional hazards model stratified by the randomization stratification factors.
Source: Reviewer Analysis

Figure 3. MB02-C-02-17: Kaplan-Meier Curves of PFS



Source: Reviewer Analysis

Figure 4. MB02-C-02-17: Kaplan-Meier Curves of OS



Source: Reviewer Analysis

Other Clinical Endpoints

Not applicable.

Additional Analyses

Not applicable.

6.3. Review of Safety Data

6.3.1. Methods

Clinical Studies Used to Evaluate Safety

The analysis of safety focuses on the combination period of Study MB02-C-02-17, during which patients received MB02 or EU-Avastin administered in combination with carboplatin and paclitaxel as first-line therapy for nsNSCLC (up to 6 cycles).

The design of Study MB02-C-02-17 allows for adequate assessment of toxicities.

Categorization of Adverse Events

mAbxience, who conducted the CCS, used the NCI CTCAE version 4.03 dictionary to grade the severity of AEs and the MedDRA Dictionary version 20.1 to code AEs. mAbxience's approach to recording, coding, and categorizing events was acceptable. FDA audited the accuracy of coding of the reported AE term (AETERM) to the lowest level term (AELLT) and assessed that the AETERM was appropriately coded to the AELLT with a high degree of accuracy and consistency.

Safety Analyses

Unless specified, safety analyses are based on per patient incidence (i.e., patients within a treatment group were counted only once in the summary row for each preferred term (PT) regardless of the number of times the patient experienced the event).

FDA's review focuses on the chemotherapy plus MB02 or EU-Avastin part of Study MB02-C-02-17 (combination period). This was consistent with the primary safety endpoint for the study. FDA's analysis utilized only treatment emergent adverse events (TEAE), vital sign assessment, and laboratory assessments that occurred from the first dose of study drugs up until 21 days after the last dose of combination therapy (carboplatin and/or paclitaxel) with MB02 or EU-Avastin.

In addition, FDA performed an abbreviated safety analysis of the monotherapy period. This analysis utilized only TEAEs that occurred from the first monotherapy dose of MB02 or EU-Avastin up to 30 days after the last dose of MB02 or EU-Avastin monotherapy and before study day 295 (Week 52 plus 30 days).

The safety assessments presented in this review are based on FDA's analysis of the data. The results of FDA analyses (e.g., frequency of AEs) differ from that presented in the Applicant's BLA submission documents due to differences in how combination and monotherapy periods are defined. For example, the Applicant defined adverse events occurring during the combination period as any AE occurring within the first 6 cycles

regardless of whether a patient received chemotherapy and bevacizumab for 6 cycles, while in FDA's analysis, if a patient received 4 cycles followed by bevacizumab monotherapy, the analysis of safety during the "combination period" consisted of the adverse events observed during the time the patient received chemotherapy plus MB02 or EU-Avastin regardless of the planned administration of chemotherapy. Despite these differences, the overall trends and safety signals identified were consistent between FDA's and the Applicant's analysis approaches.

6.3.2. Major Safety Results

Relevant Characteristics of the Population Evaluated for Safety

Of the 315 patients randomized to receive MB02, 311 received at least one dose of study drug. Of the 313 patients randomized to receive EU-Avastin, 310 patients received at least one dose of study drug. The demographic characteristics of the safety population are comparable to the randomized population. For details, refer to Table 8.

Other Product-Specific Safety Concerns

There are no product-specific safety concerns requiring specific clinical assessments.

Deaths

In the FDA's analysis of fatal AEs in the combination period, 12 (3.9%) patients in the MB02 arm and 9 (2.9%) patients in the EU-Avastin arm had a fatal TEAE within 21 days of the last dose of combination therapy. In the monotherapy period, 4 patients (1.3%) in the MB02 arm and 6 patients (1.9%) in the EU-Avastin arm had a fatal TEAE within 30 days of the last monotherapy dose of bevacizumab.

Table 13 summarizes all fatal AEs for Study MB02-C-02-17 according to treatment period. All listed causes of death as shown in the table are expected fatal events in the setting of advanced NSCLC and treatment with chemotherapy in combination with MB02 or EU-Avastin or MB02/EU-Avastin administered as single agent .

Table 13. MB02-C-02-17: Fatal AEs by Treatment Period

Preferred Term	MB02 (n: 311)		EU-Avastin (n: 310)	
	Combination Period N patients	Monotherapy Period N patients	Combination Period N patients	Monotherapy Period N patients
General physical health deterioration	2	1	3	3
Sudden death	2	0	0	0
Acute myocardial infarction	1	0	0	0
Cardiac failure acute	1	0	0	0
Cardio-respiratory arrest	1	0	0	0

Death	1	0	0	0
Embolism	1	0	0	0
Hemoptysis	1	0	0	0
Lung neoplasm malignant	1	0	0	1
Pulmonary hemorrhage	1	0	1	0
Acute coronary syndrome	0	0	1	0
Dehydration	0	0	1	0
Enterocolitis	0	0	1	0
Pneumonia	0	0	1	0
Pulmonary embolism	0	0	1	0
Empyema	0	1	0	0
Gastric ulcer	0	1	0	0
Nephrotic Syndrome	0	1	0	0
Acute kidney injury	0	0	0	1
Cardiac arrest	0	0	0	1

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX (4-13-2021)

There were no meaningful differences in the frequency and causes of death between arms.

Treatment Emergent Adverse Events

Table 14 summarizes the major safety results during the combination period. Although there is a slightly higher frequency of Grade 3-4 events (33% versus 29%) in the MB02 arm, there was not a specific toxicity or comorbidity identified to explain this difference, which is likely related to the inherent variability within the patient population and unlikely to represent a clinically significant difference.

Table 14. MB02-C-02-17: Summary of Major Safety Results

	MB02 N=311	EU-Avastin N=310
Number of reported AEs	1651	1642
Patients with AEs n(%)	286 (92)	279 (90)
Patients with SAEs n(%)	44 (14)	43 (14)
Patients with Grade 3-4 AEs n(%)	104 (33)	91 (29)
Patients with Grade 5 AEs n(%)	12 (3.9)	9 (2.9)

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX (4-13-2021)

Table 15 summarizes the per-patient incidence of AEs during the combination period by system organ class (SOC). Overall, the frequencies of TEAEs (all grade) at the SOC

level were similar between the MB02 and the EU-Avastin arms, with the difference in frequency being ≤ 2% for most SOC categories.

A higher percentage of patients in the MB02 arm (18%) experienced any grade toxicity in the infections and infestations category as compared to the EU-Avastin arm (13%), although the rate of Grade 3-4 events was similar between arms (4.2% and 2.6%). A higher percentage of patients in the MB02 arm (34%) experienced any grade toxicity in the nervous systems category as compared to the EU-Avastin arm (31%), although the rate of Grade 3-4 events was higher in the EU-Avastin arm (2.9%) compared to the MB02 arm (1%). A higher percentage of patients in the MB02 arm (17%) experienced any grade toxicity in the respiratory, thoracic, and mediastinal disorders category as compared to the EU-Avastin arm (14%), although the rate of Grade 3-4 events was similar between arms (2.3% and 2.3%).

A higher percentage of patients in the EU-Avastin arm (55%) experienced any grade toxicity in the skin and subcutaneous tissue disorders as compared to the MB02 arm (52%), although the rate of Grade 3-4 events was similar between the arms (1% and 1.6%).

This variability observed at the SOC level is inherent to clinical studies, and these results support the conclusion that the two products have similar safety profiles. No meaningful differences were observed between arms.

Table 15. MB02-C-02-17: TEAS by SOC

SOC	MB02 N=311 n (%)		EU-Avastin N=310 n (%)	
	All grades	Grade 3-4	All grades	Grade 3-4
Blood and lymphatic system disorders	128 (41)	43 (14)	123 (40)	45 (15)
Cardiac disorders	11 (3.5))	3 (1.0)	7 (2.3)	0
Congenital, familial and genetic disorders	1 (0.3)	0	0	0
Ear and labyrinth disorders	2 (0.6)	0	4 (1.3)	0
Endocrine disorders	1 (0.3)	0	0	0
Eye disorders	2 (0.6)	0	1 (0.3)	0
Gastrointestinal disorders	89 (29)	5 (1.6)	86 (28)	6 (2.0)
General disorders and administration site conditions	74 (24)	13 (4.2)	74 (24)	13 (4.2)
Hepatobiliary disorders	3 (1.0)	0	3 (1.0)	0
Immune system disorders	5 (1.6)	0	7 (2.3)	2 (0.6)
Infections and infestations	56 (18)	13 (4.2)	41 (13)	8 (2.6)
Injury, poisoning and procedural complications	5 (1.6)	2 (0.6)	4 (1.3)	1 (0.3)

Investigations	86 (28)	26 (8)	87 (28)	24 (8)
Metabolism and nutrition disorders	32 (10)	8 (2.6)	35 (11)	6 (1.9)
Musculoskeletal and connective tissue disorders	66 (21)	3 (1.0)	68 (22)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0)	0	0	0
Nervous system disorders	107 (34)	3 (1.0)	95 (31)	9 (2.9)
Psychiatric disorders	15 (4.8)	0	12 (3.9)	0
Renal and urinary disorders	13 (4.2)	0	20 (6.5)	1 (0.3)
Reproductive system and breast disorders	2 (0.6)	0	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	52 (17)	7 (2.3)	44 (14)	7 (2.3)
Skin and subcutaneous tissue disorders	163 (52)	5 (1.6)	172 (55)	3 (1.0)
Surgical and medical procedures	0	0	1 (0.3)	0
Vascular disorders	29 (9)	7 (2.3)	27 (9)	5 (1.6)

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX (4-13-2021)

Table 16 summarizes the incidence of most frequent (≥5%) AEs during the combination period by high-level term (HLT). Overall, the frequencies of TEAEs (all grade) at the HLT level were similar between the MB02 and the EU-Avastin arms with the difference in frequency being ≤ 2% for most HLT categories.

Although for some HLTs there were higher incidences (above 2%) of AEs in one arm or the other, for all categories, the difference was below 5%, the differences do not follow any pattern of toxicity, and the incidence of Grade 3-4 AEs is very similar between arms. These differences are typically observed in large clinical studies and are likely due to chance. There were no clinically meaningful differences between the MB02 and EU-Avastin arms.

Table 16. MB02-C-02-17: TEAS by HLT (incidence ≥ 5%)

HLT	MB02 N=311 n (%)		EU-Avastin N=310 n (%)	
	All grades	Grade 3-4	All grades	Grade 3-4
Alopecias	155 (50)	4 (1.3)	163 (53)	1 (0.3)
Anemias NEC	92 (30)	20 (6)	87 (28)	17 (5)
Peripheral neuropathies NEC	65 (21)	1 (0.3)	61 (20)	4 (1.3)
Asthenic conditions	52 (17)	9 (2.9)	53 (17)	9 (2.9)
Nausea and vomiting symptoms	52 (17)	1 (0.3)	46 (15)	0
Thrombocytopenias	41 (13)	9 (2.9)	36 (12)	5 (1.6)
Neutropenias	34 (11)	19 (6)	50 (16)	28 (9)
Paresthesias and dysesthesias	31 (10)	0	23 (7)	1 (0.3)
Platelet analyses	26 (8)	6 (1.9)	17 (5)	3 (1.0)

Diarrhea (excl infective)	24 (8)	1 (0.3)	23 (7)	3 (1.0)
Muscle pains	23 (7)	1 (0.3)	29 (9)	0
Leukopenias NEC	23 (7)	4 (1.3)	17 (5)	2 (0.7)
White blood cell analyses	20 (6)	11 (3.5)	22 (7)	12 (3.9)
Musculoskeletal and connective tissue pain and discomfort	20 (6)	1 (0.3)	21 (7)	0
Vascular hypertensive disorders NEC	20 (6)	4 (1.3)	18 (6)	4 (1.3)
Joint related signs and symptoms	18 (6)	2 (0.6)	18 (6)	0
Coughing and associated symptoms	17 (5)	0	15 (4.8)	1 (0.3)
Physical examination procedures and organ system status	15 (4.8)	2 (0.6)	22 (7)	0
Liver function analyses	14 (4.5)	4 (1.3)	22 (7)	7 (2.3)

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX (4-13-2021)

Table 17 summarizes the incidence of most frequent (≥5%) AEs during the combination period by preferred term (PT). Overall, the frequencies of TEAEs (all grade) at the PT level were similar between the MB02 and the EU-Avastin arms with the difference in frequency being ≤ 2% for most PTs.

Although for some PTs there were higher incidences (above 2%) of AEs in one arm or the other, for all categories the difference was below 5%, the differences do not follow any pattern of toxicity, and the incidence of Grade 3-4 AEs is very similar between arms. These differences are typically observed in large clinical studies and are likely due to chance. There were no meaningful differences in the incidence of specific toxicities between the two products.

Table 17. MB02-C-02-17: TEAS by PT (incidence ≥ 5%)

PT	MB02 N=311 n (%)		EU-Avastin N=310 n (%)	
	All grades	Grade 3-4	All grades	Grade 3-4
Alopecia	155 (50)	4 (1.3)	163 (53)	1 (0.3)
Anemia	92 (30)	20 (6.5)	87 (28)	17 (6)
Thrombocytopenia	41 (13)	9 (2.9)	36 (12)	5 (1.6)
Nausea	40 (13)	0	41 (13)	0
Neuropathy peripheral	38 (12)	1 (0.3)	38 (12)	3 (1.0)
Neutropenia	32 (10)	15 (4.8)	43 (14)	21 (7)
Fatigue	29 (9)	3 (1.0)	34 (11)	5 (1.6)
Platelet count decreased	26 (8)	6 (1.9)	17 (6)	3 (1.0)
Asthenia	24 (8)	6 (1.9)	19 (6)	4 (1.3)
Diarrhea	24 (8)	1 (0.3)	23 (7)	3 (1.0)
Leukopenia	23 (7)	4 (1.3)	17 (5)	2 (0.6)
Myalgia	23 (7)	1 (0.3)	29 (9)	0
Paresthesia	21 (7)	0	12 (3.9)	0

Peripheral sensory neuropathy	20 (6)	0	21 (7)	1 (0.3)
Hypertension	19 (6)	4 (1.3)	18 (6)	4 (1.3)
Vomiting	19 (6)	1 (0.3)	9 (2.9)	0
Arthralgia	18 (6)	2 (0.6)	18 (6)	0
Neutrophil count decreased	18 (6)	11 (3.5)	18 (6)	8 (2.6)
Weight decreased	11 (3.5)	0	21 (7)	0
Decreased appetite	10 (3.2)	0	18 (6)	1 (0.3)
Aspartate aminotransferase increased	7 (2.3)	2 (0.6)	16 (5)	3 (1.0)

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX (4-13-2021)

Hematologic toxicity

Although hematological toxicities are not commonly associated with the use of bevacizumab products as single agents, when combination bevacizumab/chemotherapy is administered, the incidence of hematological toxicity of chemotherapy is generally increased over the incidence reported for chemotherapy alone (Avastin USPI). Table 18 summarizes the incidence of hematological toxicities during the combination period based on AE reporting and on laboratory assessments. The incidence of hematological complications is consistent with the expected toxicity of the combinations. While hematologic toxicities are common, the majority of events are Grade 1-2.

In general, the incidence the different hematologic toxicities (all grades and Grade 3-4) are consistent between the MB02 and the EU-Avastin arm with differences between the arms being ≤2% for most parameters.

The frequency of thrombocytopenia by AE reporting is higher in the MB02 arm and the EU-Avastin arm with 22% of patients in the MB02 arm having at least one AE of thrombocytopenia compared to 16% of patients in the EU-Avastin arm. This is reflected with similar results in the analysis based on laboratory assessments.

Minor differences are seen with neutropenia and anemia. The frequency of neutropenia by AE reporting is slightly higher in the EU-Avastin arm compared to the MB02 arm,19% and 16% respectively, but the frequency of Grade 3-4 AEs are comparable. The incidence of anemia based on laboratory assessments is slightly higher in the MB02 arm as compared to the EU-Avastin arm, 78% versus 75%, but the incidence of Grade 3-4 assessments are comparable between the arms.

Overall, there is no clinically significant differences between the arms with respect to frequency of hematologic toxicity during the combination period and the variability is likely a product of theinherent variability in clinical trials.

Table 18. MB02-C-02-17: Hematologic toxicity during combination period

	MB02 N=311		EU-Avastin N=310	
	All grades	Grade 3-4	All Grades	Grade 3-4
Febrile neutropenia n (%)	4 (1.3)	4 (1.3)	9 (2.9)	9 (2.9)
Neutropenia[1] n (%) Lab (neutrophils)[2] n (%)[3]	51 (16) 68 (24)	27 (9) 5 (3.2)	60 (19) 74 (25)	29 (9) 5 (1.6)
Leukopenia[4] n (%) Lab (leukocytes [white blood cells])[2] n (%)[3]	31 (10) 79 (28)	4 (1.3) 4 (1.4)	25 (8) 88 (30)	6 (1.9) 0
Anemia n (%) Lab (hemoglobin)[5] n (%)[3]	92 (30) 223 (78)	20 (6) 13 (4.5)	87 (28) 224 (75)	17 (5) 9 (3)
Thrombocytopenia[6] n (%) Lab (platelets)[2] n (%)[3]	67 (22) 91 (32)	15 (5) 7 (2.5)	51 (16) 84 (28)	8 (2.5) 5 (1.6)

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX, ADLB (4-13-2021)

[1] Includes preferred terms: neutropenia, neutrophil count decreased, and neutropenic sepsis
[2] Grading based on CTCAE 4.03 Investigations
[3] Demoninator = number of patients in each arm who had a baseline and at least 1 post baseline laboratory assessment and, ranged from 285 to 298.
[4] Includes preferred terms: leukopenia and white blood cell count decreased
[5] Grading based on CTCAE 4.03 Blood and lymphatic system disorders: Anemia
[6] Includes preferred terms: thrombocytopenia and platelet count decreased

Hepatotoxicity

Based on AE reporting and analysis of laboratory assessments, hepatotoxicity was infrequent during the combination period. There were 14 patients (4.5%) in the MB02 arm and 22 patients (7%) in the EU-Avastin arm who had at least one AE in the HLT category "Liver function analyses", which includes the PTs alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, gamma-glutamyltransferase, gamma-glutamyltransferase increased, and transaminases increased. The majority of these events were Grade 1-2. In the MB02 arm, 4 patients (1.3%) had Grade ≥ 3 events, and in the EU-Avastin arm, 7 patients (2.3%) had Grade ≥ 3 events. There were no fatal events in either arm.

Based on analysis of the laboratory dataset, 16% of patients in both the MB02 and the EU-Avastin arms had at least one measurement of increased AST or ALT. The majority of these abnormalities were Grade 1-2. There was only 1 patient in the MB02 arm with Grade 3 increase AST or ALT and 3 patients in the EU-Avastin arm with Grade 3 increase AST or AST. As lab abnormalities should be reported as AEs only when they have a clinical significance, the discrepancy between safety and lab datasets is expected. There were no notable imbalances in liver-related AEs or laboratory abnormalities between the treatment arms. There were no meaningful differences between arms.

Hypersensitivity/infusion related reactions

The incidence of hypersensitivity/infusion related reactions (IRRs) is up to 2% and 36% for carboplatin and paclitaxel, respectively (U.S. product labeling for carboplatin and paclitaxel). Infusion related reactions are uncommon with the use of US-Avastin, with an incidence of about 3%.In Study MB02-C-02-17, 4 patients in the MB02 arm (1.3%) experienced a hypersensitivity reaction; no Grade ≥ 3 infusion-related reactions were reported. In the EU-Avastin arm 6 patients (1.9%) experienced a hypersensitivity reaction; of these, 2 were Grade 3. There were no Grade 4 or 5 reactions. Hypersensitivity reactions included the preferred terms: drug hypersensitivity, hypersensitivity, and infusion related reactions. There were no reports of anaphylaxis.

There were no meaningful differences between arms.

Serious adverse events

For the combination chemotherapy period, there were a total of 124 serious adverse events (SAEs): 60 in 44 patients in the MB02 arm (14%) and 64 in 43 patients the EU-Avastin arm (14%). Table 19 summarizes all SAEs occurring in at least 2 patients in at least one of the arms. The frequency for SAEs was generally within 2 patients between the arms. Analysis of SAEs does not identify any clinically meaningful difference in frequency or toxicity pattern between the arms.

Table 19. MB02-C-02-17: Serious adverse events (incidence in ≥2 patients)

Preferred Term	MB02 N=311 n (%)		EU-Avastin N=310 n (%)	
	All grades	Grade 3-4	All grades	Grade 3-4
Pneumonia	7 (2.3)	5 (1.6)	7 (2.3)	6 (1.9)
Pulmonary embolism	6 (1.9)	6 (1.9)	3 (1.0)	2 (0.7)
Febrile neutropenia	4 (1.3)	4 (1.3)	7 (2.3)	7 (2.3)
Neutropenia	3 (1.0)	3 (1.0)	6 (1.9)	6 (1.9)
Empyema	2 (0.6)	2 (0.6)	0	0
Pyrexia	2 (0.6)	0	0	0
Sudden death	2 (0.6)	0	0	0
Anemia	1 (0.3)	0	2 (0.7)	2 (0.7)
Gastroenteritis	1 (0.3)	1 (0.3)	2 (0.7)	2 (0.7)
Pneumothorax	1 (0.3)	0	2 (0.7)	2 (0.7)
Asthenia	0	0	2 (0.7)	2 (0.7)
Fatigue	0	0	2 (0.7)	2 (0.7)
General Physical Health Deterioration	0	0	2 0.7)	0

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX (4-13-2021)

Adverse events of special interest (AESI) are described below in the subsection Product Specific Safety Concerns.

Dropouts and/or Discontinuations

Toxicities were to be managed according to the Avastin, paclitaxel, and carboplatin SmPc.

Based on AE reporting, 35 patients in the MB02 arm (11%) and 32 patients in the EU-Avastin arm (10%) discontinued study drugs because of an AE (including fatal AEs) during the combination period. Based on exposure data, only one patient continued paclitaxel/carboplatin after discontinuing bevacizumab. The patient received 1 dose of carboplatin, 1 dose of EU-Avastin, and 2 doses of paclitaxel.

The reasons for MB02 or EU-Avastin discontinuation during the combination period, not including fatal AEs, are summarized in Table 20. Four (4) patients in the MB02 arm and 5 patients in the EU-Avastin arm had more than one preferred term that led to treatment discontinuation. Some of the reasons for treatment discontinuation are unrelated to administration of chemotherapy MB02 or EU-Avastin, for example, fall, pneumonia, pneumothorax, and sciatica. Overall, these results show no meaningful differences between the two treatment arms.

Table 20. MB02-C-02-17: Adverse events leading to study drug discontinuation

Preferred Term	MB02 N=311	EU-Avastin N=310
Pulmonary embolism	5	2
Anemia	2	2
Empyema	2	0
General physical health deterioration	2	6
Hemoptysis	2	1
Thrombocytopenia	2	0
Asthenia	1	0
Atrial fibrillation	1	0
Cerebral ischemia	1	0
Deep vein thrombosis	1	1
Dyspnea exertional	1	0
Embolism	1	0
Fall	1	0
Femoral neck fracture	1	0
Fibrin D dimer increased	1	0
Hemorrhage intracranial	1	0
Hypertensive crisis	1	0
Hypoalbuminemia	1	0
Intestinal perforation	1	0
Ischemic stroke	1	1
Left ventricular dysfunction	1	0

Neuropathy peripheral	1	1
Platelet count decreased	1	2
Pneumonia	1	1
Pneumothorax	1	0
Tumor lysis syndrome	1	0
Venous thrombosis	1	0
Bone pain	0	1
Condition aggravated	0	1
Diverticular perforation	0	1
Drug hypersensitivity	0	1
Febrile neutropenia	0	2
Gastric ulcer perforation	0	1
Hemoglobin decreased	0	2
Hypertension	0	1
Peripheral sensory neuropathy	0	1
Peroneal nerve palsy	0	1
Pneumothorax spontaneous	0	1
Sciatica	0	1
Septic shock	0	1
Spinal pain	0	1
Thoracic vertebral fracture	0	1
Transaminases increased	0	1
Vasculitis	0	1
Weight decreased	0	1
White blood cell count decreased	0	1

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX, ADLB (4-13-2021)

Product Specific Safety Concerns

Following FDA recommendations, mAbxience defined adverse events of special interest (AESIs) as follows:

- Gastrointestinal perforations and fistulae
- Posterior reversible encephalopathy syndrome (PRES)
- Proteinuria
- Wound healing complications
- Hypertension
- Arterial thromboembolism
- Venous thromboembolism
- Congestive heart failure
- Cardiac events (SOC cardiac disorders not included in other AESIs).
- Hemorrhage, pulmonary hemorrhage/hemoptysis

- Aneurysm and artery dissection
- Neutropenia and infections
- Hypersensitivity reactions
- Osteonecrosis of jaw.

Arterial thromboembolism (ATE) and venous thromboembolism (VTE)

To investigate the events of ATE and VTE, a narrow standard MedRA Querry (SMQ) analysis was conducted. Fifteen patients (4.8%) in the MB02 arm and 6 patients (1.9%) in the EU-Avastin arm had an event that included in at least one "embolic and thrombotic events" defined by the following narrow SMQs: "embolic and thrombotic events, arterial", "embolic and thrombotic events, venous", and "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous". The results of these queries are summarized in Table 21. The table lists each event under the umbrella category "Embolic and thrombotic events" and under the specific subcategory (an event may be included in more than one category).

Overall, there is a slight imbalance in the incidence of ATE/VTE between the MB02 and EU-Avastin arms. This is a reflection of a higher rate of pulmonary embolism AEs and embolism AEs in the MB02 arm. FDA did not identify any clinically notable differences in the frequency of ATE/VTE events between arms. The observed incidence of these events is within the expected incidence as described in the Avastin USPI and the differences between arms are likely related to the inherent variability in the study population.

Table 21. MB02-C-02-17: AESI by SMQ and PT for ATE/VTE events

SMQ NAME	Preferred Term	MB02 N=311	EU-Avastin N=310
Embolic and thrombotic events	Acute myocardial infarction	1	0
	Cerebral ischemia	1	0
	Deep vein thrombosis	1	1
	Embolism	2	0
	Ischemic stroke	1	1
	Pulmonary embolism	7	3
	Thrombophlebitis	0	1
	Thrombosis	1	0
	Venous thrombosis	1	0
Embolic and thrombotic events, arterial	Acute myocardial infarction	1	0
	Ischemic stroke	1	1
Embolic and thrombotic events, venous	Deep vein thrombosis	1	1
	Pulmonary embolism	7	3
	Thrombophlebitis	0	1
	Venous thrombosis	1	0

Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous	Cerebral ischemia	1	0
	Embolism	2	0
	Thrombosis	1	0

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX, ADLB (4-13-2021)

Bleeding/hemorrhages and pulmonary hemorrhage

To investigate hemorrhage events, a modified narrow SMQ search was conducted, including the narrow SMQs:

- "central nervous system hemorrhages and cerebrovascular conditions",
- "gastrointestinal hemorrhage",
- "gastrointestinal ulceration"
- "gastrointestinal perforation, ulceration, hemorrhage or obstruction",
- "hemorrhage terms (excl. laboratory terms)",
- "hemorrhages", and
- "hemorrhagic central nervous system vascular conditions"

The search included PTs containing the word hemorrhage or the medical term for a specific type of bleeding, such as hemoptysis or epistaxis. The PTs of anal abscess, cerebral ischemia, diverticular perforation, gastric ulcer perforation, intestinal perforation, ischemic stroke, and esophageal dilation procedure were omitted from the query.

A total of 29 (9%) and 21 (7%) patients in the MB02 and EU-Avastin arms, respectively, experienced one or more bleeding events as summarized in Table 22. There were 2 fatal bleeding events in patients on the MB02 arm (hemoptysis and pulmonary hemorrhage) and 1 fatal bleeding event on the EU-Avastin arm (pulmonary hemorrhage). There were no Grade 4 events on either arm. One patient on the MB02 arm had a Grade 3 bleeding event (purpura) while 2 patients in the EU-Avastin arm had Grade 3 bleeding events (hemoptysis and epistaxis).

The number of patients with hemorrhagic events was similar between the arms although there were differences at the level of specific PTs; most of these events were Grade 1-2 AEs. There were 10 patients in the MB02 arm (3.2%) and 5 patients the EU-Avastin arm (1.6%) who experienced events in the group term pulmonary hemorrhage.

The overall incidence of hemorrhagic events is lower than expected for this study. For example, the incidence of epistaxis ranges from > 10% to 55% in the clinical studies described in the Avastin UPSI; in contrast, the incidence of epistaxis in Study MB02-C-02-17 was 3.8% and 3.6% in the MB02 and EU-Avastin arms respectively.

Although the incidence of hemorrhagic events is inconsistent with the historical experience and likely reflects under-reporting of common Grade 1 events (epistaxis, gingivorrhagia), the incidence of clinically significant hemorrhages is similar to the incidence reported in prior clinical trials of bevacizumab products; therefore, this

discrepancy did not impact the conclusions drawn from the study. There were no clinically significant differences between arms.

Table 22. MB02-C-02-17: AESI by PT for hemorrhagic/bleeding events

Preferred Term	MB02 N=311	EU-Avastin N=310
Epistaxis	12	11
Hemoptysis	8	4
Hematuria	3	2
Pulmonary hemorrhage	2	1
Upper gastrointestinal hemorrhage	2	0
Hemorrhage intracranial	1	0
Purpura	1	0
Gingival bleeding	0	2
Hematoma	0	1
Hemorrhage	0	1
Hemorrhoidal hemorrhage	0	1
Rectal haemorrhage	0	1

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX (4-13-2021)

Cardiac disorders and congestive heart failure

To investigate cardiac disorders, a search was conducted for the following narrow SMQs: “cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)”, “cardiac arrhythmias”, “cardiac failure”,“cardiomyopathy”, and “conduction defects".

Cardiac disorders were observed in 8 (2.5%) and 6 (1.9%) of patients in the MB02 and EU-Avastin arms, respectively. Table 23 summarizes these events at the HLT level. There was 1 fatal event in the MB02 arm of the PT cardiac failure acute. Two patients in the MB02 arm had Grade 3 events of the PTs atrial fibrillation and electrocardiogram QT prolongation. There were no Grade 4 events on either arm. There were no meaningful differences in cardiac disorders between the two arms.

Table 23. MB02-C-02-17: AESI by SMQ and HLT for cardiac events

HLT	MB02 N=311	EU-Avastin N=310
Supraventricular arrhythmias	4	2
ECG investigations	2	2
Cardiomyopathies	1	0
Heart failures NEC	1	0
Myocardial disorders NEC	1	0
Cardiac function diagnostic procedures	0	1
Ventricular arrhythmias and cardiac arrest	0	1

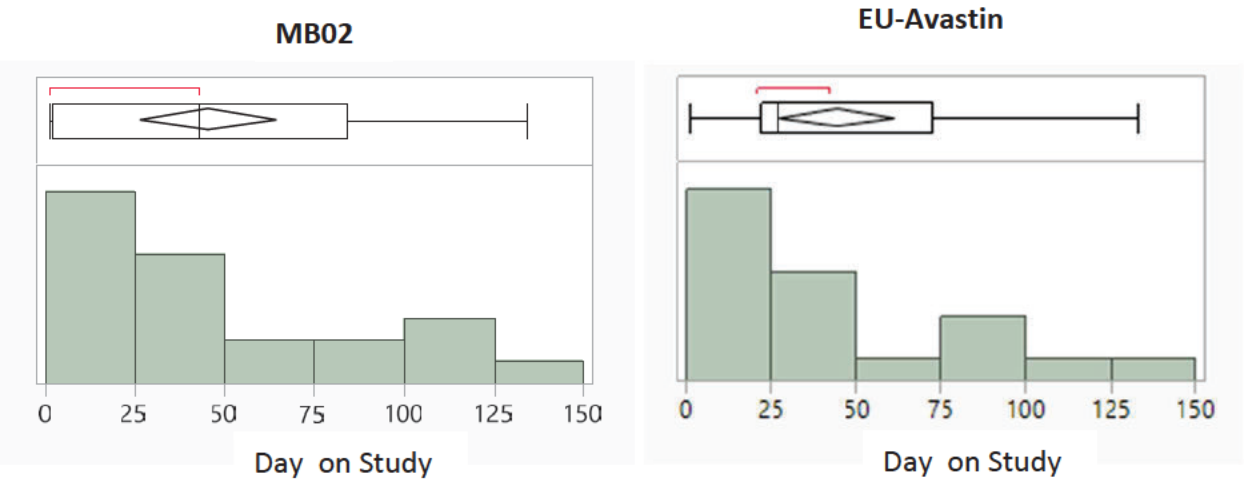
Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX (4-13-2021)

Hypertension

The database was queried for the SMQ "hypertension", which includes the following PTs: "blood pressure increased", "blood pressure diastolic increased", "essential hypertension", "hypertension", and "hypertensive crisis". At least one hypertensive event was observed in 23 (7%) patients and 20 (6%) patients in the MB02 and the EU-Avastin arm, respectively. There were no Grade 4 or 5 events. Grade 3 events were observed in 5 patients in each arm. There was no meaningful difference in hypertensive disorders between the two arms.

Figure 5 shows the distribution of the first event of hypertension with respect to the number of days on study treatment for the MB02 and EU-Avastin arms. While the median time to first hypertension event was earlier in the EU-Avastin arm as compared to the MB02 arm, 27 days and 43 days respectively, the distribution between the arms is similar, with most first events occurring within the first 50 days.

Figure 5. MB02-C-02-17: Distribution of first AE of hypertension



Source: Reviewer Figure MB02-C-02-17 ADSL, ADEX, ADAE (4-13-2021)

Blood pressure is directly affected by VEGF levels. As per study protocol, monitoring of blood pressure was conducted before each treatment administration.

Table 24 and Figure 6 summarize the distribution of systolic blood pressure measurements at the beginning of each cycle, during the combination period.

As seen in Table 24 variations in mean systolic blood pressure were minimal between cycles with a difference in the MB02 arm between Cycle 1 and the highest mean observed (Cycle 3) of 2.2 mm Hg, and a difference in the EU-Avastin arm between Cycle 1 and the highest mean observed (Cycle 4) of 2.7 mm Hg. For each cycle, the

difference in mean systolic blood pressure between arms (Δ means) ranged from -0.52 to 1.21 mmHg. The differences within an arm and between arms were minimal and of no clinical importance. The distribution of measurements are graphically displayed by cycle in side by side whisker box plots, with outliers, in Figure 6. There were no meaningful differences between arms.

Table 24. MB02-C-02-17: Mean systolic blood pressure (mm Hg) by cycle

Cycle[1]	MB02			EU-Avastin			Δ means
	N[2]	Mean SBP	Std Dev	N[2]	Mean SBP	Std Dev	
1[3]	311	122.3	8.95	309	121.9	9.20	0.48
2	288	123.0	9.50	295	123.5	9.15	-0.52
3	258	124.5	9.39	266	123.6	9.05	0.84
4	241	124.4	8.81	255	124.6	8.29	-0.17
5	218	124.0	8.43	235	122.8	8.42	1.21
6	207	122.9	9.89	220	123.1	8.45	-0.21
7[4]	119	122.7	9.00	136	123.6	8.53	-0.86

Source: Reviewer Figure MB02-C-02-17 ADSL, ADEX, ADLB (4-13-2021)

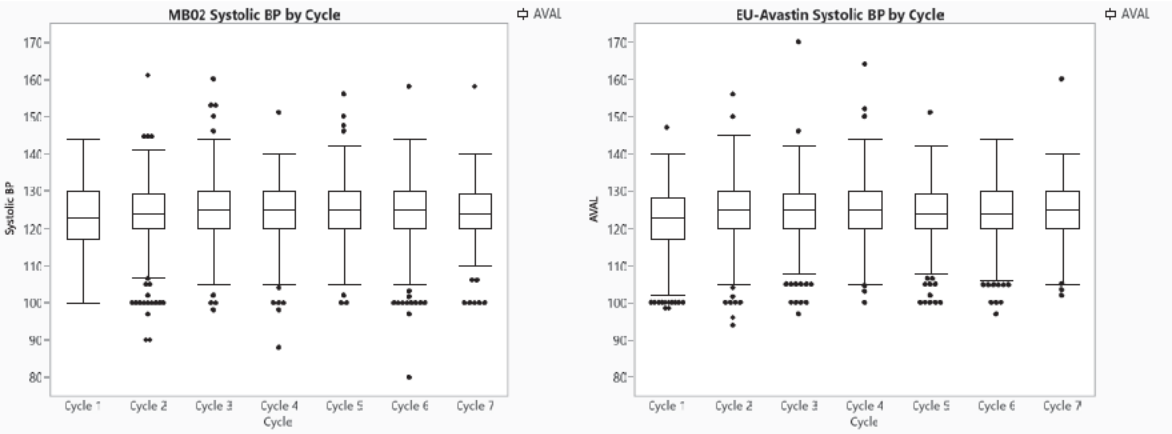
[1] Includes only vital sign assessments within 21 days of last chemotherapy administration.

[2] N = number of patients with assessment at time point

[3] Includes baseline vital assessments made prior to administration of combination therapy on Cycle 1 Day 1.

[4] Includes vital sign assessments made on Cycle 7 Day 1 prior to administration of monotherapy, if within 21 days of last chemotherapy administration.

Figure 6. MB02-C-02-17: Systolic blood pressure distribution by cycle



Source: Reviewer Figure MB02-C-02-17 ADSL, ADEX, ADLB (4-13-2021)

Table 25 and Figure 7 summarize the distribution of diastolic blood pressure measurements at the beginning of each cycle. As seen in Table 25, variations in mean

diastolic blood pressure were minimal between cycles with a difference in the MB02 arm between Cycle 1 and the highest mean observed (Cycle 3) of 1.3 mm Hg, and a difference in the EU-Avastin arm between Cycle 1 and the highest mean observed (Cycles 3,4, 5) of 1.4 mm Hg. For each cycle, the difference in mean systolic blood pressure between arms (Δ means) ranged ranged from -0.43 to 0.64 mmHg. The differences within an arm and between arms were minimal and of no clinical importance. The distribution of measurements, with outliers, are graphically displayed by cycle in side by side whisker box plots in Figure 7.

Table 25: MB02-C-02-17: Mean diastolic blood pressure (mm Hg) by cycle

Cycle[1]	MB02			EU-Avastin			Δ means
	N[2]	Mean DBP	Std Dev	N[2]	Mean DBP	Std Dev	
1[3]	311	75.9	6.95	309	75.3	7.10	0.60
2	288	76.8	7.17	295	76.2	6.75	0.64
3	259	77.2	7.07	266	76.7	7.09	0.46
4	241	77.0	7.56	255	76.7	6.24	0.33
5	218	77.1	6.75	235	76.7	6.82	0.38
6	207	76.5	7.19	220	76.3	6.69	0.21
7[4]	192	76.2	6.71	206	76.6	7.28	-0.43

Source: Reviewer Figure MB02-C-02-17 ADSL, ADEX, ADLB (4-13-2021)

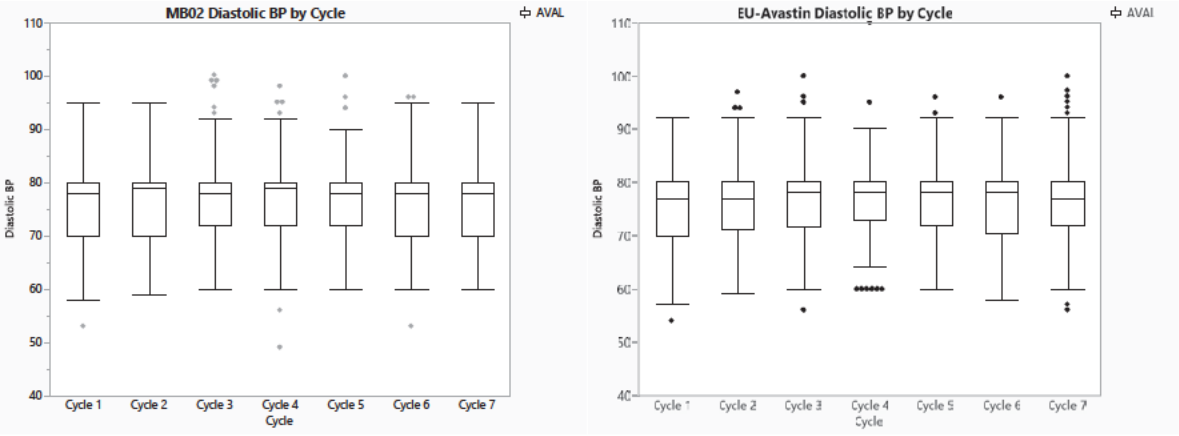
[1] Includes only vital sign assessments within 21 days of last chemotherapy administration.

[2] N = number of patients with assessment at time point

[3] Includes baseline vital assessments made prior to administration of combination therapy on Cycle 1 Day 1.

[4] Includes vital sign assessments made on Cycle 7 Day 1 prior to administration of monotherapy, if within 21 days of last chemotherapy administration.

Figure 7. MB02-C-02-17: Diastolic blood pressure distibution by cycle



Source: Reviewer Figure MB02-C-02-17 ADSL, ADEX, ADLB (4-13-2021)

The following are the grading criteria for hypertension per the CTCAE v 4.03 dictionary:

- Grade 1: prehypertension (systolic BP 120-139 mm Hg or diastolic BP 80-89 mm Hg)
- Grade 2: Stage 1 hypertension (systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg); medical intervention indicated; recurrent or persistent (≥ 24 hrs.); symptomatic increase by > 20 mm Hg (diastolic) or to > 140/90 mm Hg if previously within normal limits; monotherapy indicated
- Grade 3: Stage 2 hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
- Grade 4: life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated.

As described in the Avastin USPI, across clinical studies, the incidence of hypertension varies by study and can reach up to 42%; Grade 3-4 hypertension with Avastin ranged from 5% to 18% (Avastin USPI). In the Avastin E4599 study in patients with NSCLC, the incidence of Grade 3-4 hypertension in the Avastin arm was 8%.

Based on analyses of blood pressure measurements in the vital signs dataset, 93% and 96% of patients in the MB02 and EU-Avastin arms, respectively, had at least one systolic blood pressure measurement ≥ 120 mm Hg during the combination therapy period, with 10% of patients in each arm having at least one systolic blood pressure measurement ≥ 140 mm Hg. Fifteen percent (15%) and 12% of patients in the MB02 and EU-Avastin arms had at least one diastolic blood pressure measurement ≥ 90 mm Hg during the combination period. This analysis of vital signs shows that hypertension as reported in the vital signs dataset show, appears to be within the expected range for patients with NSCLC exposed to bevacizumab.

No events of PRES were reported; there were three events of Grade 1-2 encephalopathy, two in the MB02 arm and one in the EU-Avastin arm. No treatment discontinuation or dose modification followed this diagnosis. No events of thrombotic microangiopathy (TMA) were reported.

Based on the totality of the safety data analysed, there was no meaningful differences in the incidence or severity of hypertension between the two arms.

Proteinuria and renal function

Patients enrolled to the study must have had a urine protein to creatinine ratio of < 1 or if the urine protein to creatinine ratio ≥ 1, then < 1 g of protein in a 24 hour urine collection. Urinalysis was assessed Day 1 of each cycle until Cycle 7 and then every 3 weeks. For routine on-study urinalysis, dipstick was sufficient as long as the urine protein result was < 2+; otherwise, 24 hour urine must be < 1 g of protein in 24 hours.

Proteinuria as reported as an adverse events was observed in 5 patients (1.6%) in the MB02 arm and 12 patients (3.9%) in the EU-Avastin arm during the combination period.

There were no reports of nephrotic syndrome. There were no Grade 4 or 5 events. There was 1 Grade 3 event occurring in a patient on the EU-Avastin arm.

To further assess the incidence of proteinuria, a review of the lab dataset was conducted. On study MB02-C-02-17, 288 patients on the MB02 arm and 297 patients on the EU-Avastin arm had at least one urine protein urinalysis assessment after the first dose of study drugs during the combination period. Abnormal urine protein assessments were reported in 26% of patients in each arm (dipstick ≥ 1+).

The distribution of grades was also similar between the arms. On the MB02 arm, 19% of patients had a maximum of 1+ protein, 6% of 2+ protein, and 1.4% of 3+ protein. On the EU-Avastin arm, 16% had a maximum of 1+ protein, 8% of 2+ protein, and 1.7% of 3+ protein. While proteinuria was frequent, most events were Grade 1 or 2, and the frequency and distribution of severity was similar between arms.

Based on an assessment of AE reporting, renal injury was infrequent. There was 1 patient on the MB02 arm with AE of acute kidney injury (Grade 1) and none on the EU-Avastin arm. There was 1 patient on the bevacizumab arm with AE of renal impairment (Grade 2) and non on the EU-Avastin arm. Review of laboratory assessments for creatinine did not identify any cases of creatinine increased above upper level normal. There were no meaningful differences between arms in the incidence of proteinuria and renal toxicities.

Gastrointestinal ulcers, perforations, and fistula
To investigate events related to ulcers, perforations, or fistulas, a modified narrow SMQ search was conducted using the following SMQs: “Gastrointestinal obstruction”, “Gastrointestinal perforation”, “Gastrointestinal perforation, ulceration, haemorrhage or obstruction”, “Gastrointestinal ulceration”. The SMQ search was modified to remove the PT esophageal dilation procedure.

Three patients in the MB02 arm (1%) and 5 patients in the EU-Avastin arm (1.6%) had at least one gastrointestinal ulcer, perforation, and fistula event. There were no Grade 5 events on either arm. There was 1 Grade 4 event on the MB02 arm of intestinal perforation. There was 1 Grade 4 event (gastric ulcer perforation) and 1 Grade 3 event (diverticular perforation) on the EU-Avastin arm.

In summary, the events ulcers and perforations were rare. No clinically significant difference in the incidence of gastrointestinal ulcers, perforations, and fistula were observed between arms.

Wound healing complications
No events of wound healing complications such as cellulitis or dehiscence were reported on Study MB02-C-02-17 during the combination period.

No events of osteonecrosis of the jaw were reported on Study MB02-C-02-17 during the combination period. One patient on the MB02 arm had an AE of pain in jaw.

6.3.3. Additional Safety Evaluations

Patients completing 6 cycles of combination therapy were allowed to continue MB02 or EU-Avastin monotherapy. If a patient discontinued paclitaxel and carboplatin before completing 6 cycles of therapy with stable disease or a response, MB02 or EU-Avastin as monotherapy was allowed with justification.

In the safety population, the median number of cycles received by patients in the MB02 arm was 9 (range 1: 18) and by patients on the EU-Avastin arm was 10 (range 1:18).

To further evaluate potential differences between arms, an analysis of safety in patients in the monotherapy portion of the study was conducted. Table 26 presents all AEs with an incidence of at least 2% and Grade 3-4 toxicities. There were no meaningful differences between arms in the toxicity observed in the monotherapy period.

Table 26. MB02-C-02-17: AEs by PT (incidence ≥ 2%), monotherapy period

PT	MB02 N=311 n (%)		EU-Avastin N=310 n (%)	
	All grades	Grade 3-4	All grades	Grade 3-4
Anemia	23 (7)	6 (1.9)	29 (9)	4 (1.3)
Asthenia	15 (4.8)	7 (2.3)	9 (2.9)	5 (1.6)
Cough	14 (4.5)	1 (0.3)	15 (4.8)	1 (0.3)
Weight decreased	13 (4.2)	2 (0.6)	5 (1.6)	1 (0.3)
Fatigue	12 (3.9)	2 (0.6)	4 (1.3)	1 (0.3)
Aspartate aminotransferase increased	11 (3.5)	3 (1.0)	8 (2.6)	2 (0.6)
General physical health deterioration	11 (3.5)	6 (1.9)	16 (5)	6 (1.9)
Proteinuria	11 (3.5)	1 (0.3)	18 (6)6	4(1.3)
Thrombocytopenia	11 (3.5)	1 (0.3)	12 (3.9)	1 (0.3)
Alanine aminotransferase increased	10 (3.2)	2 (0.6)	8 (2.6)	2 (0.6)
Headache	9 (2.9)	0	9 (2.9)	0
Nausea	9 (2.9)	0	5 (1.6)	0
Respiratory tract infection viral	9 (2.9)	0	4 (1.3)	0
Dyspnea	8 (2.6)	2 (0.6)	6 (1.9)	0
Neutropenia	8 (2.6)	1 (0.3)	9 (2.9)	1 (0.3)
Hypertension	7 (2.3)	3 (1.0)	10 (3.2)	4(1.3)
Alopecia	6 (1.9)	0	15 (4.8)	0
Back pain	3 (1.0)	1 (0.3)	7 (2.3)	1 (0.3)

Source: Reviewer Table MB02-C-02-17 ADSL, ADAE, ADEX, ADLB (4-13-2021)

In addition to Study MB02-C-02-17, the Applicant submitted Study MB02-A-05-18, a randomized, double blind, three arm, single dose, PK similarity study comparing MB02, US-Avastin, and EU-Avastin, all at a dose of 3 mg/kg in healthy male volunteers. For

more details, refer to Section5.3. A total of 114 participants (38 per arm) received treatment.

For the purpose of this analysis, only AEs reported within 22 days of the single dose of investigational product are described, as events occurring beyond this period are unlikely to be related to treatment. A total of 62 participants (54%) experienced an AE (21, 23, and 18 participants in the MB02, US-Avastin, and EU-Avastin arms respectively). A total of 10 participants (9%) experienced Grade 2 events (3, 4, and 3 participants in the MB02, US-Avastin, and EU-Avastin arms respectively); there were no Grade ≥3 events.

The AEs most frequently reported in the MB02, occurring in ≥ 2 participants, were: nasopharyngitis (16%), headache (11%), oropharyngeal pain (7%), and rhinitis (8%). The AEs most frequently reported in the US-Avastin arm were nasopharyngitis (16%), headache (11%), fatigue (5%), diarrhea (5%), and dry skin (5%). The AEs most frequently reported in the EU-Avastin arm were: headache (21%), back pain (11%), nasopharyngitis (8%), epistaxis (5%), and sleep disorder (5%).

Headache and nasopharyngitis are established bevacizumab-related AEs. As the number of participants experiencing each of these AEs is small, the observed differences in incidences are likely to be due to chance and cannot be attributed to differences in product-related toxicity. There were no meaningful differences between arms.

6.4. Clinical Conclusions on Immunogenicity

Immunogenicity was evaluated in patients with NSCLC enrolled in Study MB02-C-02-17 after multiple doses of MB02 or EU-Avastin. Samples for ADA assessment were collected over 52 weeks and at study treatment discontinuation at trough PK levels timepoints to minimize interference. Serum samples collected for immunogenicity assessment were first tested for ADA. Samples confirmed as positive for ADA were further tested for neutralizing antibodies (NAb). In Study MB02-C-02-17, ADA and Nab responses were shown to be similar between the MB02 and EU-Avastin groups. No apparent impact of ADA on safety or efficacy endpoints was observed. There were no clinically meaningful differences between arms.

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6.5. Extrapolation

The Applicant submitted data and information in support of a demonstration that MB02 is highly similar to US-Avastin notwithstanding minor differences in clinically inactive

components and that there are no clinically meaningful differences between MB02 and US-Avastin in terms of safety, purity and potency.

The Applicant is seeking licensure of MB02 for the following indication(s) for which US-Avastin has been previously licensed and for which MB02 has not been directly studied:

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment.
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen.
  Limitations of Use: Alymsys is not indicated for adjuvant treatment of colon cancer.
- Recurrent glioblastoma in adults.
- Metastatic renal cell carcinoma in combination with interferon alfa.
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of MB02 as a biosimilar for each such indication for which licensure is sought and for which US-Avastin has been previously approved. This Applicant's justification was evaluated and considered adequate, as summarized below.

Therefore, the totality of the evidence provided in the BLA supports licensure of MB02 for each of the following indications for which Amenal is seeking licensure of MB02:

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment.
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen.
  Limitations of Use: Alymsys is not indicated for adjuvant treatment of colon cancer.
- Recurrent glioblastoma in adults.
- Metastatic renal cell carcinoma in combination with interferon alfa.
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens

Analytical data
As summarized in the IPQA, the Applicant's comparative analytical program included a comparison of MB02, US-Avastin, and EU-Avastin. Multiple quality attributes using multiple lots of MB02, US-Avastin, and EU-Avastin were evaluated. Functional assays relative to the mechanism of action were analyzed using a statistical approach, and the results passed the statistical equivalence testing. OBP review staff agreed with Amneal that the totality of the comparative analytical data supports a demonstration that MB02 is highly similar to US-Avastin notwithstanding minor differences in clinically inactive components.

Additionally, the pairwise comparisons of MB02, US-Avastin, and EU-Avastin support the analytical portion of the scientific bridge between the three products needed to justify the relevance of the data generated using EU-Avastin in the comparative clinical study.

Mechanism of action
Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 [VEGFR-1] and KDR [VEGFR-2]) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Neutralizing the biological activity of VEGF regresses the vascularization of tumors, normalizes remaining tumor vasculature, and inhibits the formation of new tumor vasculature, thereby inhibiting tumor growth (Avastin USPI).

In each approved indication, the MOA of bevacizumab is to inhibit VEGF-induced angiogenesis and vascular permeability (Friedman H, 2009; Hurwitz H, 2004; Sandler A, 2006; Escudier B, 2007; Tewari K, 2014). In all conditions of use, tumor expression of VEGF is increased and this expression correlates with high risk features and lower survival. In a study (Hegde P, 2013) evaluating VEGF levels across multiple clinical studies with bevacizumab either alone or in combination with other agents, 1816 samples from patients with mCRC, NSCLC, and mRCC, high VEGF levels in plasma had an adverse prognostic effect on OS, independent of treatment. In a glioblastoma multiforme (GBM) trial, VEGF expression was increased in glioblastoma cells and nuclear VEGF expression correlated with survival (Clara C, 2014). In a cervical cancer study, VEGF expression was found to be increased in adenocarcinoma as compared to squamous cell carcinoma and high VEGF expression was associated with a poorer prognosis (Gaducci A, 2013).

The Applicant provided adequate justification to support that MB02 has the same known and potential mechanisms of action as US-Avastin for all the indications summarized above.

Pharmacokinetics
In addition to the data characterizing the PK profile of bevacizumab included in the Avastin USPI, bevacizumab exhibits a dose proportional and linear PK profile over the studied dose range (1–20 mg/kg) and similar PK characteristics across CRC, NSCLC, breast cancer, RCC, GBM, and cervical cancer (Avastin USPI; EMA Avastin SmPC; Lu

JF, 2008; Han K, 2016).

The MB02 clinical pharmacology program aimed to support the demonstration of no clinically meaningful differences between MB02 and US-Avastin by

- evaluating the single-dose pharmacokinetic similarity between MB02 and US-Avastin.
- establishing the PK portion of the scientific bridge between MB02, US-, and EU-Avastin

The geometric mean ratios and their corresponding 90% confidence intervals for all PK endpoints in Study MB02-A-05-18 comapring MB02 vs. US-Avastin, MB02 vs. EU-Avastin, and EU- vs. US-Avastin fell within the pre-defined similarity margin of 0.80 to 1.25. Based on the results from Study MB02-A-05-18, Amenal and FDA conclude that PK similarity was demonstrated. The Applicant provided adequate justification that a similar PK profile is expected between MB02 and US-Avastin.

Since similar PK was demonstrated between MB02 and US-Avastin, a similar PK profile would be expected for MB02 in patients across the indications being sought for licensure.

Immunogenicity
As summarized in the Avastin USPI, only 14 of 2233 evaluable subjects (0.63%) tested positive for treatment-emergent anti-bevacizumab antibodies as detected by an electrochemiluminescent-based assay. Further analysis of these 14 subjects using an ELISA assay concluded that 3 subjects were positive for neutralizing antibodies against bevacizumab. The clinical significance of these ADA responses to bevacizumab is unknown. The analysis of Studies MB02-A-05-18 and MB02-C-02-17 indicate that immunogenicity was similar and that treatment of subjects with NSCLC with either MB02 or EU-Avastin or US-Avastin results in similar rates of ADAs (17% and 16.1% in the MB02 and EU-Avastin arms respectively in Study MB02-C-02-17) and neutralizing antibodies (3.2% and 4.2% in the MB02 and EU-Avastin arms respectively). Based on results from study MB02-A-05-18 in healthy subjects, after single dose, there was no meaningful effect of immunogenicity on the PK of MB02. Based on the data submitted, the review team concluded that based on results from Study MB02-C-02-17, the occurrence of ADA against MB02 or EU-Avastin did not appear to impact the efficacy results or correlate with safety.

The Applicant provided adequate justification that similar immunogenicity is expected between MB02 and US-Avastin for all indications summarized above.

Safety
The expected toxicities of bevacizumab are well characterized and are summarized in the Avastin USPI, as well as multiple meta-analyses of earlier clinical trial data in various solid tumors. The MOA is common to all the indications of use. While the incidence of specific toxicities may differ across the indications (e.g., fistula is more frequent in patients with cervical cancer while hemoptysis is more frequent in patients

with NSCLC), due to the common MOA, the differing toxicities are predictable in each indication for which licensure is sought for MB02 in this application. As analyzed in this review, data from Study MB02-C-02-17 demonstrated that the type and incidence of treatment-emergent adverse events of special interest were similar MB02 and EU-Avastin and that there were no meaningful differences between arms. No new safety signals were identified that would be indicative of new toxicities for the approved bevacizumab indications.

The Applicant provided adequate justification that a similar safety profile would be expected between MB02 and US-Avastin for the indications summarized above.

Conclusions

In summary, the data submitted supports a demonstration that MB02 is highly similar to US-Avastin; the mechanism(s) of action of bevacizumab in each condition of use for which licensure is sought is the same; there are no differences in the PK and biodistribution of bevacizumab across different patient populations; there are no immunogenicity differences across patient populations; differences in the incidence of the expected toxicities in each condition of use and patient population is predictable and MYL-1402O showed a very similar toxicity profile as expected for US-Avastin.
The Division of Oncology 3 review team concludes that Amneal has provided sufficient scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity and toxicity profile) for extrapolation of the data and information submitted in the application to support licensure of MB02 for

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment.
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen.
  Limitations of Use: Alymsys is not indicated for adjuvant treatment of colon cancer.
- Recurrent glioblastoma in adults.
- Metastatic renal cell carcinoma in combination with interferon alfa.
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens

Authors

Margaret Thompson
Medical Officer

Sandra J. Casak
Clinical Team Leader

7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, bevacizumab-maly, was found to be conditionally accepted by the Agency. This name has been reviewed by DMEPA, who concluded the name was acceptable (see darrts January 28, 2022 review).

7.2. Proprietary Name

The proposed proprietary name for MB02 is conditionally approved as ALYMSYS. This name has been reviewed by DMEPA, who concluded the name was acceptable

7.3. Other Labeling Recommendations

FDA determined that the proposed labeling is compliant with Physician labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

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

The Amneal proposed label follows this recommendation. All preclinical and clinical data for the indications being soughts are as in the Avastin USPI. Sections 2 and 16 have been revised to reflect MB02- specific information as well as to comply with current labeling practices.

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8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

All studies were conducted according to Good Clinical Practice (GCP) as described in International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the ethical principles outlined in the Declaration of Helsinki. The studies were conducted in compliance with the protocols. Informed consent, protocol, amendments, and administrative letters for the studies received Institutional Review Board/Independent

Ethics Committee approval prior to implementation. Subjects signed informed consent documents. Written informed consent was obtained prior to subjects entering the studies (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. The investigators conducted all aspects of these studies in accordance with applicable national, state, and local laws of the pertinent regulatory authority

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

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9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application as it was determined that there were no issues where the Agency needed input from the Committee.

Author:
Sandra J. Casak
Clinical Team Leader

10. Pediatrics

On May 27, 2021, FDA issued an agreement letter to mAbxience regarding an agreed Initial Pediatric Study Plan (iPSP) submitted April 19, 2021 to PIND 135128 MB02. The application contains a request for full waiver of the requirement for study of MB02 in pediatric patients for each of the indications approved for US-licensed Avastin.
The Agency has determined that, at this time, no pediatric studies will be required under PREA for this BLA. See QA.I.16, FDA Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act (Rev. 2) (Sept. 2021).

Authors:

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11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

No clinical postmarketing commitments or requirements are planned.

Authors:
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12. Appendices

12.1. References

AVASTIN (bevacizumab) Summary of Product Characteristics (SPC), https://www.ema.europa.eu/documents/product-information/avastin-epar-product-information_en.pdf
AVASTIN (bevacizumab) United States Prescribing Information (USPI), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125085s323lbl.pdf.
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12.2. Financial Disclosure

Amneal provided financial disclosure information for Studies MB02-A-05-18 and MB02-C-02-17.

For both Study MB02-C-02-17 and Study MB02-A-05-18, Amneal provided a signed form 3454 certifying that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in MB02 or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). A copy of a signed form 3454 was provided for all investigators and subinvestigators.

Covered Clinical Study: MB02-C-02-17: STELLA

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 565		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study:0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

Covered Clinical Study: MB02-A-05-18

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study:0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 N/A		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

12.3. Nonclinical Appendices

Author: Dubravka Kufrin and Team Leader Matthew Thompson

12.3.1. General Toxicology

MB02 (BEVZ92) (50 mg/kg) and EU-Avastin 50 mg/kg products were administered to cynomolgus monkeys by intravenous infusion once every 3 days for 28 days for a total of 8 doses. The test species, dose, regimen, and duration of the study were appropriate.

There were no toxicologically signficiant differences noted in this study. Microscopic findings of physeal thickening were present in the femurs of males and females administered BEVZ92 and in the femurs of males administered EU-Avastin. Adrenal cortical eosinophila was present in males and females administered BEVZ92 or EU-Avastin.

Repeat-Dose Toxicity/Toxicokinetics

Study Title: BEVZ92 (Biosimilar) and Avastin: 28 Day Intravenous (Infusion) Administration Toxicity Study in the Monkey

Methods

Total Doses:	0, 50 mg/kg/twice per week
Frequency of dosing:	Once on the administration day 1, 4, 8, 11, 15, 18, 22, and 25.
Number/Sex/Group:	3/sex/group
Dose volume:	10 mL/kg
Formulation/Vehicle:	Solutions in 0.9% NaCl
Route of administration:	INTRAVENOUS
Species:	MONKEY
Strain:	CYNOMOLGUS
Age / Sexual Maturity:	125 to 206 weeks old
Comment on Study Design:	None
Dosing Solution Analysis:	Acceptable

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

(Excerpted from Applicant's submission)

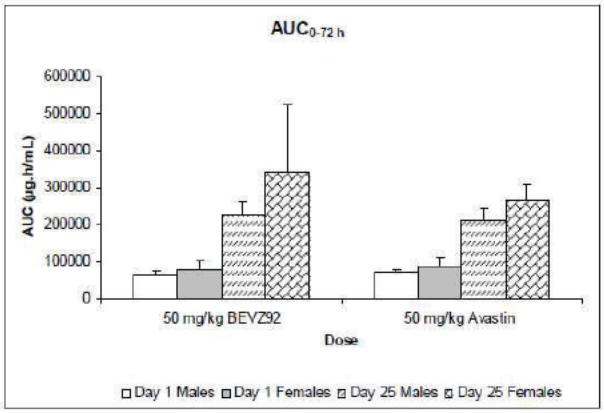
Observations and Results

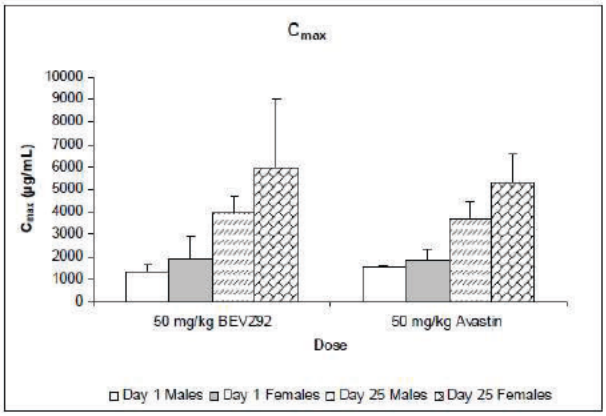
Mortality	None
Clinical Signs	Unremarkable
Body Weight	Unremarkable
Ophthalmology	Unremarkable
EKG	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Unremarkable
Histopathology	

Tissue/Finding		Male			Female		
		Control	BEVZ92	Avastin	Control	BEVZ92	Avastin
Femur/marrow	Examined/ Grade	3	3	3	3	3	3
Physeal thickening	1			1		2	
	2		2	2			
Adrenal							
Cortical eosinophilia	1		2	2		1	2
	2		1				
Uterus							
Reduced gland	1					2	2
	2					1	1

Toxicokinetics

Mean $AUC_{0\text{-}72h}$ and Cmax for BEVZ92 and EU-Avastin following IV infusion in monkeys





(Excerpted from Applicant's submission)

BEVZ92 toxicokinetic data

Occasion	Gender		C_{max} (µg/mL)	t_{max} (h)	$AUC_{0-72\ h}$ (h*µg/mL)	RA_{AUC}	RA_{Cmax}
Day 1	Male	N	3	3	3	NA	NA
		Mean	1360	1.33	62000	NA	NA
		SD	250	1.44	12800	NA	NA
		CV%	18.4	108.3	20.7	NA	NA
	Female	N	3	3	3	NA	NA
		Mean	1900	24.7	78100	NA	NA
		SD	978	41.0	24000	NA	NA
		CV%	51.3	166.2	30.7	NA	NA
Day 25	Male	N	3	3	3	3	3
		Mean	3940	2.50	227000	3.69	2.90
		SD	775	0.866	36700	0.260	0.312
		CV%	19.7	34.6	16.2	7.0	10.8
	Female	N	3	3	3	3	3
		Mean	5930	32.2	340000	4.16	3.10
		SD	3100	27.4	181000	0.933	0.482
		CV%	52.3	85.3	53.4	22.4	15.6

t applicable

(Excerpted from Applicant's submission)

EU-Avastin toxicokinetic data

Occasion	Gender		C_{max} (µg/mL)	t_{max} (h)	$AUC_{0-72\ h}$ (h*µg/mL)	RA_{AUC}	RA_{Cmax}
Day 1	Male	N	3	3	3	NA	NA
		Mean	1520	0.833	70300	NA	NA
		SD	56.0	0.577	8080	NA	NA
		CV%	3.7	69.3	11.5	NA	NA
	Female	N	3	3	3	NA	NA
		Mean	1830	0.833	87600	NA	NA
		SD	502	0.577	22300	NA	NA
		CV%	27.4	69.3	25.4	NA	NA
Day 25	Male	N	3	3	3	3	3
		Mean	3720	8.67	213000	3.03	2.45
		SD	744	13.3	31800	0.391	0.476
		CV%	20.0	153.3	15.0	12.9	19.4
	Female	N	3	3	3	3	3
		Mean	5300	4.00	265000	3.07	2.91
		SD	1300	4.33	41100	0.276	0.179
		CV%	24.5	108.3	15.5	9.0	6.2

ot applicable

(Excerpted from Applicant's submission)

12.4. Clinical Pharmacology Appendices

12.4.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity study (MB02-A-05-18), serum MB02, US-Avastin and EU-Avastin concentrations measured using a validated enzyme-linked immunosorbent assay (ELISA) method (Report 8370499 (1009537-HAR-IC17-045)) were suitable for assessment of PK similarity. Both the method validation entitled "Method validation for the determination of Avastin and MB02 in human serum" and sample analysis for the

study were performed at [redacted] (b) (4) In this method, recombinant human VEGF165 [redacted] (b) (4) coated in 96-well microtiter plate was used to capture serum bevacizumab and Anti-Human IgG1-HRP [redacted] (b) (4) was used to detect the bound analytes. shows the summary of ELISA assay method performance in quantification of serum MB02, US-Avastin and EU-Avastin during the method validation.

Table 27. Summary of the bioanalytical method validation and in-study performance for measurement of MB02, US-Avastin and EU-Avastin

Bioanalytical method review summary	Method validation was adequate to support the study of trial MB02-A-05-18.	
Materials used for calibration curve & concentration	MB02: lot 17A043 (method validation), lot 19A010 (sample analysis in study MB02-A-05-18). Calibrator concentrations: 200 (anchor), 400, 600, 1000, 1500, 2200, 2800, 3500, 4000 and 5000 (anchor) ng/mL.	
Validated assay range	400 (LLOQ) – 4000 (ULOQ) ng/mL.	
Material used for QCs & concentration	For method validation: • MB02: lot 17A043, US-Avastin: 3155155, EU-Avastin: B8027. For sample analysis in Study MB02-A-05-18: • MB02: lot 19A010. Matrix: Pooled human serum QC concentrations: 400 ng/mL (LLOQ), 800 ng/mL (LQC), 1800 ng/mL (MQC), 3000 ng/mL (HQC), 4000 ng/mL (ULOQ).	
Minimum required dilutions (MRDs)	1:10	
Source & lot of reagents (LBA)	For method validation: • VEGF165: [redacted] (b) (4), lot II5116061, II5617071, II6018012. • Anti-Human IgG1-HRP: [redacted] (b) (4), lot E0016-Q787, D0317-W207, L3117-PH28B. • Pooled Human Serum: [redacted] (b) (4) multiple lots (not specified). For sample analysis in study MB02-A-05-18: • VEGF165: [redacted] (b) (4) lot II6018012. • Anti-Human IgG1-HRP: [redacted] (b) (4) lot L3117-SH69. • Pooled Human Serum: Pooled in house, various lots (not specified).	
Regression model & weighting	4PL with $1/Y^2$ weighting	
Validation Parameters	**Method Validation Summary**	**Acceptability**

Calibration curve performance during accuracy & precision Per BMV, At least 75% and minimum of 6 non-zero calibrators without anchor points and LBA: ±20% bias (±25% at lower limit of quantitation [LLOQ]), ≤ 20%CV	No of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)	8 Calibrators were used in the validation and analysis runs	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ MB02 US-Avastin EU-Avastin	 -7.0 to 5.4% -3.8 to 5.4% -8.4 to 10.1%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ MB02 US-Avastin EU-Avastin	 ≤ 4.5% ≤ 1.9% ≤ 4.2%	Yes
QCs performance during accuracy & precision Per BMV, LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) in 5 QCs MB02 US-Avastin EU-Avastin	 9.5 to 13.1% -3.5 to 1.5% -1.6 to 6.3%	Yes
	Inter-batch %CV MB02 US-Avastin EU-Avastin	 ≤ 6.2% ≤ 8.7% ≤ 7.6%	Yes
	Percent total error (TE) MB02 US-Avastin EU-Avastin	 ≤ 18.6% ≤ 12.2% ≤ 13.9%	Yes
Selectivity & matrix effect	Normal matrix MB02 9 of 10 (90%) samples met criteria at the LLOQ, 9 of 10 (90%) samples met criteria at the HQC, 10 of 10 (100%) unspiked samples generated a result less than the LLOQ. EU-Avastin 10 of 10 (100%) samples met criteria at the LLOQ, 9 of 10 (90%) samples met criteria at the HQC, 10 of 10 (100%) unspiked samples generated a result less than the LLOQ. US-Avastin 9 of 10 (90%) samples met criteria at the LLOQ, 10 of 10 (100%) samples met criteria at the HQC, 10 of 10 (100%) unspiked samples generated a result less than the LLOQ.		Yes
Lipemic Effect	MB02		Yes

	4 of 5 (80%) samples met criteria at the LLOQ, 5 of 5 (100%) unspiked samples generated a result less than the LLOQ. EU-Avastin and US-Avastin 5 of 5 (100%) samples met criteria at the LLOQ, 5 of 5 (100%) unspiked samples generated a result less than the LLOQ.	
Hemolysis Effect	MB02, EU-Avastin and US-Avastin 5 of 5 (100%) samples met criteria at the LLOQ, 5 of 5 (100%) unspiked samples generated a result less than the LLOQ.	Yes
VEGF Interference	No interference at LLOQ with up to 15 ng/mL of $VEGF_{165}$ present. No interference at ULOQ with up to 100 ng/mL of $VEGF_{165}$ present.	Yes
Dilution linearity & hook effect	Dilution factors of 312.5, 625, 1250 and 2500 were confirmed for MB02, US-Avastin and EU-Avastin. No hook effect was observed.	Yes
Bench-top/process stability	Samples for MB02, US-Avastin and EU-Avastin at the LQC and HQC were stable for 24 hours on the bench top.	Yes
Refrigerator Stability	Samples for MB02, US-Avastin and EU-Avastin at the LQC and HQC were stable for 72 hours at 2-8 °C.	Yes
Working Stock Solution Stability	Samples for MB02, US-Avastin and EU-Avastin at the LQC and HQC were stable for at least for 179 days for EU-Avastin and US_Avastin and 37 days for MB02 following storage at <-50°C.	Yes
Freeze-Thaw stability	Samples for MB02, US-Avastin and EU-Avastin at LQC and HQC were stable for up to 6 F/T cycles for all drugs following storage at <-10°C and <-50°C.	Yes
Long-term storage	Samples for MB02, US-Avastin and EU-Avastin at LQC and HQC were stable for 367 days for MB02 and 366 days for US-Avastin and 36 days for EU-Avastin following storage at <-10°C, and stability was retained for for 366 days for EU-Avastin and US-Avastin and 367 days for MB02 following storage at <-50°C.	Yes
Parallelism	MB02 and EU-Avastin: Absolute difference between inter-run QC mean %Bias: ≤-12.8%. MB02 and US-Avastin: Absolute difference between inter-run QC mean %Bias : ≤13.86%.	Yes
Method Performance in Study MB02-A-05-18		
Assay passing rate	• 106/133 (79.7%) including ISR	Yes

Standard curve performance	MB02 • Cumulative bias range: not calculated • Cumulative precision: ≤ 5.4% CV	Yes
QC performance	MB02 (LQC to HQC) • Cumulative bias range: -0.9 to 1.1% • Cumulative precision: ≤ 13.5% CV	Yes
Method reproducibility	92% of the 200 samples evaluated for ISR were within specification (%variability within ±30%). This satisfied the ISR acceptance criteria of >67% of samples evaluated for ISR within specification.	Yes
Study sample analysis/ stability	The maximum sample storage duration between collection and analysis for samples was 238 days, which was within the current demonstrated long term stability of 366 days at -50°C.	

**Concentration data from impacted samples removed for PK analysis*

12.4.2. Other Clinical Pharmacology Information

Study MB02-A-06-20 was conducted to compare PK between MB02-SP (the product used during clinical development), MB02-DM (the to-be-marketed product) and US-Avastin. The 90% CI for GMRs of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} were within 80 - 125% for comparisons between MB02-SP to MB02-DM; MB02-SP to US-Avastin; MB02-DM to US- Avastin. These resultssupport comparability between MB02-SP and MB02-DM and confirms that the changes in the manufacturing process do not preclude the ability to leverage the clinical studies that were performed with MB02-SP lots.

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

/s/

GINA M DAVIS
04/13/2022 11:46:20 AM

SANDRA J CASAK
04/13/2022 11:58:45 AM

IBILOLA A FASHOYIN-AJE
04/13/2022 12:05:47 PM