EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 February 2021
EMA/CHMP/680012/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lextemy

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/005611/0000

Note

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

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Table of contents

List of abbreviations

ADA	anti-drug antibodies
AE	adverse event
AEI	adverse event of interest
AEX	anion exchange chromatography
ANOVA	analysis of variance
AS	active substance
ATC	Anatomical Therapeutic Chemical classification
ATE	arterial thromboembolic events
AUC	area under the concentration-time curve
BDR	blinded data review
BOR	best overall response
BORR	best overall response rate
CE-SDS	Capillary Electrophoresis-Sodium Dodecyl Sulphate
CEX	cation exchange chromatography
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovarian
CI	confidence interval
cIEF	Capillary Isoelectric Focusing
CLB	competitive ligand binding
Cmax	maximum observed drug concentration
CMH	Cochran-Mantel-Haenszel
Cmin	minimum observed drug concentration
CP	carboplatin-paclitaxel
CPP	critical process parameter
CR	complete response
CRF	case report form
CT	computed tomography
CV	coefficient of variation
DCR	disease control rate
DNA	Deoxyribonucleic Acid
DOR	duration of response
ECG	electrocardiogram
ECL	electrochemiluminescence
ECLU	electrochemiluminescence units
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
EML4-ALK	echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase
EOS	end of study
EOT	end of treatment
EU	European Union
FP	finished product
FU	fluorouracil
GBM	glioblastoma multiforme
GI	gastrointestinal
GMR	geometric mean ratio

HC	heavy chains
HCP	host cell proteins
HIC	Hydrophobic Interaction Chromatography
HMWP	high molecular weight proteins
HQC	high quality control
HPLC	high performance liquid chromatography
HUVEC	Human Umbilical Vein Endothelial Cells
IA	interim analysis
ICH	International Council for Harmonization
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively Coupled Plasma Optical Emission Spectrometry
Ig	immunoglobulin
IMP	investigational medicinal product
IPC	in-process control
IRS	internal reference standard
ITT	intent to treat
IV	intravenous
Kel	elimination rate constant
LC	light chains
LCQ	last quantifiable concentration
LLOQ	lower limit of quantification
LMWP	Low molecular weight protein species
LS	least squares
(s)MCB	(secondary) Master Cell Bank
mCRC	Metastatic colorectal cancer
MRI	magnetic resonance imaging
Nab	neutralizing antibody
NC	negative control
nsNSCLC	non-squamous non-small cell lung cancer
ORR	objective response rate / overall response rate
OS	overall survival
PAR	proven acceptable ranges
PC	positive control
PD	progression of disease/ pharmacodynamics/s
PFS	progression free survival
PK	pharmacokinetic/s
Pop PK	population pharmacokinetics
PP	per protocol
PPQ	process performance qualification
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PT	preferred term
QC	quality control
qPCR	Quantitative Polymerase Chain Reaction
REC	recommendation
RECIST	Response Evaluation Criteria in Solid Tumours
RH	relative humidity
SAP	statistical analysis plan

SEC-HPLC	Size Exclusion-High Performance Liquid Chromatography
SD	stable disease
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOC	system organ class
SS	safety set
t1/2	half-life
TEAE	treatment emergent adverse event
Tmax	time at which peak plasma concentration occurs
UF/DF	Ultra-filtration/Dia Filtration
VEGF	vascular endothelial growth factor
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan IRE Healthcare Limited submitted on 20 February 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Lextemy, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

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

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

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

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

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

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

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

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

The legal basis for this application refers to:

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

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

This application is submitted as a multiple of Abevmy simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen reference product is: Avastin

Medicinal product which is or has been authorised in accordance with Union provisions in force for not

less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Avastin, 25mg/ml Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 12-01-2005
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/04/300/001/2

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

- Product name, strength, pharmaceutical form: Avastin, 25mg/ml Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration GmbH
- Date of authorisation: 12-01-2005
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/04/300/001/2

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

- Product name, strength, pharmaceutical form: Avastin, 25 mg/ml Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 12-01-2005
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation numbers: EU/1/04/300/001/2

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant received Scientific advices from CHMP on 23 October 2014, 26 May 2016 and 25 January 2018. The scientific advice pertained to quality and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Ondřej Slanař

The application was received by the EMA on	20 February 2020
The procedure started on	26 March 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	17 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	24 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	6 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	17 November 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 November 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	10 December 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 January 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 February 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lextemy on	25 February 2021

2. Scientific discussion

2.1. Problem statement

About the product

MYL-1402O has been developed by Mylan as a proposed biosimilar product to the reference medicinal product Avastin having bevacizumab as the active substance. MYL-1402O (bevacizumab) belongs to the pharmacotherapeutic group "monoclonal antibodies" (ATC code: L01XC07).

Bevacizumab (Avastin, Genentech/Roche) is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) G1 class that selectively binds to Vascular endothelial growth factor (VEGF). The binding of bevacizumab to VEGF inhibits the binding of VEGF to its receptors on the surface of endothelial cells, Flt-1 (also known as VEGF receptor-1 [VEGFR-1]) and kinase insert domain receptor (also known as VEGF receptor-2 [VEGFR-2]). Neutralizing the biological activity of VEGF inhibits the formation of new tumour vasculature, causes regression in newly formed tumour vasculature, and normalises the remaining tumour vasculature, thereby inhibiting tumour growth.

The applicant applied for the same therapeutic indications for MYL-1402O as granted for Avastin in the EU. Lextemy is intended for the treatment of carcinoma of the colon or rectum, breast cancer, non-small cell lung cancer, renal cell cancer, epithelial ovarian, fallopian tube or primary peritoneal cancer, and carcinoma of the cervix (see section 1). The recommended posology and method of administration correspond to those of Avastin.

2.2. Quality aspects

2.2.1. Introduction

Lextemy has been developed as biosimilar to the reference medicinal product Avastin (EMA product number EMEA/H/C/000582). The finished product is presented as concentrate for solution for infusion containing 25 mg/mL of bevacizumab as active substance. The product is supplied in two presentations, i.e. 100 mg /4 mL and 400 mg/16 mL in single-use vials (6 mL (6R) and 20 mL, respectively).

Other ingredients are: α,α-trehalose dihydrate, sodium phosphate (E339), polysorbate 20 (E432) and water for injections.

The product is available in Type I glass vials closed with a flurotec coated, chlorobutyl rubber stopper and sealed with an aluminium seal with plastic flip-off cap.

2.2.2. Active Substance

General information

The active substance (AS) of Lextemy (also referred to as MYL-1402O) is bevacizumab (INN), a recombinant humanised IgG1 humanised monoclonal antibody which selectively binds to vascular endothelial growth factor (VEGF) and prevents the interaction of VEGF to its receptors (VEGFR-1 and

VEGFR-2) on the surface of endothelial cells, thus inhibiting endothelial cell proliferation, angiogenesis, and VEGF-induced vascular permeability.

The active substance is expressed in Chinese hamster ovarian (CHO) cells (CHO-S cell line) and contains two identical heavy chains (HC) and two identical light chains (LC). The heavy and light chains are connected by intra- and interchain disulphide bonds. MYL-1402O has an approximate molecular weight of 149 kDa and has one N-linked Glycosylation site located on the heavy chain at Asparagine 303 (Asn-303).

Manufacture, characterisation and process controls

Manufacturers

The active substance manufacture, quality control testing are performed at Biocon Biologics India Limited in Bengaluru, India (Bommasandra-Jigani Link Road).

Description of manufacturing process and process controls

The active substance is manufactured using a fed-batch process in a production bioreactor. Following cell culture and harvest, active substance is purified from the harvest culture fluid through a series of filtration and chromatography steps. The process includes steps to inactive/remove potential containing viruses. Excipients are added to generate the formulated active substance.

Process control classifications and acceptance ranges are considered acceptable. The process parameters are controlled by acceptable ranges. All operations from the thawing of the vial until the harvest from the production bioreactor are performed aseptically. All gases are filter-sterilised. Feed solutions, which are added to the production bioreactor, are filter-sterilised. The hold times for the AS process intermediates have been adequately validated. Tables with the main operational parameters, their classification, and acceptable ranges for the individual steps were provided. The parameters were classified into critical process parameter (CPP) and non-critical process parameter (NCPP) based on process characterisation studies. CPP are controlled by in-process control (IPC) testing.

Overall, the process parameters and IPCs with the other control measures are considered sufficient to ensure quality and safety of MYL-1402O as well as to monitor process consistency.

Control of materials

The raw materials used during the production of MYL-1402O AS are either of compendial or non-compendial quality. Non-compendial raw materials are tested according to in-house specification. The composition of the cell culture media, feed solutions and buffers used during purification is described in detail.

The history and stability of the host cell line has been well established. Bevacizumab amino acid sequence for the heavy and light chain was confirmed in comparison with that of the reference medicinal product. The construction of the expression vectors and their genetic elements are described in sufficient detail. A two-tiered cell bank system with Master Cell Bank (MCB)/Working Cell Bank (WCB) has been established by the applicant. The MCB and WCB have been adequately described; they have been qualified and characterised in line with ICH Q5D guideline. An end of production cell bank (EPCB) and a post-production cell bank (PPCB) were prepared and tested according to ICH Q5A and ICH Q5D.

Control of critical steps and intermediates

The input CPPs have been defined during process characterisation. These CPPs were validated using three batches. IPCs are performed at each stage during the manufacture of AS to ensure that the process is controlled to yield consistent product quality.

All IPCs and tests of the active substance manufacturing process were provided; the critical IPCs with respective limits and justifications are summarised in section 3.2.S.2.4. Either acceptance criteria or action limits are proposed for the IPCs.

Overall, the proposed controls appear adequate to ensure consistent quality of the MYL-1402O AS. IPC tests have been sufficiently described and validated. In-process data for the Process Performance Qualification (PPQ) batches was presented; all batches met the specifications.

Process validation and/or evaluation

Performance of the AS manufacturing process was verified at commercial site and scale using three consecutive process validation batches.

The data from process validation was assessed with the proven acceptable ranges (PARs) and manufacturing operating range (MORs) obtained from process characterisation studies.

The validation results, which were all within their specified acceptance criteria, demonstrate that the process performs consistently and delivers AS complying with the release specifications under commercial operating conditions.

Validation also includes buffer preparation, details of clearance of process-and product related impurities, at-scale hold time studies, Chromatographic column resin and TFF membrane reusability studies, extractable and leachable evaluation for critical product contact materials.

Extractables/leachables studies were conducted for critical product contact materials. A tabulated summary of identified critical product contact materials has been provided. A tabulated summary of identified critical product contact materials has been provided. No elemental impurities above the limit of quantification were observed. Two compounds with potential leachable exposure above the safety concern threshold were further assessed based on extractable data. The conducted toxicological assessment confirmed that the potential leachables do not impact patient safety.

No formal shipping validation has been performed for the MYL-1402O. This is deemed acceptably justified considering the applied procedures and the AS and finished product facilities locations.

Manufacturing process development

The manufacturing process development of bevacizumab active substance was initially based on a manufacturing process which was then optimised to the commercial process. Changes introduced during scale-up and among the different versions for the process (development process and commercial process) have been explained and justified.

A comparability study has been carried on pre- and post-change batches according to ICHQ5E, and data provided demonstrated that the change did not have impact on the process performance and quality of the product.

Comprehensive process characterisation (PC) studies have been performed and based on the results the process parameters were classified with respect to their criticality. The scaled-down model used for these studies was qualified and representative of the at scale manufacturing process.

Characterisation

A range of state-of-the-art orthogonal methods has been employed to characterise the active substance. The primary structure, higher order structures, and the biological activity were evaluated using a series of biochemical, biophysical, and functional characterisation techniques. The methods were qualified or validated (release testing methods).

Characterisation was performed using active substance manufactured at commercial scale by the final commercial manufacturing process. In the scope of the biosimilar exercise, the primary, secondary,

and higher order structure, glycosylation patterns, product-related variants, and functional activity of MYL-1402O have been characterised side-by-side against the US and EU reference product Avastin (see also biosimilarity section).

For the primary structural analysis, the amino acid composition of MYL-1402O was determined by peptide mapping (LC ESI-MS). The average molecular mass was determined by intact and reduced LC-ESI-MS.

The higher order structure was evaluated by a combination of Fourier transform Infrared Spectroscopy (FTIR) Far- and Near-UV Circular Dichroism and Intrinsic Fluorescene. MYL-1402O contains a total of 16 disulfide bonds: 12 intra-chain disulfide bonds and 4 inter-chain disulfides bonds. Disulfide linkages were found to be identical for MYL-1402O and the reference medicinal product Avastin.

The glycan profile of MYL-1402O was determined by normal phase HPLC (NP-HPLC). In addition, an O-Glycan analysis using NP-HPLC has been conducted.

To estimate the content of N-acetyl neuraminic acid (NeuAc/NANA), Sialic acid analysis has been performed. Charge and size variants were determined using complementary analytical methods (IEX, cIEF and CE-SDS (reduced and non-reduced), reduced peptide map and SEC).

The biological characterisation included *in vitro* functional assessments of Fab and Fc regions. The biological characterisation included binding to VEGF165 by ELISA and functional activity in a cell-based assay (HUVEC anti-proliferation assay). Fc binding assays include FcγRIIIa-V158 and FcRn binding by SPR, and C1q binding by ELISA.

Characterisation was done using batches that have been manufactured using active substance from the intended commercial active substance process. In summary, the presented data confirm the expected structural and functional characteristics of bevacizumab.

Impurities

Process related impurities arising during upstream and downstream manufacturing processes include host cell proteins (HCP), host cell DNA, and leached protein A and media/buffer components. Data presented for the three PPQ runs in the scope of the process validation studies demonstrate that the process consistently and effectively removes HCP, host cell DNA, and leached protein A to very low levels (below quantitation limit). A detailed control strategy of product-related impurities for commercial batches was provided and is deemed satisfactory.

Overall, MYL-1402O has been sufficiently characterised; the used methods are adequate.

Specification

The proposed set of quality attributes included in the specifications for release and stability testing of bevacizumab complies with ICH Q6B, Ph. Eur. 2031 and EMA/CHMP/BWP/532517/2008 and is acceptable. The release specification, includes tests for appearance, identity, purity and impurities, process-related impurities, quantity, potency, microbial safety, and general attributes.

For all internal methods, reference is made to the same standard testing procedure document. Each method is expected to have a specific code. Therefore, the respective internal reference code of the single method should be added (REC).

Relevant methods have been demonstrated to be stability-indicating in forced degradation and stress studies. It is noted that the potency seems not to be stability-indicating.

The glycosylation profile of the AS has been extensively characterised. The mode of action for bevacizumab justifies omitting a comprehensive glycosylation study from the specifications.

The CHMP requested the applicant to revise the specification for potency after a total of 30 AS batches used for commercial finished product batches will be available (REC).

Analytical Methods

The in-house analytical methods were sufficiently described and validated. However the CHMP requested the serial numbers to the respective in-house methods listed in the specification and reference the Standard testing procedure to be provided and added to the specification table (REC). For compendial methods (Colour, Clarity/Opalescence, Bacterial Endotoxin, Bioburden, pH, Osmolality) reference to the respective Ph. Eur. monograph has been provided.

Satisfactory bridging data has been provided for the two methods, HCP and leached protein A, which have changed in the course of development.

Potency is controlled by a cell-based assay that measures inhibition of proliferation (HUVEC cells). The anti-proliferation effect of MYL-1402O on HUVEC is evaluated using a fluorescent dye. This inhibition is compared to an internal reference standard.

Reference Standards

A historical overview of the reference standards was presented. Detailed information on the current and previous reference standard lots has been provided. A two-tier system of primary reference standard and secondary reference standard will be established for MYL-1402O AS and finished product. The protocol for establishment and monitoring of the Secondary Reference Standard was provided.

Batch analysis data

The applicant has provided batch data for several active substance lots from different versions of the manufacturing processes. These are the batches used in the non-clinical studies, clinical studies, stability studies and process validation studies. The results were within the predefined specifications in place at the time of testing and confirm consistency of manufacturing process.

Container closure

The formulated bulk AS is stored in single-use, sterile bag. A description of the container closure system has been provided, including the identity of materials of construction of each primary packaging component.

Stability

The proposed l shelf-life of active substance is based on long-term stability data (real-time, recommended storage conditions) generated from commercial scale batches from both the development and the commercial process.

Stability data for three batches from the commercial process stored under long-term conditions for 18 months and under accelerated conditions up to 6 months, as per ICH guidelines were provided.

Supportive stability data was provided for ten commercial scale development batches. Stability data from samples stored under long-term for up to 36 months and for up to 6 months at accelerated conditions were presented.

Furthermore, stability data were presented from three developmental batches. For these batches long-term stability data for 24 months and for six months under accelerated conditions are available. In addition, stress stability data are available up to 1 month.

All batches were manufactured at Biocon facility located in India and stored in representative container closures.

Overall, the parameters tested are as per the tests in the release specification. Process-related impurities, primary sequence and microbial attributes are not part of the stability programme, which is acceptable.

All the stability results provided for the different processes were within specifications and no significant trending has been observed. The available stability data for samples stored at the recommended storage conditions show good stability. Under accelerated conditions a slight decrease in purity is observed. Furthermore, purity is slightly decreasing; total impurities increase.

The stability data presented from the development process can be considered representative for the commercial process. Given the high comparability between the manufacturing processes, the proposed shelf-life based on the development process is acceptable.

The applicant should present the real time data obtained for the three primary stability AS batches manufactured at commercial scale using the commercial process as soon as available and report any out of specification value found during the stability studies for these primary stability batches will be immediately communicated to the Agency (REC).

Overall, the provided stability data support a shelf-life at the recommended storage condition for bevacizumab active substance in the proposed container closure system.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product (FP) is a sterile, preservative-free clear to slightly opalescent, colourless to pale brown concentrate for solution for infusion in a single dose vial for intravenous use containing 25 mg/mL of bevacizumab as active substance and is supplied in two presentations: 100 mg/ 4 mL and 400 mg/ 16 mL single-use vials.

Bevacizumab is formulated with trehalose dihydrate, sodium phosphate (as monobasic sodium phosphate dihydrate and as dibasic sodium phosphate anhydrous), polysorbate 20 and water for injections.

The excipients used in Lextemy 100 mg/4 mL and 400 mg/16 mL formulation are standard pharmacopoeial excipients commonly used in intravenous formulations. The formulation is identical to that of the reference medicinal product. The compatibility of the AS with the used excipients has been shown in stability studies.

Minor formulation changes between early (initial formulation) and late (final formulation) development phase studies have been described and explained. A comparability assessment has been performed to assess the impact of the formulation changes. Overall, the applicant concluded that the changes do not have any impact on the quality of the product. However, a slightly higher pH and reduced osmolality can be observed. Since the values are still within the release specifications, the issue was not further pursued. The MYL-1402O 400 mg/16 mL formulation was developed with the same molar composition as the 100 mg presentation based on the "Final formulation".

There is no overage in the manufacturing process. The vials are filled to ensure a deliverable volume of 4 mL for the 100 mg presentation and 16 mL for the 400 mg presentation.

Manufacturing process development

The manufacturing process of Lextemy 100 mg/vial and 400 mg/vial involves thawing of AS, pre-filtration, sterile filtration, aseptic filling of the formulated AS and sealing of vials containing liquid FP.

Changes made to the finished product manufacturing process during the development have been described and explained.

The batch history was provided for process development together with the implemented changes. An overview of the FP manufacturing process development from initial development through the intended commercial process for the 100 mg/vial and 400 mg/vial was provided.

There are no differences in the manufacturing process and controls between 100 mg/vial and 400 mg/vial except for the fill volume and vial size.

A comparability studies has been performed for change in filling line according to ICH Q5E; although the approach chosen to show similarity is rather liberal, the actual results of the comparability exercise do not raise any concerns and is thus acceptable. The comparability assessment indicates that batches derived from different filling lines are comparable.

Container closure system
The primary container closure system for Lextemy 100 mg/4 mL and 400 mg/16 mL consists of a Type I glass vial (6R for 100 mg and 20 mL for 400 mg presentation) closed with a chlorobutyl rubber stopper (20 mm) coated with a fluoro-resin laminate. The rubber stopper is sealed with an aluminium cap with a plastic flip-off cap. The glass vial and rubber stopper comply with the appropriate Ph. Eur. monographs for primary containers and closures.

Extractables and leachables were also assessed. Overall, the results from the leachable and extractable studies demonstrate that the components of the container closure system are compatible with the FP and confirm its suitability for the storage of Lextemy finished product.

Manufacture of the product and process controls

Finished product manufacture, quality control testing (physico-chemical and biological functional) are performed at Biocon Biologics India Limited in Bengaluru, India.

Lextemy is manufactured according to a standard manufacturing process (fill-and-finish) for monoclonal antibodies. The process comprises the following main steps: 1) Thawing of formulated AS, 2) Pooling of formulated AS in bags followed by mixing, 3) Prefiltration (offline filtration), 4) Sterile filtration (online filtration), aseptic filling, and stoppering of vials, 5) Sealing, visual inspection, and labeling, and 6) Storage of vials and shipment.

The manufacturing process for Lextemy concentrate for solution for infusion consists of a standard aseptic manufacturing process and is controlled by IPC testing performed during manufacture. The process has been adequately described.

Corresponding in-process-results for the three consecutive commercial scale process validation batches were provided. The results of all batches were found to be consistent and within the acceptance criteria. The control strategy for critical process steps is considered adequate.

There are no intermediates in the FP manufacturing process. The maximum duration of filtration is supported by the maximum duration of media fill simulations. The time out of refrigeration (TOR), i.e. the maximum allowable processing time at temperatures above the recommended storage temperature from the end of filling to the end of secondary packaging, has been indicated.

Process validation
Prior to the process validation studies, risk assessment and process characterisation studies were conducted in order to define process parameters and their effective ranges.

The manufacturing process has been validated by manufacture of an appropriate number of full-scale commercial batches for the 100mg/4 mL and 400 mg/16 mL vial presentations.

All process parameters, as well as performance parameters, monitored during the process validation studies were maintained within their specific ranges for all process validation batches. Based on the data provided, it can be concluded that the process is robust and consistently delivers finished product of the anticipated quality. Ranges have been studied and defined during process characterisation studies and are considered justified. None of the ranges was challenged during process validation.

The glass vials are sterilised and depyrogenated prior to use by dry heat sterilisation by using a validated process. The rubber stoppers are supplied ready to use.

Filter validation

The validation of the filters used for bioburden reduction and sterilisation of the finished product solution is conducted. All results complied with the predetermined acceptance criteria and verify that the filters are appropriate for filtering finished product volumes.

Media fills

The aseptic process used for the sterilisation has been validated through media fills.

Finally, successful cleaning validation on parts of equipment that come into direct contact with the FP and transport validation using the proposed commercial primary and secondary packaging configuration covering an actual shipment of a currently proposed worst-case shipping route has been presented.

Product specification

The specification for the finished product includes tests for appearance, identity, purity and impurities, quantity, potency, general attributes (, and microbial safety.

Both the FP presentations (100 mg/4 mL and 400 mg/16 mL) have identical specifications with an only exception to acceptance criteria for extractable volume, which is specific for each presentation due to difference in their fill volume.

The panel of quality attributes proposed for release and stability testing of Lextemy finished product is considered adequate and in line with ICH Q6B, EMA/CHMP/BWP/532517/2008 guideline, and Ph. Eur. 2031. The specification limits have been adequately justified taking into account data from AS and the reference medicinal product Avastin as well as Lextemy batch analysis data and stability data.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and elemental analysis results of three commercial scale MYL-1402O PV batches, it is confirmed that elemental impurities are within the limits set out in ICH Q3D and that testing for elemental impurities does not need to be included in the finished product specification. The information on the control of elemental impurities is satisfactory.

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

Analytical methods

For the in-house analytical methods, the descriptions are sufficiently detailed and acceptable. However the CHMP requested the serial numbers to the respective in-house methods listed in the specification and reference the Standard testing procedure to be provided and added to the specification table (REC). All analytical methods used for release testing of the FP have been appropriately validated based on the principles provided in ICH Q2 (R1) guideline. For compendial methods reference to the respective Ph. Eur. monograph has been provided. The methods have been verified. The analytical procedures used for bacterial endotoxin, sterility, and container closure integrity test have been validated for the MYL-1402O FP to determine their suitability. The presented validations for analytical methods are acceptable and demonstrate the suitability of the analytical procedures for their intended use.

For the release of the commercial product, there has been a change in the analytical method for identity. A method comparability assessment was done with the existing and new reagents for bevacizumab FP samples. Both methods with old and new reagent exhibited positive identity with respect to standard and samples.

Reference Standards

Detailed information on the current and previous reference standard lots has been provided and discussed previously in the respective AS section in this report.

Batch Analyses

The applicant has provided batch data for several 100 mg and 400 mg finished product lots from different versions of the manufacturing processes. These are the batches used in the development studies, non-clinical studies, clinical studies, stability studies and process validation studies.

The available results demonstrate that the manufacturing process(es) are capable of delivering FP of consistent quality. Batches derived from the different developmental phases are comparable.

Stability of the product

The proposed long-term storage condition for Lextemy (100 mg/4mL and 400 mg/16 mL vial presentations) is 5 ± 3°C. A shelf-life of 24 months is proposed, based on long-term primary stability data (real-time, recommended storage conditions).

For the 100 mg/4 mL and 400 mg/16 mL vial presentations long-term stability data for three PPQ batches each are available up to 12 months for 100 mg/4 mL and for 400 mg/16 mL). Stability data at accelerated conditions (25 ± 2°C/60% ± 5% RH) are available up to 6 months.

Supportive stability data for the 100 mg/4 mL vial presentation was provided for nine batches manufactured at previous filling line using AS from development process. Long-term stability data are available for up to 36 months. Stability data at accelerated conditions are available up to 6 months. Additionally, for the three batches, stability data are available at stress conditions (40 ± 2°C/75% ± 5% RH) for 2 months.

Furthermore, stability data were presented for three developmental batches. Long-term stability data at the recommended storage condition are available for 36 months and at accelerated conditions for 6 months; stress stability data (40 ± 2°C/75% ± 5% RH) for these batches are available up to 2 months.

Supportive stability data for the 400 mg/16 mL vial presentation was provided for ten batches manufactured at previous filling line using AS from development process. Long-term stability data are available for up to 36 months and at accelerated conditions for up to 6 months. No stability data at

stress conditions are available for these batches but data from a forced degradation study were presented.

The design of the registration stability studies was in line with ICH Q5C guideline. Overall, the parameters tested as per the tests in the release specification. All PPQ batches, for both presentations, were manufactured at the proposed site and stored in the containers intended for commercial use. For the stability studies the vials are stored in horizontal position.

For the stability data provided for the different processes, all results were within specifications. The available stability data for samples stored at the recommended storage conditions (5 ± 3°C) show a trending for the purity/impurities parameters. A slight decrease of purity is observed. The trending is visible after 6 months for the PPQ batches. For the supportive and developmental batches, the trending can also be observed – however further specifics cannot be made since some of the parameters are not tested for these batches. The batches remain within specifications for the proposed shelf-life of 24 months. Under accelerated conditions (25 ± 2°C/60% ± 5% RH), an obvious decrease in purity can be observed. Potency is still within limits. Only at stressed (40 ± 2°C/75% ± 5% RH) conditions, a clear signal for potency is observed.

For the batches filled in the previous filling line some analytical methods parameters are different compared to the commercial batches; differences have been discussed. Since the analytical methods per se remain identical and the main parameters have always been determined, this issue can be accepted. The data has also been generated for the "missing" parameters and support the specifications.

Given the high comparability between both the FP from the previous and proposed filling lines and the AS manufacturing processes , it can be acceptable to claim a shelf-life of 24 months based on product batches manufactured at previous filling line that are derived from AS from the development process. The manufacturing process at the previous filling line can be considered representative for the commercial process. The CHMP requested the applicant to present up to 24 months real time data obtained for the three commercial scale process validation batches of MYL-1402O FP 100 mg and 400 mg presentations as soon as available, and to immediately report to the Agency any out of specification value found during the ongoing stability study for the commercial scale batches of MYL-1402O FP 100 mg and 400 mg presentations.

Stability comparability has been evaluated for the two presentations 100 mg/vial and 400 mg/vial at real-time long-term storage condition of 2-8°C. Stability-indicating parameters were evaluated. Overall stability profiles for MYL-1402O 100 mg/vial and 400 mg/vial presentations were found comparable.

A comparative forced degradation study using both MYL-1402O and the reference medicinal product Avastin has been conducted. Overall, the results were similar for biosimilar MYL-1402O product and the reference medicinal product Avastin.

A photostability study in line with ICH Q1B guideline has been included and the study showed that FP is light sensitive. Upon photo exposure a significant degradation in the samples were observed.

A compatibility study was conducted to evaluate the stability of finished product after dilution. Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 30°C in sodium chloride 9 mg/mL (0.9%) solution for injection. If not used immediately, the diluted Lextemy should not be stored longer than 24 hours at 2°C to 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions (SmPC section 6.3).

Taken together, the presented stability data sufficiently support the proposed shelf-life of 2 years at the intended storage conditions (i.e. 2-8°C, protected from light) as per SmPC sections 6.3 and 6.4.

Biosimilarity

Analytical similarity of MYL-1402O was assessed in a comprehensive similarity exercise using EU- and US-sourced Avastin as reference medicinal product. US-sourced Avastin was included as supportive data. The approach and methodology of the analytical similarity assessment is sufficiently described and overall acceptable.

The number of batches of EU-Approved Avastin and US-Licensed Avastin as well as of Abevmy were considered adequate for the analytical similarity assessment. To support the known mechanism of action, binding to VEGF and inhibition of cell proliferation was assessed by functional and binding assays in the scope of the biosimilarity exercise. Assays include binding to VEGF (VEGF-165 and VEGF-121 and VEGF-189), inhibition of VEGF (VEGF-165, VEGF-121 and VEGF-189) induced proliferation of endothelial cells (HUVECs), and inhibition of VEGF-165 induced VEGFR-2 phosphorylation. Information on "standard test procedure" and method qualification are provided. From the information provided, it can be concluded that MYL1402O is similar to the European reference medicinal product in terms of VEGF-binding, inhibition of VEGF induced proliferation of endothelial cells and inhibition of VEGF-165 induced VEGFR-2 phosphorylation. MYL-1402O showed minor difference when compared to US- and EU-Avastin lots for VEGF-121 binding kinetics (KD). The differences in kinetic constants observed are within the method variability. Furthermore, the inhibition of VEGF-121 induced HUVEC proliferation shows similarity. Therefore, this issue does not preclude similarity.

In addition to Fab-associated antigen binding, MYL-1402O binding to Fc receptors and complement factor C1q were evaluated in the scope of the biosimilarity exercise using *in vitro* assays. C1q binding was assessed via ELISA and binding kinetics with FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb and FcRn were assessed via surface plasmon resonance. Furthermore, antibody dependent cellular cytotoxicity and complement dependent cytotoxicity assays were included as part of the comparability exercise - even though bevacizumab is not known to act through either of these mechanisms. From the information provided, it can be concluded that MYL1402O is similar to the European reference medicinal product in terms of Fc receptor and C1q binding. No ADCC or CDC activity could be detected. Some observed differences in FcγRIIIb and FcRn are small and do not preclude biosimilarity.

In conclusion, the similarity assessment of MYL-1402O and the EU reference medicinal product showed highly similar biological activity of both the Fab and Fc-based functionality.

For protein concentration – as measured by UV spectrophotometry, one MYL-1402O batch was found to contain lower concentration of bevacizumab. The protein concentration value of this batch was however within the current release and stability specifications.

With regard to purity/impurities, as measured by SEC, MYL-1402O lots were found to contain lower amounts of HMWP and higher content of monomer compared to EU-Approved Avastin and US-Licensed Avastin lots. No impact on PK was observed in the comparative PK study compared to the US-Licensed Avastin There was no impact of higher monomer content on the inhibition of VEGF165 induced proliferation assay. No impact on safety and efficacy was observed during the comparative clinical study. Therefore, MYL-1402O is considered similar for HMWP and monomer.

Differences were also observed for fragments and the distribution of charged variants. The total impurity content and the monomer content of MYL-1402O were within the quality ranges of EU-Approved Avastin and US-Licensed Avastin. Overall, the differences in fragments showed no effect on the relative potency and binding kinetics data in different Fab and Fc function assays. Furthermore, no

apparent impact on safety, efficacy and immunogenicity was seen in the Phase III comparative safety and efficacy study (MYL-1402O-3001).

Differences were observed in the content of basic and main peak between MYL-1402O and the reference medicinal product lots. No impact on PK was observed in the comparative PK study MYL-1402O- 1002 which used a MYL-1402O lot compared to the US-Licensed Avastin. There was no impact of lower basic and higher main peak content on the inhibition of VEGF165 induced HUVEC proliferation assay. The lower basic peak and higher main peak in MYL-1402O lots is not considered to have an impact on potency, PK, safety, efficacy and immunogenicity and MYL- 1402O is considered similar to EU-Approved Avastin and US-Licensed Avastin for the charge variants.

Oxidation level observed in MYL-1402O lots were comparable and any reported differences have not been ranked as critical and essential in demonstrating analytical similarity. The non-glycosylated heavy chain (NGHC) was lower and outside the quality range for MYL-1402O batches. NGHC levels are reported to impact efficacy through Fc effector functions (CDC and ADCC); antibodies with high levels of NGHC have significantly reduced effector functions. Since Fc effector functions are not part of the mechanism of action for bevacizumab, and no differences in C1q and FcγRIIIa binding has been observed, this aspect is not considered relevant for overall biosimilarity. In the comparative phase III clinical study, no apparent impact on safety, efficacy and immunogenicity was seen.

Higher levels of high mannose species have been observed for MYL-1402O batches compared to the reference medicinal product. High mannose levels may result in faster clearance of the FP *in vivo* and therefore may affect the PK. However, no impact on PK was observed in the comparative PK study which used a MYL-1402O batch with higher levels of mannose compared to the US-Licensed Avastin. Additionally, high mannose species are reported to enhance ADCC activity. Since ADCC is not part of the mechanism of action of bevacizumab, this aspect is not regarded relevant for overall biosimilarity.

Furthermore, higher levels were observed for terminal galactose and total afucosylated species (with and without high mannose). Lower levels were observed for fucosylated species. Galactosylation, afucosylation and fucosylation have been reported to be relevant for Fc mediated effector functions including CDC, ADCC, and FcγRIIIa binding. However, ADCC/CDC is not part of the mechanism of action for bevacizumab and no difference was observed in FcγRIIIa binding. Therefore, the differences are not regarded relevant in terms of overall biosimilarity.

Higher levels of total sialic acid (NANA) are observed in MYL-1402O batches compared to EU-Approved Avastin and US-Licensed Avastin lots. NANA levels are reported to impact PK, CDC and ADCC. In the comparative PK study and the phase III comparative safety and efficacy study, a MYL-1402O batch with higher levels of total sialic acid compared to the reference medicinal product was used. No impact on PK, safety, efficacy and immunogenicity was seen, so far. Furthermore, since Fc effector functions are not part of the mechanism of action for bevacizumab, and no differences in C1q and FcγRIIIa binding has been observed, this aspect is not considered relevant for overall biosimilarity.

Overall, it is concluded that the minor differences in the levels of aggregates, fragments, charged species and the glycosylation pattern observed for MYL-1402O would have no impact on PK, activity, safety and immunogenicity.

The presented analytical data support the claim for biosimilarity between the proposed biosimilar MYL-1402O and the reference product EU-Avastin. MYL-1402O is regarded similar to its reference medicinal product. The results are summarised in Table 1.

Table 1. Summary of analytical similarity assessment between MYL-1402O and EU-Avastin

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
	Primary sequence	Peptide Mapping	Sequence identity confirmed.

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
Primary structure	Intact Mass	LC-ESI-MS	Highly similar; match the expected mass
	Reduced Mass	LC-ESI-MS	Highly similar; match the expected mass
	Isoelectric point	cIEF	Similar isoelectric point
General	Protein content	UV-280	The protein concentration value was within the current release and stability specifications.
Higher order structure	Secondary structure	Far-UV-CD	Highly similar secondary structure
	Tertiary Structure	Near UV CD	Near-UV CD spectra were superimposable and highly similar
	Secondary Structure	FTIR	Similar with respect to shape and location of the amide-I band and amide-II band
	Free cysteine	Free cysteine analysis	Free cysteine content is similar (below LOQ).
	Di-sulfide bridging	RP-HPLC-ESI-MS	All 16 disulphide bonds are detected.
	Higher order structure	DSC	Comparable transition temperatures were observed
	Higher order structure	Intrinsic Fluorescence	Highly similar spectra
Purity	Sub-visible Particles	MFI	Sub-visible particle counts are comparable.
	Monomer and Aggregates	SEC-HPLC	Lower amounts of HMWP and higher amounts of monomer were observed. There was no impact of higher monomer content on the inhibition of VEGF165 induced proliferation assay. No impact on safety, efficacy and immunogenicity in the Phase III comparative safety and efficacy study (MYL- 1402O-3001) was observed.
		AUC	Similar monomer population; similarity in overall size and shape of the molecules
		SEC-MALS	Similar size range for monomer
	Total Fragments	CE-SDS (NR)	Differences in minor variants: Slightly higher amount of %LC and lower amount of %HL and %2H. No apparent impact on safety, efficacy and immunogenicity was seen in the Phase III comparative safety and efficacy study (MYL-1402O-3001).
Charge variants and oxidation	Charge Variants	Isoelectric point bycIEF	No difference in isoelectric point
	Charge Variants (Deamidation, C-terminal Lysine)	CIEX-HPLC	Differences in charge distribution. The difference in basic and main peak could be attributed to the carboxypeptidase B treatment which removes the C-terminal lysine residues and changes the distribution of the charge variants. No impact was observed on potency and PK. No apparent impact on safety, efficacy and immunogenicity was seen in the Phase III comparative safety and efficacy study (MYL-1402O-3001).
	Hydrophobic variants	HIC	Lower content of hydrophobic variants. Small differences in hydrophobic variants are not likely to be clinically significant due to their low content.
	Methionine Oxidation	Peptide Mapping by RP HPLC ESI-MS	Comparable Met-258 oxidation level; Lower level of Met-434 oxidation.
Post-translational modification	Ng-HC and p75	CE-SDS(Reduced)	Lower Ng-HC amount outside the quality range and lower p75 levels. Ng-HC levels are reported to impact efficacy through Fc effector functions CDC and ADCC. Results of C1q ELISA, FcγRIIIa binding kinetics, CDC assay and ADCC assay demonstrated similarity.

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
			No apparent impact on safety, efficacy and immunogenicity was seen in the Phase III comparative safety and efficacy study (MYL-1402O-3001).
	Afucosylation	NP-HPLC	Higher levels of high mannose, total galactose and total afucosylated species. Higher levels of high mannose species may result in faster clearance of the finished product *in vivo* and therefore may affect the PK. However, no impact on PK was observed in the comparative PK study (MYL-1402O-1002). Additionally, high mannose species are reported to enhance ADCC activity. Since ADCC is not a mechanism of action for bevacizumab, the observed difference for total high mannose has no impact on potency. Levels of galactosylation, afucosylation and fucosylation have been reported to be relevant for Fc mediated effector functions including CDC, ADCC, and FcγRIIIa binding. Results of C1q ELISA, FcγRIIIa binding kinetics, CDC assay and ADCC assay were similar. No apparent impact on safety, efficacy and immunogenicity was seen in the Phase III comparativesafety and efficacy study (MYL-1402O-3001).
	Total High Mannose		
	Total Galactose		
	Sialic Acid Content	RP-HPLC	Higher levels of total sialic acid (NANA). NANA levels are reported to impact PK, CDC and ADCC. No apparent impact on safety, efficacy and immunogenicity was seen in the Phase III comparability safety and efficacy study.Results of C1q ELISA, FcγRIIIa binding kinetics, CDC assay and ADCC assay demonstrated similar C1q and FcγRIIIa binding and lack of Fc mediated effector functions (CDC and ADCC).
Biological activity (Fab-mediated)	VEGF165 Binding	VEGF-165 Binding ELISA	Similar relative binding
	Inhibition ofVEGF165 Induced Proliferation HUVEC	HUVEC -cell based assay	Similar relative potency
	Inhibition ofVEGF121 induced HUVEC proliferation	HUVEC -cell based assay	Similar relative potency
	Inhibition of VEGF189 induced HUVEC proliferation	HUVEC -cell based assay	Similar relative potency
	Inhibition of VEGF165 induced VEGFR-2 phosphorylation	HUVEC -cell based assay	Similar relative potency
	VEGF165 binding kinetics by Surface Plasmon Resonance	Surface Plasmon Resonance based assay	Similar relative affinity and KD
	VEGF121 binding kinetics by Surface Plasmon Resonance	Surface Plasmon Resonance based assay	Similar relative affinity and KD
	VEGF189 binding kinetics by Surface Plasmon Resonance	Surface Plasmon Resonance based assay	Similar relative affinity and KD
	FcγRIIIa-V158kinetics by	Surface Plasmon Resonance based assay	Similar relative affinity and KD

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
Biological activity (Fc-mediated)	Surface Plasmon Resonance		
	FcγRIIIa-F158kinetics by Surface Plasmon Resonance	Surface Plasmon Resonance based assay	Similar relative affinity and KD
	FcγRIa Kinetics by Surface Plasmon Resonance	Surface Plasmon Resonance based assay	Similar relative affinity and KD
	FcγRIIa-R131kinetics by Surface Plasmon Resonance	Surface Plasmon Resonance based assay	Similar relative affinity and KD
	FcγRIIa-H131kinetics by Surface Plasmon Resonance	Surface Plasmon Resonance based assay	Similar relative affinity and KD
	FcγRIIb kinetics Measured Using SPR-Based Assay	Surface Plasmon Resonance based assay	Similar relative affinity and KD
	FcγRIIIb kinetics Measured Using SPR-Based Assay	Surface Plasmon Resonance based assay	Small difference in KD. Difference is within method variability. FcγRIIIb is not a clinically relevant mechanism of action for bevacizumab and thus the differences is not considered significant.
	C1q binding	C1q binding ELISA	Similar relative binding
	FcRn kinetics by Surface Plasmon Resonance	Surface Plasmon Resonance	Minor differences (broader distribution) in the kinetic constants which are within method variability.
	ADCC	Cell based assay	No ADCC activity
	CDC	Cell based assay	No CDC activity

Adventitious agents

Overall, the risk of contamination of MYL-1402O with adventitious agents is considered low. The applicant implemented multiple complementing measures to ensure product safety with regard to non-viral and viral adventitious agents. The measures include selection of materials, testing of cell banks and process intermediates (bulk), testing of microbial attributes at release, and implementation and validation of dedicated virus clearance steps and steps contributing to virus reduction:

- For the production cell culture process of MYL-1402O, except two raw materials, no other animal- or human-derived material is used. Due to the manufacturing steps there is no specific concern for viral contamination. Compliance with TSE-Guideline EMEA/410/01 rev03 has been demonstrated. There are three animal-derived raw materials that were used in the various stages of stable cell line development. The risk from these animal-derived raw materials used at development of the MCB is considered by extensive testing of MCB. No excipients of human and/or animal origin are used in the manufacture of finished product.
- Cells have been tested for adventitious and endogenous viruses according to ICH Q5A and human viruses and Replication Competent Retrovirus (RCR).
- The testing programme for the un-processed bulk is compliant with Guideline ICH Q5A and acceptable. Considering the data from multiple tested lots and overall viral clearance capacity

it could also be justified to abandon retrovirus testing and RCR testing from the routine testing programme.

- Endotoxin levels and bioburden/sterility are adequately controlled throughout the manufacturing process and at active substance and finished product release.
- New and aged chromatographic resins were assessed with regard to viral particle contamination and sufficiently wide safety margin has been demonstrated.

The ability of the purification process to remove viruses was evaluated with a suitable panel of model viruses. The choice of model viruses and selection of process steps validated for virus reduction is acceptable. The viral clearance study was performed. Validation studies for virus inactivation/removal were performed. Full study reports on virus inactivation/removal have been provided. Controls for cytotoxicity and interference of test material with virus detection were performed.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The data provided support biosimilarity versus the EU reference medicinal product (Avastin) at the quality level. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

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

- to review the acceptance criteria for potency based on a total 30 AS batches used for commercial FP batches.
- to present real time stability data for commercial scale and commercial process AS batches and report any out of specification results.
- to present real time stability data for commercial scale and commercial process FP batches and report any out of specification.
- to provide the serial numbers to the respective in-house methods for the control of AS and add them to the table in section S.4.1 in Module 3.
- To provide the serial numbers to the respective in-house methods for the control of FP and add them to table in section P.5.1 in Module 3.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

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

1. to review the acceptance criteria for potency based on a total 30 AS batches used for commercial FP batches.

2. to present real time stability data for commercial scale and commercial process AS batches and report any out of specification results.

3. to present real time stability data for commercial scale and commercial process FP batches and report any out of specification.

4. to provide the serial numbers to the respective in-house methods for the control of AS and add them to the table in section S.4.1 in Module 3.

5. To provide the serial numbers to the respective in-house methods for the control of FP and add them to table in section P.5.1 in Module 3.

2.3. Non-clinical aspects

2.3.1. Introduction

Bevacizumab is a recombinant IgG1 humanised monoclonal antibody (mAb) that binds to soluble VEGF (VEGF-A) and prevents the interaction of VEGF to its receptors (VEGFR-1 and VEGFR-2) on the surface of endothelial cells, thus inhibiting endothelial cell proliferation, angiogenesis, and VEGF-induced vascular permeability.

2.3.2. Pharmacology

The MYL-1402O pharmacology programme was focused on the evaluation of analytical similarity compared to the reference medicinal product (EU-Avastin) (Table 2). *In vitro* studies were included in Module 3, therefore the assessment can be found in the quality part, section 2.2.3 of this report. No *in vivo* non-clinical pharmacology studies were conducted.

A short summary of the *in vitro* assays is provided in the sections below.

Table 2. Overview of non-clinical pharmacology studies for MYL-1402O

Study	Test system	Main Parameter Measured	Study Number
Primary Pharmacodynamics			
Inhibition of VEGF-165 induced proliferation	HUVEC	Proliferation (inhibition)	
Inhibition of VEGF-121 induced proliferation			
Inhibition of VEGF-189 induced proliferation			
VEGF-121 binding assay	SPR	Binding kinetics	
VEGF-165 binding assay			
VEGF-189 binding assay			
VEGF-165 binding assay	ELISA	Steady state binding	
VEGFR-2 phosphorylation assay	HUVEC lysates	Tyr1175 phosphorylation	
FcγRIa binding assay	SPR	Receptor binding kinetics	

FcγRIIa R131 binding assay			
FcγRIIa H131 binding assay			
FcγRIIb binding assay			
FcγRIIIa V158 binding assay			
FcγRIIIa F158 binding assay			
FcγRIIIb binding assay			
FcRn binding assay			
C1q binding assay	ELISA	C1q binding at steady state	
ADCC	Effector and target cells	Cytotoxicity	
CDC	Target cells		

Abbreviations: HUVEC, human umbilical vein endothelial cells; SPR, Surface Plasmon Resonance; ELISA, enzyme linked immunosorbent assay; ADCC, antibody dependent cellular cytotoxicity; CDC, complement dependent cytotoxicity

Primary pharmacodynamic studies

Pharmacological *in vitro* assays with MYL1402O, EU-Avastin and US-Avastin included binding to VEGF (VEGF-165 and VEGF-121 and VEGF-189), inhibition of VEGF (VEGF-165, VEGF-121 and VEGF-189) induced proliferation of endothelial cells (HUVECs), and inhibition of VEGF-165 induced VEGFR-2 phosphorylation.

From the information provided, it can be concluded that MYL1402O is similar to the European reference medicinal product in terms of VEGF-binding, inhibition of VEGF induced proliferation of endothelial cells and inhibition of VEGF-165 induced VEGFR-2 phosphorylation.

Secondary pharmacodynamic studies

In addition to Fab-associated antigen binding, MYL1402O binding to Fc receptors and complement factor C1q were evaluated in the scope of the biosimilarity exercise using *in vitro* assays. C1q binding was assessed via ELISA and binding kinetics with FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb and FcRn were assessed via surface plasmon resonance. Furthermore, antibody dependent cellular cytotoxicity and complement dependent cytotoxicity assays were included as part of the comparability exercise - even though bevacizumab is not known to act through either of these mechanisms.

From the information provided, it can be concluded that MYL1402O is similar to the European reference medicinal product in terms of Fc receptor and C1q binding. No ADCC or CDC activity could be detected.

MYL1402O shows a slightly lower FcγRIIIb binding activity and a slightly higher C1q binding activity.

In comparison with the EU-and US-reference medicinal product, a broader distribution for FcRn binding can be observed for the proposed biosimilar. The results are still within the range of EU-Avastin.

Safety pharmacology programme

No safety pharmacology studies have been conducted.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted.

2.3.3. Pharmacokinetics

No stand-alone pharmacokinetics studies were submitted. However, the toxicokinetics of MYL-1402O and Avastin-US were compared in a repeat-dose toxicity study performed in cynomolgus monkeys and additional toxicokinetic data for an older version of MYL-1402O (namely Bmab-100) were collected in two supportive studies conducted in mice and rabbits.

The supportive repeat-dose study in mice was comparative in nature and showed a similar toxicokinetic profile of Bmab-100 and Avastin at the dosage of 50 mg/kg on day 1. At day 29, a difference in exposure was observed, which might be due to variable immunogenicity owing to repeated administration of Bmab-100 and Avastin. ADAs have not been determined in this study.

The supportive repeat-dose study in rabbits was not comparative. The toxicokinetic profile of Bmab-100 resembles the profile of a typical monoclonal antibody. Accumulation occurred at repeated dosing.

The supportive repeat-dose study in cynomolgus monkeys was comparative in nature and showed a similar toxicokinetic profile of MYL-1402O and Avastin at the dosage of 50 mg/kg. The biosimilarity ratio (MYL-1402O/Avastin) for C0 was between 0.7 and 1.2 and the ratio for AUC0-24 was between 1.0 and 1.3.

2.3.4. Toxicology

Single dose toxicity

Two acute toxicity studies were conducted with Bmab-100 (an older version of MYL-1402O) in Swiss Albino mice (Study 9336) and New Zealand White rabbits (Study 9337). No significant toxicities were observed in either study. There were no signs of toxicity, pathological changes or mortality.

Repeat dose toxicity

Four repeat dose toxicity studies were conducted with the proposed biosimilar (MYL-1402O) (

Table 3).

Table 3. Overview of repeat dose toxicity studies with MYL-1402O

Study ID	Species	Dose/Route	NOAEL	Major findings	OECD GLP
Study 9335 (comparative) 4 w + 2 w recovery	**Swiss Albino mice** 5/sex/main group 5/sex/toxicokinetic group 2/sex/recovery group	Bmab-100: (0), 50, 150 and 445 mg/kg i.v. US-Avastin: 50 mg/kg i.v.	> 445 mg/kg	No significant toxicities.	No
Study 9340 90 d + 28 d recovery	**New Zealand White rabbits** 4/sex/main group 3/sex/recovery group	(0), 15, 50 and 133.5 mg/kg i.v.	>133.5 mg/kg	No significant toxicities.	No
Study BIO-TX 2561 4 w + 2 w recovery	**New Zealand White rabbits** 4/sex/main group 3/sex/recovery group	(0), 500, 2000 µg/dose ivt.	-	Abnormal ocular clinical signs in the control and high dose groups were observed. Abnormal phenotypes were attributed to the injection procedure.	No
Study TOX-070-002 28 d (comparative)	**Cynomolgus monkeys**	MYL-1402O: 50 mg/kg US-Avastin: 50 mg/kg i.v.		In female animals, absolute uterus weight and uterus/brain weight ratio were significant decreased in the groups given 50 mg/kg MYL 1402O or Avastin without having a clear morphological correlate. Both compounds induced comparable effects in the femoral growth plates of young growing male animals. Safety pharmacology: no changes in neurological examinations, ophthalmic examinations and cardiovascular parameters. Local tolerance: histopathological changes at the intravenous injection sites for all groups (including controls) and regarded as related to the application procedure.	Yes (not claimed)

Reproduction Toxicity

No developmental or reproductive toxicology studies were conducted with MYL-1402O. However, within the repeat-dose toxicity study in cynomolgus monkeys (TOX-070-002), a reduction in uterus gland size in treated female animals was observed with both Avastin and MYL-1402O.

2.3.5. Ecotoxicity/environmental risk assessment

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

2.3.6. Discussion on non-clinical aspects

For global development, the toxicological profile of the proposed biosimilar candidate was determined in several *in vivo* acute and repeat-dose studies in mice, rabbits and cynomolgus monkeys.

No toxicities were observed in the conducted single-dose toxicity studies in mice and rabbits. The conducted single dose toxicity studies in mice and rabbits are not considered relevant for demonstration of biosimilarity. In general, it is not recommended to conduct separate single-dose

studies (see ICH M3 guideline), or toxicity studies with monoclonal antibodies in non-relevant animal species, *i.e.* mice (see ICH S6 guideline).

In the repeat-dose studies, no unexpected toxicities have been observed. Studies 9335 in mice and TOX-070-002 in cynomolgus monkeys are comparative and seem to demonstrate biosimilarity of MYL1402O and Avastin. However, the group size in these studies is low and inter-individual variability should be considered. Furthermore, an older version of MYL-1402O (namely Bmab-100) and US-Avastin were used in the repeat-dose studies conducted in mice and rabbits (Study 9335 and Study 9340, respectively). The results of the studies are regarded supportive and do not add further value for the demonstration of biosimilarity.

Additionally, a repeat-dose toxicity study has been conducted in rabbits to investigate potential ocular and/or systemic toxicity of MYL- 1402O when administered as an intravitreal injection (Study BIO-TX 2561). Since the frequency and severity of the observed abnormal ocular clinical signs were similar between test item and placebo control groups, the observed ophthalmologic effects were considered independent of the test article. The conducted study is not considered relevant for demonstration of biosimilarity.

ADAs have not been determined within the scope of the repeat-dose toxicity studies and no assay has been developed. Since exposure was not changed in the conducted repeat-dose toxicity studies (except for Study 9335), and animal immunogenicity studies are not relevant in terms of predicting potential immunogenicity of human or humanised proteins in humans, this is accepted.

No genotoxicity studies, carcinogenicity studies and reproductive/developmental toxicity have been conducted with MYL-1402O. The waiving is acceptable and in line with relevant guidelines.

2.3.7. Conclusion on the non-clinical aspects

In vitro studies are included in Module 3 and the assessment can be found in the quality part of the report.

For global development, the toxicological profile of the proposed biosimilar candidate was determined in several *in vivo* acute and repeat-dose studies in mice, rabbits and cynomolgus monkeys. Two of the studies are comparative in nature. In a repeat-dose study in mice (Study 9335), Bmab-100 (an older version of MYL-1402O) was compared to US-Avastin. In a repeat-dose study in cynomolgus monkeys, MYL-1402O and US-Avastin were compared (Study TOX-070-002).

Overall, Studies 9335 and TOX-070-002 seem to demonstrate biosimilarity of MYL1402O and Avastin. The results of the studies are regarded supportive and do not add further value for the demonstration of biosimilarity.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Table 4: Tabular Overview of Clinical Studies in MYL-1402O clinical programme

Type of study	Study Number	Study Design	Test Product(s), Dosage Regimen, Route of administration	Number of subjects/ population	Duration of treatment	Study status
Pivotal studies						
Phase I PK comparability, safety and immunogenicity	MYL-1402O-1002	Single Centre, Randomised, Double-Blind, 3-Arm Parallel group	Single 1 mg/kg administered by IV infusion (25mL over approximately over 90 minutes) of MYL-1402O, or US-Avastin or EU-Avastin	111 Healthy adult male volunteers	Single dose	complete
Phase III, confirmatory efficacy, safety and immunogenicity	MYL-1402O-3001	Global, Multi-centre double blind, randomised, parallel group	MYL 1402O or Avastin 15 mg/kg IV infusion every 21 days (±3 days) treatment in combination with Carboplatin-Paclitaxel chemotherapy during Period 1	671 Patients with Stage IV non squamous No Small Cell Lung Cancer	18 weeks (period 1) 24 weeks (Period 2) Total study duration was upto 42 weeks	complete
Supportive studies						
Phase III, comparative PK, efficacy, safety and immunogenicity	BM100-CC-03-I-01	Multisenter, Double-blind, Randomised Parallel group	Bmab-100(MYL-1402O) or Avastin, 7.5 mg/kg IV every 21 days up to 6 cycles Treatment in combination with Xelox therapy (oxaliplatin and Capecitabine)	10 patients in part 1 136 patients in part 2 Patients with metastatic colorectal cancer	18 weeks	complete

2.4.2. Pharmacokinetics

The PK was characterised in two clinical comparative studies to Avastin. The **pivotal phase I study in healthy subjects (Study MYL-1402O-1002)** was a double-blind, single-dose, three-treatment, parallel group design, PK comparability study of MYL-1402O solution manufactured for Mylan compared to US-Avastin solution and EU-Avastin solution. The purpose of this study was to assess PK bioequivalence of MYL-1402O to Avastin in healthy subjects.

PK evaluation was further supplemented with data from **a supportive study in mCRC patients (Study BM100-CC-03-I-01).** This was a double blind, randomised, active controlled, parallel design,

comparative PK, efficacy, safety and immunogenicity study of Bmab-100 and Avastin, both in combination with oxaliplatin-capecitabine (XELOX) chemotherapy in patients with metastatic colorectal cancer.

In addition, the applicant submitted available data from the **pivotal confirmatory efficacy and safety study in nsNSCLC patients** (**MYL-1402O-3001)**. This dossier included efficacy, safety, PK and immunogenicity data, which reflect data for the primary efficacy endpoint as well as for safety, population pharmacokinetics (PopPK) and immunogenicity.

Bioanalytical methods

Detection and quantitation of MYL-1402O and Avastin

A single ELISA assay using MYL-1402O calibration curve was used for quantitation of MYL-1402O and Avastin (EU and US). The performance of the bioanalytical method was demonstrated in the validation carried out in accordance with the Guideline on Bioanalytical Method Validation. Intra-assay and inter-assay accuracy and precision, selectivity/specificity, sensitivity (LLOQ), dilutional linearity, prozone effect, effect of haemolysis and lipemia, VEGF interference and stability tests were carried out. The validations demonstrated that a single biosimilar calibration curve can be used for quantitating MYL-1402O, US Avastin and EU Avastin in normal and disease-state serum. The validations demonstrated accuracy and precision in normal serum within a working range 160.00-2500.00 ng/mL, in NSCLC serum within the working range 320.00-5000.00 ng/mL, and in mCRC serum within the working range 160.00-2500.00 ng/mL. Stability of bevacizumab was evaluated in solutions and in normal and disease-state serum at three levels of QC samples. The short-term and freeze/thaw stability results demonstrated that MYL-1402O, EU-Avastin, or US-Avastin were stable under defined conditions. The long-term stability data of MYL1402O and EU-Avastin at -80 °C±10°C or -25°C±5°C were provided and demonstrated sufficient stability of MYL1402O and EU-Avastin in both normal and diseased state serum. The values of back-calculated calibration standards, the in-study results of inter-assay QC samples accuracy and precision and ISR results demonstrated reliable performance of the method during study samples analysis.

Analysis of anti-MYL-1402O/anti-Avastin antibodies

The immunogenicity assays included homogeneous bridging electrochemiluminescence (ECL) assay validated for testing of anti-MYL-1402O/anti-Avastin antibodies in normal and disease-state serum and a non-cell-based assay to determine Nab in NSCLC serum. A multi-tiered approach was employed as recommended in EMA guidelines. The single assay strategy was used for ADA and NAb assays. Samples from three clinical studies were analysed by the same assay format but the assays were modified due to VEGF interference observed in the Phase I Study MYL-1402O-1002 to achieve better performance for Phase III study samples. Full assay validation data were submitted, antibodies were reliably detected (see discussion).

Study MYL-1402O-1002 - Pivotal Pharmacokinetics

A single centre, randomised, double-blind, three-arm parallel phase I study to assess pharmacokinetics, safety and tolerability of MYL-1402O solution for intravenous infusion after 90 minute intravenous infusion at one dose level (equivalent weight-adjusted dose [1 mg/kg]) compared to the EU and US marketed drug product (Avastin) in healthy male volunteers was conducted in Europe.

After randomisation, subjects received one of the following treatments: a single 1 mg/kg dose administered by iv infusion (25 mL over approximately 90 minutes) of MYL-1402O, an equivalent iv infusion of US-Avastin (1 mg/kg), or an equivalent iv infusion of EU-Avastin (1 mg/kg).

For the determination of the PK, a total of 28 blood samples were collected per subject from pre-dose to Day 99. Blood sampling for PK of bevacizumab in serum was performed at pre-dose and the following times after the start of infusion: Day 1 (0.33, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 h), Day 2 (24 h), Day 3 (48 h), Day 4 (72 h), Day 5 (96 h), Day 6 (120 h), Day 7 (144 h), Day 8 (168 h), Day 9 (192 h), Day 12 (264 h), Day 15 (336 h), Day 22 (504 h), Day 29 (672 h), Day 43 (1008 h), Day 57 (1344 h), Day 71 (1680 h), Day 85 (2016 h), and Day 99 (2352 h).

Pharmacokinetic results

Summary of the PK data without subject 0213 (n=110) can be found in Table 5.

Table 5. Summary of Bevacizumab Pharmacokinetic Parameters (Mean [CV%])

Parameter	MYL-1402O (n=37)	US-Avastin (n=37)	EU-Avastin (n=36)
$AUC_{0\text{-}inf}$ (µg*hr/mL)	7663.6 (11.7%)	7904.2 (13.7%)	8186.4 (15.1%)
$AUC_{0\text{-}t}$ (µg*hr/mL)	7526.5 (11.8%)	7764.8 (13.6%)	8031.3 (14.8%)
C_{max} (µg/mL)	24.41 (11.5%)	25.97 (13.0%)	27.50 (18.7%)
k_{el} (hr^{-1})	0.0019 (11.0%)	0.0020 (13.3%)	0.0019 (15.2%)
$t_{1/2}$ (hr)	374.1 (11.3%)	356.2 (14.0%)	369.1 (15.0%)
t_{max} (hr)	2.533 (31.1%)	2.798 (31.6%)	2.338 (26.9%)

For all three pairwise comparisons, the bioequivalence criterion was based on the LS mean ratios of the primary PK parameter ($AUC_{0\text{-}inf}$). Bioequivalence was to be concluded if the 90% geometric CIs of the ratios (MYL-1402O/US-Avastin, MYL-1402O/EU-Avastin, and EU-Avastin/US-Avastin) of LS means from the ANOVA of the natural log transformed $AUC_{0\text{-}inf}$ were within 80% to 125%.

The statistical analyses of the PK parameters for bevacizumab based on 110 subjects (excluding the subject with anomalous bevacizumab concentrations) are summarised in Table 6.

Table 6. Summary of LS Means Ratios and 90% Confidence Intervals

Parameter	MYL-1402O/ US-Avastin®	MYL-1402O/ EU-Avastin®	EU-Avastin®/ US-Avastin®
$LNAUC_{0\text{-}inf}$ (µg*hr/mL)	0.97 (92.32% - 102.33%)	0.94 (89.23% - 98.98%)	1.03 (98.20% - 108.93%)
$LNAUC_{0\text{-}t}$ (µg*hr/mL)	0.97 (92.30% - 102.25%)	0.94 (89.31% - 99.01%)	1.03 (98.12% - 108.77%)
LNC_{max} (µg/mL)	0.94 (89.21% - 99.24%)	0.90 (84.90% - 94.52%)	1.05 (99.55% - 110.83%)

The 90% CIs for the primary PK parameter, $AUC_{0\text{-}inf}$, fell within the bioequivalence limits of 0.80 to 1.25 for all three pairwise comparisons, MYL-1402O/US-Avastin, MYL-1402O/EU-Avastin, and EU-Avastin/US-Avastin, following a single, 1 mg/kg iv dose in healthy adult male volunteers. This study demonstrates that MYL-1402O is bioequivalent to US-Avastin and EU-Avastin, and that EU-Avastin is bioequivalent to US-Avastin.

As the study participants of the study MYL-1402O-1002 were divided in the randomisation process to several groups, further analyses were provided accounting for a group effect in the ANOVA model for

the biosimilarity assessment of C_{max}, AUC_{0-t} and AUC_{0-inf}. Two analyses were considered: 1) primary analysis with ANOVA model applied on data excluding subject 0213 and 2) secondary analysis with ANOVA model applied on data from all subjects. In both cases, bioequivalence was concluded as 90% confidence intervals for key pharmacokinetic parameters (C_{max}, AUC_{0-t} and AUC_{0-inf}) were entirely within the bioequivalence range (80%, 125%).

Study MYL-1402O-3001

This study was a multicentre, randomised, double-blind, 2-arm, parallel-group, equivalence study to evaluate patients with Stage IV nsNSCLC when treated in first-line with bevacizumab (either MYL-1402O [test product] or Avastin [reference product]) in combination with carboplatin-paclitaxel (CP) and subsequently, with monotherapy of bevacizumab (either MYL-1402O or Avastin). A total of 671 patients were randomised with 337 patients to the MYL-1402O arm and 334 patients to the Avastin arm.

Bevacizumab (MYL-1402O or Avastin) was administered by iv infusion at a dose of 15 mg/kg every 21 days (± 3 days) for up to 6 treatment cycles (1 treatment cycle = 21 days).

Blood samples for PK analysis were collected:

- at baseline (if possible within 1 hour prior to bevacizumab dosing)
- pre-dose (if possible, within 1 hour prior to first dose of bevacizumab) at Cycles 2 through 6
- post-dose (immediately after infusion, < 15 minutes) at Cycles 1, 2, 4, 6

Two additional PK samples were to be collected from all patients in any cycle (1 to 6): 1 sample to be collected between Days 3 and 8 (inclusive) in any cycle, and 1 sample to be collected between Days 10 and 18 (inclusive) in any cycle; and an additional sample collected at Safety Follow-Up Visit/EOT Visit, as applicable.

Pharmacokinetic analysis

- Pharmacokinetic concentrations and covariate data have been analyzed by PopPK methods for all patients with evaluable PK data. Empiric Bayesian estimates of PK model parameters have been obtained for all patients.
- Pharmacokinetic parameters and exposure estimates (area under the concentration-versus-time curve (AUC), maximum concentration, minimum concentration, clearance, volume, and terminal elimination half-life) have been compared between treatment arms.

Pharmacokinetic results

A two-compartment linear mammillary model with zero- order- input was used as a starting point to evaluate bevacizumab PK in the pooled dataset. Data utilised in the creation of analysis datasets included dosing information (amount, route, timing), PK sampling information (time relative to dosing, bevacizumab serum concentration), treatment assignment, demographic data, laboratory values, and presence of ADA levels, where available. The datasets for use in the PopPK modeling included subject data from all treatment arms. Analysis datasets provided a time-ordered sequence of relevant events constructed for each subject from time of first dose until time of last sample. The exact times of sampling relative to dosing, as captured on the case report form, were used for PK analysis.

The model describing the PK of MYL-1402O versus Avastin was considered to be robust, and the structure and parameter estimates were similar to a previously published model. The low frequency of antidrug antibodies was similar between treatments. However, a model-based assessment of ADA as a covariate of clearance (CL) was inconclusive due to the low frequency of ADA development with each treatment, which was restricted to the time-varying binary variable ADA (positive/negative).

Population pharmacokinetic profiles of MYL-1402O versus Avastin were not different in patients with nsNSCLC. Treatment was not a significant covariate of CL (P = 0.453) or volume of the central compartment (P = 0.161) using the likelihood ratio χ^2 test.

Individual Exposure Measurements

The individual exposure parameters AUC, half-life, C_{max}, and C_{min} were predicted based on the final model for all Phase III patients in steady state. The results were summarised by treatment group (Table 7).

Table 7. Bayesian parameter-based exposure estimates for patients from Study MYL-1402O-3001 at steady state (Final Model), stratified by treatment

Subject Characteristic	Statistic	Treatment	
		Mylan-1402O	EU-Avastin
$AUC_{0\text{-}21}$ in steady-state (mcg x day/mL)	Mean (StdDev)	3881.591 (1289.571)	4035.769 (1364.511)
	Median	3752.200	3874.700
	Min, Max	866.85, 9793.10	878.52, 10641.00
	n	333	327
C_{max} (mcg/mL)	Mean (StdDev)	389.274 (111.376)	395.161 (104.605)
	Median	373.650	387.120
	Min, Max	113.83, 1090.60	136.16, 830.57
	n	333	327
C_{min} (mcg/mL)	Mean (StdDev)	107.603 (47.783)	112.747 (50.947)
	Median	102.730	105.800
	Min, Max	14.05, 354.58	10.78, 393.48
	n	333	327
Half-life (days)	Mean (StdDev)	20.611 (4.681)	21.078 (4.891)
	Median	20.267	20.601
	Min, Max	9.86, 43.87	8.56, 46.48
	n	333	327
Body Surface Area (m^2)	Mean (StdDev)	1.75 (0.25)	1.81 (0.28)
	Median	1.70	1.80
	Min, Max	1.1, 2.7	1.2, 2.5
	n	333	327
Lean Body Mass (kg)	Mean (StdDev)	49.49 (9.57)	51.25 (10.40)
	Median	49.00	50.30
	Min, Max	27.7, 76.5	27.8, 78.1
	n	333	327
Albumin (g/L)	Mean (StdDev)	39.992 (5.233)	39.797 (5.168)
	Median	40.600	40.700
	Min, Max	21.00, 52.00	21.00, 51.00
	n	333	327
Platelets Count (cells/mm^3/1000)	Mean (StdDev)	233.14 (117.55)	221.34 (97.32)
	Median	204.00	201.00
	Min, Max	40.0, 1011.0	19.3, 601.0
	n	333	327
Sum of Tumor Diameters (mm)	Mean (StdDev)	66.82 (46.10)	63.53 (41.99)
	Median	56.50	54.00
	Min, Max	5.0, 329.1	2.9, 256.8
	n	333	327
Race, n (%)	White	223 (67.0)	228 (69.7)
	Other	110 (33.0)	99 (30.3)

The results demonstrated the similarity of treatments in familiar PK terms. While statistical analyses were not performed of these extrapolated exposure measures, these estimates of exposure were comparable between treatments.

Study BM100-CC-03-I-01

Forest plots were presented to explore the magnitude of impact of significant covariates in the final PK model on measures of drug exposure. The covariate data were divided into titres, then stratified by treatment, and the second titre exposures were used as reference for the higher and lower titres. The impact of all covariates on AUC, half-life, and C_{max} was modest since geometric mean ratio (GMRs) and 90% CI ranges fell mostly within a range of 0.8 to 1.25 indicating the first and third tertile exposures were not substantially different from the second tertile (reference group). Additionally, these ranges were similar between the treatment groups. The greatest impact of some covariates on exposure appears to be on C_{min} levels, since for some covariates the GMR and 90% CI ranges fell below 80% of the second tertile covariate range.

Overall, however, the AUC, half-life, C_{max}, and C_{min} values were similar between MYL-1402O and EU-Avastin in patients with nsNSCLC. In addition, since the ranges of exposures between upper and lower titre exposures for most covariates fell within the 0.8 to 1.25 range, there is no anticipated need for dose adjustment in the clinic, based on identified covariates.

The study was a multicentre, double blind, randomised, parallel-group, phase III study to compare the PK, efficacy, safety, and immunogenicity of Bmab-100 and bevacizumab in combination with XELOX (oxaliplatin and capecitabine) chemotherapy in patients with metastatic colorectal cancer. The study consisted of two parts. Part 1 of the study was an open-label safety study which included 10 patients who had received prior chemotherapy for mCRC and received Bmab-100 at the dose of 7.5 mg/kg along with XELOX chemotherapy, for up to 6 cycles. Part 2 was a double-blind, randomised, active controlled, parallel-arm study in patients with mCRC and included patients who had not received any chemotherapy for mCRC (i.e. only first line mCRC patients). Patients received Bmab-100/Avastin at 7.5 mg/kg and XELOX chemotherapy for up to 6 cycles. Each cycle consisted of a 21-day period.

Pharmacokinetic sampling was performed (only in Part 2 of the study) on the following days and time points. Day of first bevacizumab infusion (first Dose, Cycle 1): Pre dose (-5 min), and Post dose (after end of infusion) at 20 min, 1, 1.5, 3, 5 , 8, 24 hours (Day 2); and 72 (Day 4), 120 (Day 6), 192 (Day 9), and 360 hours (Day 16) post dose. Cycles 2-6: Pre dose (-5 min).

The primary PK parameters, i.e. C_{max} and AUC_{0-t} (AUC_{0-504}), were similar for both Bmab-100 and Avastin. This was demonstrated by the point estimates of the ratio (%) of least square means of Bmab-100 to Avastin which were close to 1 (C_{max}: 92.91% and AUC_{0-504}: 95.79%). In addition, the 90% CIs were within the pre-defined bioequivalence range of 80.00% to 125.00% (C_{max}: 85.86% and 100.54%; AUC_{0-504}: 87.56% and 104.79%), confirming the single dose pharmacokinetic equivalence of the two products. The total patient variability for C_{max} was 27.42%; AUC0-504h was 31.38%.

The data from this study are considered supportive and confirm that there are no significant differences in PK parameters C_{max} and AUC_{0-t} (AUC_{0-504}) for Bmab-100 and Avastin.

2.4.3. Pharmacodynamics

No dedicated pharmacodynamics (PD) and/or pharmacokinetic (PK)/PD studies were performed in healthy subjects or in a patient population as part of this Marketing Authorisation Application.

PD parameters (i.e. plasma VEGF levels) were evaluated in the supportive study BM100-CC-03-I-01 with Bmab-100, an "earlier version" of MYL-1402O. In this study, the exploratory PD endpoint was to evaluate and compare the plasma VEGF levels between Bmab-100 and Avastin.

Immunogenicity

Study MYL-1402O-1002

As part of immunogenicity assessment, samples were tested for presence of ADA. ADA samples were taken at baseline, Day 15 (336 h), Day 43 (1008 h), Day 71 (1680 h) and Day 99 (2352 h). ADA results were reported from all subjects at all the above stated time points (Table 8).

Table 8. Incidence of anti-drug antibodies by visit and treatment

Visit	MYL-1402O (N=37)		EU-Avastin (N=37)		US-Avastin (N=37)	
	n´	n (%)	n´	n (%)	n´	n (%)
Baseline	37	1 (2.70)	37	1 (2.70)	37	2 (5.41)
Day 15	37	35 (94.59)	37	37 (100.00)	37	33 (89.19)
Day 43	37	28 (75.68)	37	28 (75.68)	37	31 (83.78)
Day 71	37	8 (21.62)	36	12 (33.33)	37	12 (32.43)
Day 99	37	2 (5.41)	37	6 (16.22)	37	4 (10.81)

n´ = number of subjects with available ADA results; n = number of subjects with positive ADA results
N = the # of subjects exposed to the treatment;
The percentage of ADA positive samples was calculated based on the number of subjects with available ADA results.
Source: Addendum CSR MYL-1402O-1002 Listing 16.2.8.6

Prior to dosing (baseline), 1 of the 37 (2.70%) subjects were positive for ADA in the MYL-1402O and EU-Avastin groups and 2 of the 37 (5.41%) subjects were positive for ADA in the US-Avastin group. The highest pre-dose ADA titre obtained was 5.03 in the EU-Avastin arm, and 1 in the US-Avastin and MYL-1402O arms.

Post dosing, none of the baseline positive subjects showed a significant increase in titre with time. The percentage of ADA positive subjects on Days 15, 43, 71 and 99 was comparable across treatments.

The treatment-induced ADA positivity seen on Day 15 was transient. In all 3 arms, the percentage of treatment-induced ADA positive subjects declined with time and by day 99, >85% subjects became ADA negative. Table 9 summarises the ADA titres by visit and treatment. Overall, ADA titres were comparable across all 3 arms across all time points. The highest post-dose ADA titre obtained was 20.9, 16.3 and 14.7 respectively in the MYL-1402O, EU-Avastin and US-Avastin arms.

Table 9. Summary of anti-drug antibody titres by visit and treatment

Visit	Statistics	MYL 1402O (N=37)	EU-Avastin (N=37)	US-Avastin (N=37)
Baseline	n	1	1	2
	Mean (SD)	1 (0)	5.03 (0)	1.000 (0)
	Median	NA	NA	1
	Min, Max	NA	NA	1, 1
Day 15	n	35	37	33
	Mean (SD)	2.712 (2.698)	2.708 (1.626)	3.254 (2.998)
	Median	2.28	2.36	2.85
	Min, Max	1, 15.45	1, 6.68	1, 14.72
Day 43	n	28	28	31
	Mean (SD)	1.287 (0.892)	1.403 (0.903)	1.336 (0.719)
	Median	1	1	1
	Min, Max	1, 4.79	1, 3.73	1, 3.23
Day 71	n	8	12	12
	Mean (SD)	1.000 (0)	2.538 (4.438)	1.568 (1.679)
	Median	1	1	1
	Min, Max	1, 1	1, 16.34	1, 6.82
Day 99	n	2	6	4
	Mean (SD)	10.985 (14.121)	1.695 (1.077)	1.000 (0)
	Median	10.985	1	1
	Min, Max	1, 20.97	1, 3.14	1, 1

Max = maximum; Min = minimum; n = number of subjects with positive ADA results; N = the # of subjects exposed to the treatment; NA = not applicable; SD = standard deviation. Source: Listing 16.2.8.6

Study MYL-1402O-3001

A total of 12 (3.6%) and 16 patients (5.0%) were positive for ADA at baseline in the MYL-1402O and Avastin arms, respectively. The incidence of baseline ADA positivity in a small proportion of patients has been observed in other bevacizumab studies and may be due to potential cross-reactivity with pre-existing antibodies. Post-baseline, the number of ADA positive patients were low, declined over time and were comparable between both treatment arms (Table 10).

Table 10. Summary of ADA samples analysed by visit and treatment – Safety set

Visit	Results	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)
Baseline	Positive	12 (3.6)	16 (5.0)
	Negative	318 (96.4)	307 (95.0)
	Missing	1	0
Period1 W4	Positive	12 (4.0)	11 (3.5)
	Negative	291 (96.0)	300 (96.5)
	Missing	1	0
Period1 W10	Positive	10 (4.0)	10 (3.9)
	Negative	243 (96.0)	246 (96.1)
	Missing	0	1
Period1 W16	Positive	3 (1.4)	8 (3.7)
	Negative	219 (98.6)	207 (96.3)
	Missing	0	0
EOT	Positive	1 (2.3)	1 (2.1)
	Negative	43 (97.7)	46 (97.9)
	Missing	0	0
Safety Follow-Up	Positive	1 (2.7)	2 (4.4)
	Negative	36 (97.3)	43 (95.6)
	Missing	0	0

Percentages are based on the number of patients in safety set with non-missing ADA data at corresponding visit. Missing are the number of patients who attended the visit but did not have an ADA sample collected.
Source Data: Listing 16.2.10 and Table 14.5.1.2

A total of 2 (0.6%) and 4 (1.2%) patients were positive for NAb at baseline in the MYL-1402O and Avastin arms, respectively. Post-baseline, the incidence of NAb positivity was very low, transient in nature, and the number of positive patients were comparable between both treatment arms (

Table 11).

Table 11. Summary of NAb samples analysed by visit and treatment – Safety set

Visit	Results	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)
Baseline	Positive	2 (0.6)	4 (1.2)
	Negative	328 (99.4)	319 (98.8)
	Missing	1	0
Period 1 W4	Positive	1 (0.3)	2 (0.6)
	Negative	302 (99.7)	309 (99.4)
	Missing	1	0
Period 1 W10	Positive	0	2 (0.8)
	Negative	253 (100.0)	254 (99.2)
	Missing	0	1
Period 1 W16	Positive	0	3 (1.4)
	Negative	222 (100.0)	212 (98.6)
	Missing	0	0
EOT	Positive	0	1 (2.1)
	Negative	44 (100.0)	46 (97.9)
	Missing	0	0
Safety Follow-Up	Positive	0	0
	Negative	37 (100.0)	45 (100.0)
	Missing	0	0

Samples were taken before administration of IMP since elevated antibody titer levels against IMP plasma levels can interfere with the antibody assays. Percentages are based on the number of patients in safety set with non-missing ADA data at corresponding visit. Missing are the number of patients who attended the visit but did not have an ADA sample collected..
Source Data: Listing 16.2.10 and Table 14.5.1.3

The overall ADA incidence was similar between the treatment arms (18 [5.9%] in the MYL-1402O arm vs 13 [4.2%] in the Avastin arm). Additionally, no boosted ADA was reported (the titre ≥ 4*baseline titre while on treatment) for MYL-1402O group, but it was reported for 2 patients in Avastin arm (Table 12).

Table 12. Overall incidence of treatment emergent ADA – Safety set

	MYL-1402O (N=335) n m n/m%	Avastin (N=329) n m n/m%
Treatment Induced ADA	18 306 (5.9)	11 309 (3.6)
Treatment Boosted ADA	0 306 (0.0)	2 309 (0.6)
ADA Incidence	18 306 (5.9)	13 309 (4.2)

m=number of patients with evaluable ADA results (baseline and at least one post-baseline).
n=number of patients with treatment induced ADA or treatment boosted ADA results.
Treatment induced ADA: ADA developed any time after the initiation of drug administration in a patient without pre-existing ADA. Treatment boosted ADA: Any time after the initiation of drug administration the ADA titer is at least 4* the baseline titer. ADA incidence: Sum of both treatment induced and treatment boosted ADA-positive patients as a proportion of the evaluable patient population.
Source Data: Listing 16.2.10 and Table 14.5.1.5

The incidence of binding ADA was similar between the treatment arms (22 [7.1%] in the MYL-1402O arm vs 21 [6.6%] in the Avastin arm, as shown in Table 13. The incidence of NAb was lower in MYL-1402O arm (1 [0.3%]) compared to Avastin arm (8 [2.5%]).

Table 13. Overall summary of immunogenicity – Safety set

	MYL-1402O (N=335)	Avastin (N=329)
Anytime Post-Baseline		
Binding ADA Positive/Total	22 /310 (7.1)	21 /316 (6.6)
Neutralizing ADA Positive/Total	1 /310 (0.3)	8 /316 (2.5)

Binding ADA positive counts are based on patients who test positive for ADA for the timeframe specified post-baseline.
Neutralizing antibody positive results are summarized for patients who test positive for ADA.
Percentages are calculated based on number of patients with available ADA results post baseline.
Source Data: Listing 16.2.10 and Table 14.5.1.6

Study BM100-CC-03-I-01

At baseline, prior to dosing, 5 of the 68 (7.35%) and 2 of the 67 (2.99%) patients were positive for ADA in the Bmab-100 and the Avastin arm, respectively. The highest individual pre-dose ADA titre was 7.0 ng/mL in the Bmab-100 arm and 6.0 ng/mL in the Avastin arm. At visit 4 and EOS, the percentage of ADA-positive patients was comparable between the two treatments (Visit 4: 86.54% patients in Bmab-100 arm and 87.27% patients in the Avastin arm; EOS: 90.20% patients in the Bmab-100 arm and 90.38% patients in the Avastin arm).

Table 14. Incidence of anti-drug antibodies by visit and treatment

	Bmab-100 (N = 68)			Avastin (N = 67)		
Visit	n'	n	(%)	n'	n	(%)
Baseline	68	5	(7.35)	67	2	(2.99)
Visit 4	52	45	(86.54)	55	48	(87.27
EOS	51	46	(90.20)	52	47	(90.38)

n' = number of subjects with available ADA results
n = number of subjects with positive ADA results
Percentage of ADA positive samples was calculated based on number of subjects with available ADA result.
Reference: Listing 16.2.42

The titres in ADA positive patients were low post-dose and did not change significantly over time. Titres were comparable in both arms. The highest individual post-dose ADA titres obtained in the Bmab-100 and Avastin arms were 9.0 ng/mL and 7.0 ng/mL respectively. The overall ADA rate was calculated using a conservative approach, which considers all patients who tested positive for ADA at least once, at any time point post-baseline regardless of the ADA result at baseline. Overall, ADA rate was found to be comparable across treatments (80.88% [55/68] in the Bmab-100 arm and 88.06% [59/67] in the Avastin arm).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

A pivotal Phase I PK comparability, safety, immunogenicity study in healthy subjects (MYL-1402O-1002) following a 1 mg/kg IV infusion was conducted to demonstrate PK comparability of the developed bevacizumab product with the reference EU-product (as well as US-product) bevacizumab. The study was well designed with no significant issues identified. PK equivalence between the products was concluded following single 1 mg/kg IV infusion.

Furthermore, available PK data of study MYL-1402O-3001, a pivotal confirmatory phase III efficacy and safety study in nsNSCLC patients, was submitted. The obtained data were analysed in population pharmacokinetics (PopPK) analysis. The pharmacokinetic profiles of MYL-1402O versus Avastin were not different in patients with nsNSCLC. Treatment was not a significant covariate of CL (P = 0.453) or volume of the central compartment (P = 0.161) using the likelihood ratio χ2-test. Model-based exposure measures were similar between treatments.

The presented PopPK analysis and individual parameters did not provide sufficient information needed to conclude comparability between MYL-1402O and EU-Avastin. Therefore, for the purpose of comparing the PKs, a statistical comparison of the C_{max} and C_{trough} at steady state (test versus reference) was performed (data not shown). Confidence intervals for both the parameters were within standard bioequivalence limits. The results confirmed equivalence between the test and the reference product also at steady state, therefore pharmacokinetic equivalence can be concluded.

In addition, a supportive PK, comparative efficacy, safety and immunogenicity study in mCRC patients (BM100-CC-03-I-01) was conducted.

Overall, the PK similarity was shown in the presented studies.

Pharmacodynamics

No dedicated PD or PK/PD studies were performed in healthy subjects or in a patient population.

PD parameters (*i.e.* plasma VEGF levels) were evaluated in the supportive study BM100-CC-03-I-01 with an earlier version of MYL-1402O, Bmab-100. In this study, the exploratory PD endpoint was to evaluate and compare the plasma VEGF levels between Bmab-100 and Avastin. However, distinct variations were seen in the VEGF levels.

Since no validated biomarker exists that is considered relevant to predicting clinical outcomes for bevacizumab in patients, this is considered not to be of clinical relevance.

Immunogenicity

The immunogenicity profile of Lextemy was evaluated within three clinical studies and the respective recommendations on immunogenicity evaluation delineated in EMA guidelines "Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use" (EMA/CHMP/BMWP/86289/2010; 24-May-2012) and "Guideline on immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1)" were followed except for several points mentioned below.

In the pharmacokinetic study MYL-1402O-1002, the antibody formation was investigated at baseline and four additional time points. Although, the baseline results indicated only few patients with positive ADA results, the majority of enrolled subjects have ADA-positive results on D15. The same data were obtained across all treatment groups suggesting the false positivity of obtained data. Although the ADA positivity was transient within the time and only several patients remained ADA-positive on D99. ADA assay sensitivity was high, which may have contributed to the detection of high ADA rates in study MYL- 1402O-1002. In addition, assay interference with VEGF (released from the drug during the acid dissociation step) was identified as the main reason for the high incidence of ADA-positive samples. NAb analysis was not planned to be included in the single dose PK comparability study MYL-1402O-1002 given the low risk of NAb development identified in multidose phase III clinical studies with the originator Avastin. The applicant further justified the absence of NAb analysis by the lack of clinical relevance of the low ADA levels detected in study MYL-1402O-1002.

To understand the potential impact of ADA exposure on the PK endpoints subjects were allocated to two groups based on the calculated AUC of the ADA titre values for each subject (data not shown). The groups were made by splitting the total of 110 subjects with available ADA results into a "Low ADA" group, which included the 55 subjects with the lowest ADA AUC values, and a "High ADA" group, which included the 55 subjects with the highest ADA AUC values. Subjects in the "High ADA" group had AUC values over 80.00 with individual titres values ranging from 1 to 20.97, while subjects in the "Low ADA" group had AUC values less than 80.00 with individual titre values ranging from 1 to 3.20. Although a more detailed analysis including quartiles of ADA values (AUC and titre) and its impact on PK parameters would have been more meaningful, the provided analysis did not hint at any differences in PK comparing subjects with high ADA values to subjects with rather low ADA values. However, results revealed that the "High ADA" group had higher bevacizumab exposure based on the AUC0-inf ratio of 1.11 relative to the "Low ADA" group. The higher exposure seen for the "High ADA" group compared to the "Low ADA" group could be a result of the ADA assay conditions employed for this study, since the split into the high and low groups was based on AUC of ADA titre values, which may

not have truly reflected the presence or amount of anti-drug antibodies present in each sample. With regard to biosimilarity, the applicant provided plots comparing Cmax versus AUCada, AUCt versus AUCada, and AUCinf versus AUCada for MYL-1402O and EU-Avastin. PK parameters have not been plotted against ADA titre itself. However, AUCada was calculated from the ADA titre values for each subject across all time points. The analyses do not reveal significant differences of the impact of ADA status on PK parameters comparing MYL-1402O and EU-Avastin.

The crucial immunogenicity data were obtained from the phase III study MYL-1402O-3001. In line with the two above mentioned guidelines, the appropriate multi-tiered approach was applied including conduction of three key assays (screening, confirmatory and NAb). The samples were collected at Baseline (pre-dose), Cycle 2, 4, and 6 in Period 1, and at Safety Follow-up visit, which is considered acceptable. At first time point, W4, 12 (4.0%) and 11 patients (3.5%) were ADA positive in the MYL-1402O and Avastin arms, respectively. On the last time point, EOT, there was only 1 patient with ADA-positive results in each treatment group showing a transient nature of developed ADAs. In total, in 18 and 11 patients the treatment-induced ADA were observed in the MYL-1402O and Avastin groups, respectively. Additionally, no boosted ADA was reported (the titre ≥ 4*baseline titre while on treatment) for MYL-1402O group, but it was reported for 2 patients in Avastin arm.

Regarding the incidence of NAb positivity, only 2 and 4 patients, respectively, were tested as positive at baseline and only 1 patient in Avastin groups was tested Nab positive at EOT. Results from the first period including 6 cycles demonstrate the similar immunogenicity profile between both arms. After 42 weeks of treatment, the overall incidence of Treatment Emergent ADA (Treatment Induced plus Treatment Boosted) was similar between the treatment arms (20 [6.5%] in the MYL-1402O arm vs 15 [4.8%] in the Avastin arm) (data not shown). ADA incidence rate was generally low, as expected for bevacizumab. Post baseline, NAb occurred at a slightly lower rate in the MYL-1402O arm 2 [0.6%] compared to Avastin arm 8 [2.5%]). However, this difference is not considered significant.

In the supportive study BM100-CC-03-I-01, the immunogenicity baseline data showed only few patients with positive ADA samples. At second timepoint (Visit 4), the incidence of ADA was around 85% in both investigated treatment arms. This is quite unusual for this substance, but the same conclusions were also seen in the Phase I MYL-1402O-1002 study as indicated above. The high number of ADA positive patients, in this study even persisting until EOS, was again explained by the detection of low-level ADA due to high assay sensitivity coupled with target (VEGF) interference. No other immunogenicity data within the treatment period were provided. According to the low relative ADA concentration calculated for all ADA positive samples, there was no clinical impact of the observed ADA levels. In accordance with the study MYL-1402O-1002, no determination of NAb was made, which was justified by the low risk of NAb development identified in multi-dose phase III clinical studies with the originator Avastin and the lack of clinical relevance of the low ADA levels detected in study BM100-CC-03-I-0.

2.4.5. Conclusions on clinical pharmacology

Overall, the PK similarity was shown in the presented studies.

Identified issues with regard to immunogenicity were adequately addressed. The incidence of ADA was generally comparable between MYL-1402O and the reference product within each trial, so that biosimilarity with regard to immunogenicity can be concluded, despite the presence of high ADA incidence rates clinical studies BM100-CC-03-I-01 and MYL-1402O-1002.

With respect to proposed legal basis, submitted data on pharmacodynamics are considered acceptable.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

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

Table 15. Clinical studies with efficacy endpoints

Studies/Treatment	Efficacy Endpoints	Study Type
MYL-1402O-3001 / MYL-1402O and EU-Avastin	ORR at Week 18 (MYL-1402O versus Avastin) (Period 1, primary endpoint) DCR, DOR, PFS, and OS at Week 18 (MYL-1402O versus Avastin) (Period 1, secondary endpoints) DCR, DOR, PFS, and OS at Week 42; (MYL-1402O versus Avastin) (Period 2, secondary endpoints)	Pivotal Study
BM100-CC-03-I-01/ Bmab-100 and EU-Avastin	PFS rate and ORR at Week 18 (Bmab-100 versus Avastin) (secondary endpoint)	Supportive Study

DCR=disease control rate; DOR=duration of response; EU=European Union; ORR=overall response rate (according to Response Evaluation Criteria in Solid Tumor Version 1.1); OS=overall survival; PFS=progression-free survival.

Period 1 - the period of study where tumor assessments were performed every 6 weeks following Day 0 of Cycle 1 (the first dose of bevacizumab, either MYL-1402O or Avastin, in combination with CP) and continued every 6 weeks (window of ±3 days) through Week 18, regardless of delays of the cycles of treatment. Total duration of Period 1 was 18 weeks. Period 1 included 3 assessments at the pre-specified time points (Week 6, Week 12, and Week 18) regardless of delays in treatment cycles.

Period 2 – the period of study where tumor assessments which started after the end of Period 1 (Week 18 tumor assessments) and occurred every 12 weeks, regardless of delays of the cycles of treatment, at pre-specified time points (i.e., Week 30 and Week 42) until PD, discontinuation. Total duration of Period 2 was 24 weeks

2.5.2. Main study(ies)

Phase III NSCLC Study (MYL-1402O-3001)

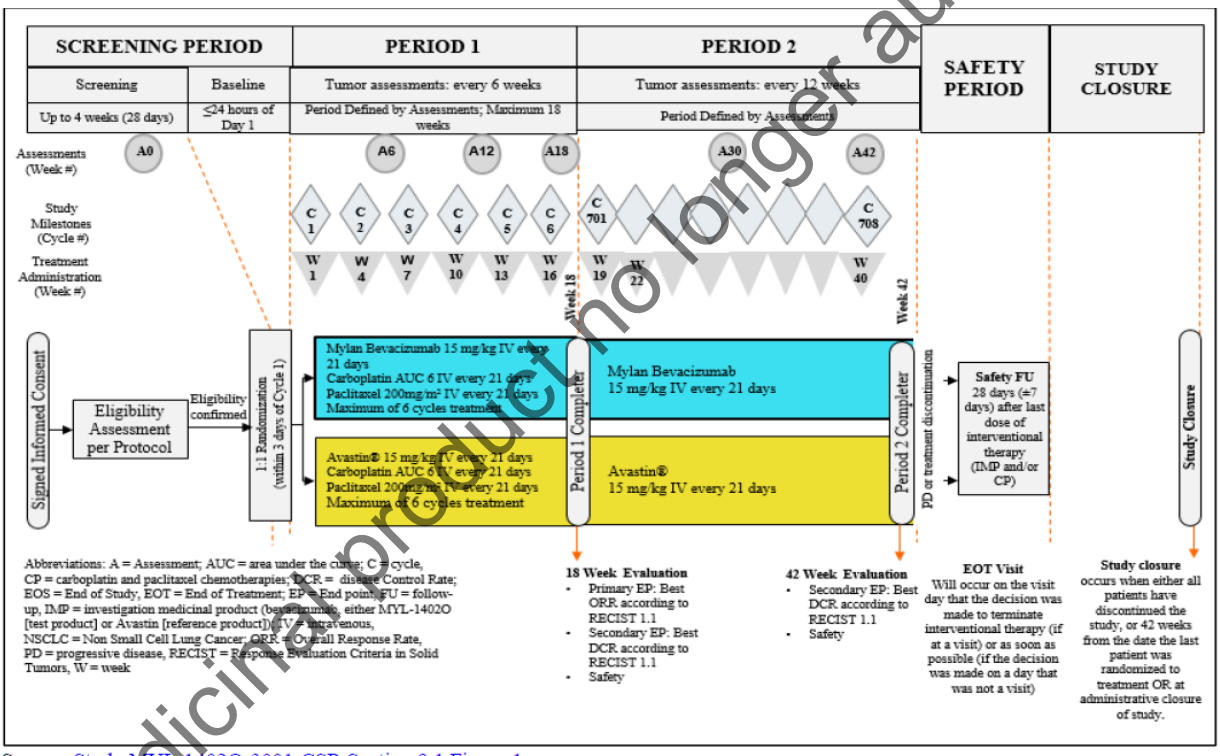
A multicentre, randomised, double-blind, 2-arm, parallel-group, equivalence study to assess the efficacy and safety of MYL-1402O compared with EU-sourced Avastin, in the first-line treatment of patients with Stage IV nsNSCLC in combination with carboplatin-paclitaxel (CP) and subsequently, with monotherapy of bevacizumab (either MYL-1402O or Avastin).

MYL-1402O	Primary objective -To compare the overall response rate (ORR) of MYL 1402O with that of EU-Avastin, in combination with carboplatin-paclitaxel chemotherapy during the first 18 weeks of first-line treatment. Secondary objectives: -To assess safety profile of MYL 1402O as compared with that of Avastin. -To assess other efficacy parameters at 18 weeks and 42	Multicentre, Double-Blind, Randomised, Parallel-Group Study	Bevacizumab (MYL-1402O or EU-Avastin) 15 mg/kg IV infusion every 21 days Treatment in combination with Carboplatin-Paclitaxel chemotherapy during Period 1	ITT = 671 MYL-1402O = 337 EU-Avastin = 334	Patients with Stage IV nsNSCLC	42 weeks	Period 1 (18 Weeks) Completed Period 2 (42 weeks completed) Total duration 42 weeks

	weeks: disease control rate (DCR), duration of response (DOR), progression free survival (PFS), and overall survival (OS) rate of MYL 1402O as compared to Avastin. -To assess the potential immunogenicity during 42 weeks of treatment of MYL 1402O as compared with that of Avastin.						

EU: European Union, IV: Intravenous, nsNSCLC: Nonsquamous non-small cell lung cancer

The study consisted of screening/baseline (4 weeks), Treatment Period 1 (18 weeks) and Treatment Period 2 (from week 18 through 42 weeks), an extended treatment period and safety follow up.



Source: Study MYL-1402O-3001-CSR Section 9.1 Figure 1

Figure 1. Study design for MYL-1402O-3001

Study Participants

671 subjects with Stage IV unresectable, recurrent or metastatic non-squamous NSCLC with negative or unknown activating EGFR gene mutations and negative or unknown ALK gene translocations were randomised in a 1:1 ratio, stratified by gender, smoking status (smoker or <100 cigarettes in entire life-time) and number of metastasis sites (one site or multiple sites) to receive either MYL-1402O or EU-Avastin.

A total of 89 sites randomised patients into the study. Study sites were located in Belarus, Bosnia, Bulgaria, Croatia, Georgia, Hungary, India, Italy, Philippines, Poland, Romania, Russia, Spain, Taiwan, Turkey, Ukraine and Vietnam.

The mean age was 59 years; 424 male and 247 female patients were included. 68.3% of patients were white. The most dominant cancer type was adenocarcinoma (95.5%).

The presented baseline characteristics were balanced between treatment arms, and the inclusion/ exclusion criteria were in accordance with the Avastin study in advanced NSCLC patients.

Treatments

IMP: Patients were randomised to receive either MYL-1402O or EU-Avastin 15 mg/kg iv infusion every 21 days for up to 6 treatment cycles. Supplied for use as a concentrate for solution (100 mg or 400 mg per vial).

Non-IMP: Paclitaxel 200 mg/m^2 iv infusion over 3 hours / Carboplatin AUC 6 iv infusion over 30 minutes on Day 1 of each cycle during the induction treatment period. Each cycle started with administration of bevacizumab followed by carboplatin and paclitaxel.

In countries where the initial paclitaxel dose was 175 mg/m^2 based on institutional protocols, PIs were allowed to initiate dosing at 175 mg/m^2.

Study phases and conduct

Screening/Baseline Period was up to 4 weeks.

Period 1: Patients received bevacizumab combination therapy (MYL-1402O or Avastin, plus CP) on Day 0 of Cycle 1 for up to 6 cycles (21 days ± 3 days) of therapy. Tumour assessments (CT scan or MRI) were performed every 6 weeks.

Period 2: A patient was eligible to continue into Period 2 if he/she had a response of SD or better (i.e., CR or PR) as assessed using RECIST 1.1 criteria at the end of Period 1. Eligible patients continued to receive either MYL-1402O or Avastin every 3 weeks as monotherapy. Tumour assessments were performed every 12 weeks at pre-specified time points, regardless of the delays of the cycles of treatment until progression of disease (PD) or discontinuation of interventional therapy (for any reason), or withdrawal of consent.

If a patient was discontinued from treatment prior to completion of Period 2 due to an adverse event, the patient's tumour assessment was performed per the schedule until Week 42. Patients who had started on a new anticancer treatment (surgery, radiotherapy or systemic treatment) or who had PD were followed for OS until Week 42.

Extended Treatment Period: Patients who had maintained SD or better (CR or PR) by RECIST 1.1 criteria at Week 42 entered into the extended treatment period and continued to receive bevacizumab monotherapy (either MYL-1402O or Avastin) until PD, discontinuation of treatment, or termination of study.

The End of Treatment (EOT) Visit was performed after the last dose of any interventional therapy, primarily to record the reason for discontinuation of the first-line treatment.

Safety Follow-Up Visit was held 28 days (± 7 days) after the last dose of bevacizumab.

The treatment scheme and the administered doses of bevacizumab are according to the SmPC for Avastin as indicated for non-squamous NSCLC patients and in line with current guidelines.

This applies also to the ChT regimen with 200 mg/m^2 paclitaxel and carboplatin AUC 6.0, which is in line with current guidelines and commonly used by clinicians in the EU. However, in countries where the initial dose for paclitaxel was 175 mg/m^2 based on institutional protocols, the investigators were allowed to initiate dosing at 175 mg/m^2 instead of 200 mg/m^2. The majority of patients (69.9%) received the higher initial dose of 200 mg/m^2. In addition, the number of patients with the different paclitaxel doses was balanced between the treatment arms.

Disease status was evaluated by CT scans or MRI every 6 weeks during Period 1 (first 18 weeks of combination treatment) and thereafter every 12 weeks during Period 2 (24 weeks of monotherapy treatment). In individual cases, treatment was delayed, discontinued, switched to bevacizumab monotherapy (due to intolerance of CP) or switched to CP (due to intolerance of bevacizumab). Thus, the number of treatment cycles varies between individual patients. As the number of cycles varies between 1 and 6 and due to possible study discontinuation before the end of the induction period, the number of response assessments can range from 0-3 during Period 1. The duration of exposure to study drug and the overall number of doses/ cycles were presented by treatment group with descriptive statistics using the Safety set. In addition, the number of patients with a certain number of cycles have been presented per treatment arm, for both the ITT and the PP set. There is a numerical imbalance with regard to the number of treatment cycles received, both in the ITT and PP set – there was a higher number of subjects who were treated for only 1 cycle in the MYL-1402O arm than in the Avastin-arm, whereas patients who were treated for 4 cycles had a higher frequency for Avastin than for MYL-1402O. However, this levels off for cycle 6 – the majority of patients and, importantly, similar numbers of subjects per treatment arm received a total number of 6 treatment cycles (PP set: 65.0% in the MYL-1402O arm vs 65.6% in the Avastin arm). Thus, overall, the two treatment arms are considered comparable.

Overall the duration of exposure, the number of doses administered and the cumulative doses of bevacizumab, paclitaxel and carboplatin were comparable between treatment arms in the induction period. With regard to the duration of IMP exposure, the total number of cycles received was similar between both treatment arms during the induction period (1627 vs 1626 cycles). For the maintenance period, a numerically higher number of treatment cycles was administered in the MYL-1402O arm (1278 vs 1242 cycles). This could be attributed mainly to a higher number of patients having received 7 cycles in the MYL-1402O arm than in the Avastin arm (n=20 vs n=9).

The primary efficacy analysis was based on the data from independent central review.

Objectives

The primary objective of this study was to compare the ORR of MYL-102O with that of EU-Avastin, in combination with chemotherapy, during the first 18 weeks of first-line treatment in subjects diagnosed with Stage IV non-squamous NSCLC.

Outcomes/endpoints

The primary efficacy endpoint was the ORR based on best tumour response as assessed by an independent review at any time point during the first 18 weeks, according to RECIST1.1. The ORR was defined as the proportion of patients with CR or PR as the best overall response (BOR) during the first 18 weeks; the number of patients in the ITT set was used as the denominator for the calculation.

The primary efficacy analysis was based on difference in ORRs in the ITT population, and equivalence between the two treatment groups was declared if the 95% CI of the difference in the best ORR was

entirely contained within the pre-defined equivalence margin of [-12.5%, 12.5%]. The analysis was repeated in the PP set to support the primary analysis.

Subjects underwent radiographic assessment of disease status (CT or MRI) according RECIST v1.1 in cycles 2, 4, and 6, and then every 4 cycles until there was radiographic documentation of progressive disease (PD), unacceptable toxicity, death, or end of study (EOS), whichever occurred first. Patients with response who could not be evaluated per RECIST1.1 or without any tumour assessment prior to or on Week 18 were scored as non-responders.

Tumour response was assessed using RECIST1.1 criteria locally by investigators and centrally by independent reviewers. The primary efficacy analysis is based on the data from the independent central review.

The secondary efficacy endpoints for the study were:

• DCR (CR, PR, or stable disease) during the first 18 weeks

• PFS, defined as the time from randomisation to the first documentation of PD or to death due to any cause, whichever comes first; PFS rate at 18 weeks and 42 weeks, median PFS at 42 weeks.

• OS, defined as the time from randomisation to date of death due to any cause, OS rates at 18 weeks and 42 weeks.

• DOR, defined as the time from start of the first documentation of objective tumour response (CR or PR) to the first documentation of tumour progression (i.e., PD) or to death due to any cause, whichever comes first.

The pharmacokinetics endpoints were as follows:

• PopPK measures of exposure of MYL-1402O and the reference product Avastin (e.g., Area Under the Concentrate Curve (AUC), maximum concentration (C_{max}), minimum concentration (C_{min}), clearance (CL), volume (Vc), and terminal elimination half-life.

The safety endpoints were as follows:

• Incidence, nature, and severity of AEs including adverse drug reactions graded according to NCI CTCAE.

• Detection of antibodies to bevacizumab.

The immunogenicity variable, the formation of ADA against MYL-1402O or Avastin, was assessed to examine and compare the clinical immunogenic response to the study drugs.

Sample size

A sample size of 628 patients (314 per treatment group) provided 80% power for testing equivalence of MYL-1402O and Avastin at 1-sided 2.5 % level of significance, for the primary endpoint ORR at week 18. This sample size assumed that the ORR was 38.0% for both MYL-1402O and Avastin. Statistical equivalence was declared if the 2-sided 95% CI of the difference of the 2 treatment groups fell wholly within an equivalence margin of (-12.5%, 12.5%).

Given that a single post-baseline assessment was needed for a patient's inclusion in the ITT population, an attrition rate of 2% was assumed for the study, which led to the number of 640 patients (320 per treatment group) to be randomised. The final sample size was determined at the interim analysis using the sample size re-estimation approach described in the SAP.

For the ITT set, the IA provided an objective response rate (ORR) of 25.2%. Based on the pre-specified algorithm in the protocol and SAP, the sample size was re-estimated for the risk difference and increased up to a maximum of 670 patients to maintain the power for testing primary endpoint per EMA requirement.

Randomisation and blinding (masking)

Patients were randomised 1:1 stratified by gender, smoking status, and number of metastasis sites. The randomisation schedule was administered by an interactive voice or web response system (IVRS/IWRS).

This was a double-blind study. Principle investigator and study site personnel, the study patients and the local and central radiologists were planned to be blinded throughout the study. An unblinded pharmacist was planned to allocate treatment via the IVRS/IWRS by preparing infusion bags of MYL-1402O and Avastin to the PI in a blinded manner. Parts of the sponsor clinical team was planned to be unblinded to the randomisation list after all patients have completed Week 18 or discontinued the study.

Statistical methods

The following analysis sets were defined:

- Intent-to-Treat (ITT) Set: The ITT set was planned to consist of all randomised patients. Analyses using the ITT set group patients according to randomised treatment.

- Safety Set (SS): The safety set was planned to consist of all randomised patients who received at least one dose or partial dose of MYL-1402O or Avastin. Analyses using SS group patients according to treatment actually received.

- Per Protocol (PP) set: The PP set was planned to consist of all randomised patients who received at least one dose of MYL-1402O or Avastin and do not have major protocol deviations. Analyses using PP group patient according to randomised treatment.

- Population PK (PopPK) Set: The PopPK set was planned to consist of all randomised patients who completed at least 1 dose of allocated study medication and who provide at least 1 evaluable post-dose drug concentration for PopPK analyses. Analyses using PopPK set group patients according to treatment actually received.

In general data were summarised by statistical characteristics (categorical data: absolute and relative frequencies; continuous data: mean, standard deviation, median, minimum, and maximum).

Efficacy analyses

The ITT set was used for the efficacy analyses.

Primary efficacy endpoint was planned to be the difference in ORR at Week 18, according to RECIST 1.1. It was planned to be analysed using an unstratified Cochran-Mantel-Haenszel (CMH) test together with an asymptotic 2-sided 95% CI for the difference in ORRs at Week 18. Equivalence was to be concluded in case the 95% CI for the difference in ORRs at Week 18 fell completely into the pre-defined equivalence range of -12.5% to 12.5%.

Missing values due to difficulties in assessing the ORR by RECIST 1.1 were scored as non-responders. However, for the primary EP of ORR, no missing values by reason of no assessment by RECIST1.1

occurred, and therefore, no sensitivity analysis due to this reason of missingness was performed. A justification how missing values by other reasons were handled was provided.

For the PP population, patients were treated as non-responders with missing values due to disease progression, death, or AE. Patients with missing values for reasons other than that were excluded from the PP population. This procedure is considered comprehensible and suitable for the given study design.

In order to assess the homogeneity of study results in important subgroups, the following variables were used to define subgroups: Age (<65 years of age median or ≥65 years of age median), Gender (Male or Female), Race (Caucasian or non-Caucasian; Asian or non-Asian), Smoking status (smoker or <100 cigarettes in entire lifetime), Number of metastasis sites (1 or multiple), Prior weight loss (≥5% from the historical weight during the last 3 months or <5%), Prior radiation therapy (0 or ≥1), Prior adjuvant chemotherapy (0 or 1), ECOG performance scale at screening (0 or 1), EGFR mutation status (unknown or negative), EML4-ALK alterations (unknown or negative).

The secondary efficacy endpoints were disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). DCR was planned to be analysed as treatment difference and treatment ratio. The difference in DCRs between treatment groups were planned to be estimated with unstratified CMH test and an asymptotic 2-sided 95% CI.

Survival endpoints (PFS, OS) were planned to be analysed by Kaplan-Meier plots, median PFS and OS, and log-rank test for descriptive purposes. In addition, a Cox regression model was planned to be used for estimating hazard ratios with 95% CI for the treatment effect. The main model was planned to be performed without covariates. Sensitivity analysis was planned by adding covariates to the model.

No formal hypothesis testing was planned for the secondary efficacy endpoints, therefore, no adjustments for multiplicity were planned.

Safety analysis

The safety set was planned to be used for the safety analyses. Safety analyses were mainly based on the frequency of AEs summarised by system organ class, preferred term, and treatment group. Changes from baseline on performance status (ECOG) and clinical laboratory parameters were summarised similarly for each visit and treatment group.

PK analyses

A 2-compartment linear model was planned to be performed with CL, inter-compartmental clearance, Vc, and volume of the peripheral compartment (Vp). Inter-individual variability in CL and Vc was planned to be assigned with log-normal distribution.

The provided clinical study report contains the results of the primary efficacy analysis and all other efficacy and safety results up to Week 18. A final study report is announced to be written after all patients have completed Week 42 or discontinued.

Results

Participant flow

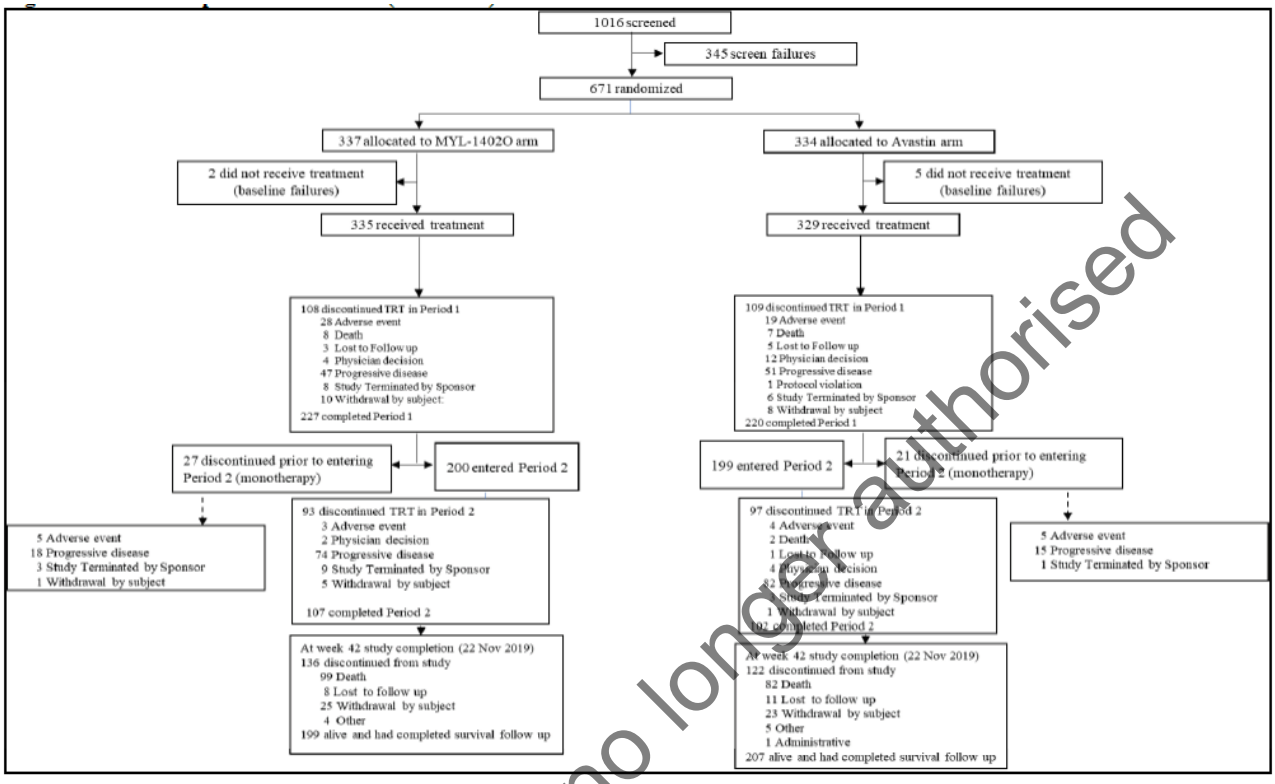


Figure 2. Patient disposition – ITT set (42 weeks)

A total of 1016 patients were screened; 345 patients were screening failures. The most common reasons for screening failures were; 57 (16.5%) patients met exclusion criteria 10b (thoracic, central, mediastinal tumour location in contact with major vessels); 46 (13.3%) patients withdrew consent during screening period (inclusion criteria 1); 37 (10.7%) patients did not meet inclusion criteria 10 (brain metastasis which was treated and stable at the time of signing ICF) and 36 (10.4%) patients did not meet inclusion criteria 5 (at least one measurable lesion as defined by RECIST 1.1).

A total of 671 patients were randomised with 337 patients to the MYL-1402O arm and 334 patients to the Avastin arm. All randomised patients were included in the ITT population. Comparable numbers of patients from both treatment arms completed the combination therapy period (MYL-1402O: n=227, Avastin: n=220). Of those who had completed the induction period, similar numbers discontinued treatment prior to entering the maintenance period (n=27 vs n=21). Furthermore, a similar number of patients discontinued (n=93 vs n=97) as well as completed treatment in Period 2 (n=107 vs n=102).

Table 16. Disposition of patients – Period 1 and Period 2

	MYL-1402O	Avastin®	Total
Screened	NA	NA	1016
Screen failures	NA	NA	345
Randomized (ITT)	**337**	**334**	**671**
Not Treated (Baseline Failures)	2	5	7
Treated (Safety)	**335**	**329**	**664**
Discontinued TRT in period 1 (<6 doses of IMP)	**108 (32.2)**	**109 (33.1)**	**217 (32.7)**
Adverse event	28 (8.4)	19 (5.8)	47 (7.1)
Death	8 (2.4)	7 (2.1)	15 (2.3)
Lost to follow-up	3 (0.9)	5 (1.5)	8 (1.2)
Physician decision	4 (1.2)	12 (3.6)	16 (2.4)
Progressive disease	47 (14.0)	51 (15.5)	98 (14.8)
Protocol violation	0	1 (0.3)	1 (0.2)
Study terminated by sponsor	8 (2.4)	6 (1.8)	14 (2.1)
Withdrawal by subject	10 (3.0)	8 (2.4)	18 (2.7)
Completed period 1 TRT (>= 6 doses of imp)	**227 (67.8)**	**220 (66.9)**	**447 (67.3)**
Discontinued TRT prior to IMP monotherapy in period 2	**27 (8.1)**	**21 (6.4)**	**48 (7.2)**
Adverse event	5 (1.5)	5 (1.5)	10 (1.5)
Death	0	0	0
Lost to follow-up	0	0	0
Physician decision	0	0	0
Progressive disease	18 (5.4)	15 (4.6)	33 (5.0)
Protocol violation	0	0	0
Study terminated by sponsor	3	1 (0.3)	4 (0.6)
Withdrawal by subject	1 (0.3)	0	1 (0.2)
Entered period 2 (received IMP monotherapy)	**200 (59.7)**	**199 (60.5)**	**399 (60.1)**
Discontinued TRT in period 2	**93 (27.8)**	**97 (29.5)**	**190 (28.6)**
Adverse event	3 (0.9)	4 (1.2)	7 (1.1)
Death	0	2 (0.6)	2 (0.3)
Lost to follow-up	0	1 (0.3)	1 (0.2)
Physician decision	2 (0.6)	4 (1.2)	6 (0.9)
Progressive disease	74 (22.1)	82 (24.9)	156 (23.5)
Protocol violation	0	0	0
Study terminated by sponsor	9 (2.7)	3 (0.9)	12 (1.8)
Withdrawal by subject	5 (1.5)	1 (0.3)	6 (0.9)
Completed period 2 TRT (no EOT until W42 cut-off date)	**107 (31.9)**	**102 (31.0)**	**209 (31.5)**
Week 42 study terminators[1]	**136 (40.4)**	**122 (36.5)**	**258 (38.5)**
Administrative	0	1 (0.3)	1 (0.1)
Death	99 (29.4)	82 (24.6)	181 (27.0)
Lost to follow-up	8 (2.4)	11 (3.3)	19 (2.8)
Withdrawal by subject	25 (7.4)	23 (6.9)	48 (7.2)
Other	4 (1.2)	5 (1.5)	9 (1.3)
Week 42 study completers[2]	**199 (59.1)**	**207 (62.0)**	**406 (60.5)**

Source data: Week 42 CSR MYL-1402O-3001 Table 14.1.1.5; Table 14.1.1.3b; Table 14.1.1.1; Table 14.1.1.4 (week 18 CSR)
Week 42 study terminators[1] – Patients who discontinued study before completing week 42 survival follow up
Week 42 study completers[2] – Patients who were alive and completed week 42 survival follow up

Patient flow was comparable between treatment arms, except for imbalances in the proportion of patients who discontinued treatment due to an AE as well as in the number of deaths. This imbalance occurred predominantly during the first 30 days of the study (MYL-1402O n= 13 deaths, EU-Avastin n=3 deaths) and was, among others, attributed to the higher incidence of AEs in the MYL-1402O arm. Nevertheless, overall the number of deaths is higher in the MYL-1402O than in the EU-Avastin arm. For more detailed assessment please refer to the respective safety sections below.

Baseline data

The mean age of patients was 59 years in both treatment arms, and majority (63.2%) of patients were males; and 53.5% were smokers. In both groups, the majority of patients were White (MYL-1402O 67.1% and Avastin 69.5%) and about 30% of patients were Asian (32.9 vs 30.5%). About 62% of the patients had multiple metastasis sites.

The mean body weight (± SD) was slightly lower in the MYL-1402O arm (66.14 ± 16.7 kg) than in the Avastin arm (70.4 0 ± 18.67 kg). However, the mean BSA (± SD) was similar between the treatment arms (1.737 ± 0.2432 in the MYL-1402O arm and 1.794 ± 0.2701 in the Avastin arm). The dosing was based on body weight for bevacizumab and BSA for chemotherapy.

In general, the demographic profile was balanced between treatment groups with respect to age, race, height, and ECOG status. Gender, smoking status, and number of metastasis sites were used for stratification, leading to balance between the treatment arms (Table 17).

Table 17. Demographic characteristics by treatment group – ITT set

	MYL-1402O (N=337)	Avastin (N=334)	Total (N=671)
Age (years)			
Mean (SD)	59.3 (9.60)	59.2 (9.73)	59.3 (9.66)
Median	60.0	59.0	60.0
Min, Max	23, 86	35, 83	23, 86
Age Category (years) n (%)			
< 65	237 (70.3)	236 (70.7)	473 (70.5)
>= 65	100 (29.7)	98 (29.3)	198 (29.5)
Sex n (%)			
Male	213 (63.2)	211 (63.2)	424 (63.2)
Female	124 (36.8)	123 (36.8)	247 (36.8)
Race n (%)			
White	226 (67.1)	232 (69.5)	458 (68.3)
Asian	111 (32.9)	102 (30.5)	213 (31.7)
Ethnicity n (%)			
Hispanic or Latino	5 (1.5)	4 (1.2)	9 (1.3)
Not Hispanic or Latino	332 (98.5)	330 (98.8)	662 (98.7)
Height (cm)			
Mean (SD)	165.9 (9.57)	166.5 (9.73)	166.2 (9.65)
Median	166.0	166.0	166.0
Min, Max	140, 188	142, 189	140, 189
Weight (kg)			
Mean (SD)	66.14 (16.746)	70.40 (18.670)	68.26 (17.844)
Median	65.00	70.00	67.00
Min, Max	30.0, 153.0	32.0, 124.0	30.0, 153.0
Body Mass Index (BMI) (kg/m^2)			
Mean (SD)	23.95 (5.522)	25.23 (5.883)	24.59 (5.736)
Median	23.42	24.69	23.94
Min, Max	13.9, 59.0	13.1, 50.9	13.1, 59.0
Body Surface Area (BSA) (m2)			
n	336	330	666
Mean (SD)	1.737 (0.2432)	1.794 (0.2701)	1.765 (0.2583)
Median	1.720	1.800	1.755
Min, Max	1.11, 2.62	1.17, 2.48	1.11, 2.62
ECOG Performance Status n (%)			
0	83 (24.6)	76 (22.8)	159 (23.7)
1	254 (75.4)	258 (77.2)	512 (76.3)
Smoking Status per CRF n (%)			
Smoker	180 (53.4)	179 (53.6)	359 (53.5)
Non-Smoker	157 (46.6)	155 (46.4)	312 (46.5)
Number of Metastasis Sites Per IWRS n (%)			
One	126 (37.4)	126 (37.7)	252 (37.6)
Multiple	211 (62.6)	208 (62.3)	419 (62.4)
Region n (%)			
Europe	225 (66.8)	231 (69.2)	456 (68.0)
India	99 (29.4)	92 (27.5)	191 (28.5)
Southeast Asia	13 (3.9)	11 (3.3)	24 (3.6)

BMI=(body weight in kg)/(height in m)^2, BSA = ((body weight in kg*(height in cm)$^{0.5}$/60.
ECOG = Eastern Cooperative Oncology Group
Source Data: Listing 16.2.4.1 ; Table 14.1.4.1.1

In general, both treatment arms were similar in terms of medical history. The majority of patients had at least 1 medical condition in their history (MYL-1402O, 86.1%, Avastin, 87.1%). The most commonly reported medical history disorders (>25% of total) were in the SOC of Respiratory, Thoracic and Mediastinal disorders (MYL-1402O, 141 [41.8%] and Avastin 142 [42.5%]); Vascular disorders (MYL-1402O, 133 [39.5%] and Avastin 112 [33.5%]); and Gastrointestinal disorders (MYL-1402O, 96 [28.5%] and Avastin 100 [29.9%]).

Baseline disease characteristics were comparable between the two treatment arms. However, there were slightly higher proportion of patients with M1C sub-stage in MYL-1402O arm, 125 (37.1%) patients compared to 117 (35.0%) patients in Avastin arm. Table 18 provides the stage wise distribution of patients between the two treatment arms at the time of initial diagnosis.

However, all the patients were in Stage IV at the time of randomisation into the study, as per the protocol requirement.

Table 18. Tumour history and baseline characteristics by treatment group: ITT set

	MYL-1402O (N=337)	Avastin (N=334)	Total (N=671)
Disease Stage at Initial Diagnosis; n (%)			
I	15 (4.5)	9 (2.7)	24 (3.6)
II	6 (1.8)	10 (3.0)	16 (2.4)
III	16 (4.7)	9 (2.7)	25 (3.7)
IV	298 (88.4)	303 (90.7)	601 (89.6)
Unknown	2 (0.6)	3 (0.9)	5 (0.7)
Disease Sub-Stage for Stage IV Patient*; n (%)			
M1A	109 (32.3)	108 (32.3)	217 (32.3)
M1B	64 (19.0)	78 (23.4)	142 (21.2)
M1C	125 (37.1)	117 (35.0)	242 (36.1)
Tumor Histology; n (%)			
Adenocarcinoma	321 (95.3)	320 (95.8)	641 (95.5)
Large Cell Carcinoma	7 (2.1)	6 (1.8)	13 (1.9)
Bronchoalveolar	1 (0.3)	0	1 (0.1)
Not Other Specified	8 (2.4)	8 (2.4)	16 (2.4)
EGFR Status; n (%)			
Negative	36 (10.7)	42 (12.6)	78 (11.6)
Unknown	301 (89.3)	292 (87.4)	593 (88.4)
EML4-ALK Alternation; n (%)			
Negative	34 (10.1)	42 (12.6)	76 (11.3)
Unknown	303 (89.9)	292 (87.4)	595 (88.7)
Time Since Initial Diagnosis of Disease (months)			
n	333	333	666
Mean (SD)	3.69 (11.500)	3.71 (11.003)	3.70 (11.246)
Median	1.15	1.12	1.13
Min, Max	0.2, 152.8	0.2, 122.5	0.2, 152.8
Time Since Initial Diagnosis of Metastatic or Advanced Disease (months)			
n	326	321	647
Mean (SD)	1.55 (1.434)	1.73 (3.186)	1.64 (2.464)
Median	1.12	1.12	1.12
Min, Max	0.1, 16.1	0.1, 45.6	0.1, 45.6

EGFR=Epidermal Growth Factor Receptor; EML4-ALK = Echinoderm Microtubule-Associated Protein-Like 4-Anaplastic Lymphoma Kinase.
* All patients were stage IV at the time of enrollment. Substage is not collected for 70 patients who were not stage IV at the time of initial diagnosis.
Source Data: Listing 16.2.4.2; Table 14.1.4.2

The number of patients with prior anti-cancer surgery was 86 (25.5%) in MYL-1402O arm compared to 100 (29.9%) in the EU-Avastin arm; prior anti-cancer radiotherapy was n=44 (13.1%) in MYL-1402O arm compared to n=33 (9.9%) in the EU-Avastin arm.

The randomised study population was considered appropriate to represent the intended indication. Baseline characteristics were mostly balanced between treatment arms. There were slightly higher numbers of patients with M1C sub-stage in the MYL-1402O arm (n=125 (37.1%)) compared to the EU-Avastin arm (n= 117 (35.0%)). However, all patients had Stage IV disease state at the time of randomisation into the study.

Numbers analysed

Table 19. Summary of the analysis sets

	MYL-1402O (N=337) n (%)	Avastin (N=334) n (%)	Total (N=671) n (%)
Intent-To-Treat (ITT)	337	334	671
Safety	335 (99.4)	329 (98.5)	664 (99.0)
Per Protocol (PP)	320 (95.0)	314 (94.0)	634 (94.5)
Pop PK	333 (98.8)	327 (97.9)	660 (98.3)

Percentages were calculated based on number of subjects in the ITT set.
Source Data: Listing 16.2.1.2; Table 14.1.1.2

The ITT set consisted of a total of 671 patients (337 in the MYL-1402O arm and 334 in the Avastin arm) who were randomised into the study under Protocol. The primary efficacy and other analyses were conducted using the ITT population.

The Safety set consisted of 664 patients (335 in the MYL-1402O arm and 329 in the Avastin arm), who completed at least one dose or partial dose of MYL-1402O or Avastin. A total of 7 (1.0%) patients, 2 (0.6%) patients in MYL-1402O arm and 5 (1.5%) patients in the Avastin arm were excluded from safety analyses as they were baseline failures.

The PP set consisted of 634 patients (320 in the MYL-1402O arm and 314 in the Avastin arm). The PP set consisted of all randomised patients who completed at least one dose of MYL-1402O or Avastin and did not have protocol deviations with significant impact on the study endpoints. Pre-defined rules described in SAP were applied to exclude patients from the PP population. Exclusion of patients from the PP set due to major protocol deviations were decided in a BDR meeting on August 16, 2019 before database lock (CSR Tables 14.1.1.2, 14.1.3, and Listing 16.2.3).

A total of 37 (5.5%) patients (17 [5.0%] patients in the MYL-1402O arm and 20 [6.0%] in the Avastin arm) were excluded from the PP set due to reasons summarised below (

Table **20**):

Table 20. Patients exclusion from analysis sets

	MYL-1402O (N=337) n (%)	Avastin (N=334) n (%)	Total (N=671) n (%)
Patients Excluded from Safety Set	2 (0.6)	5 (1.5)	7 (1.0)
Baseline failure	2 (0.6)	5 (1.5)	7 (1.0)
Patients Excluded from Per Protocol Set	17 (5.0)	20 (6.0)	37 (5.5)
Baseline Failure	2 (0.6)	5 (1.5)	7 (1.0)
Less Than 4 Cycles of Doses and No Tumor Assessment with the Exception of Death or PD or AE	12 (3.6)	12 (3.6)	24 (3.6)
Major Protocol Deviation	2 (0.6)	2 (0.6)	4 (0.6)
No Measurable Disease	1 (0.3)	1 (0.3)	2 (0.3)

Source Data: Listing 16.2.3; Table 14.1.3

The number of patients with protocol deviations by 10 categories as defined in SAP, Version 2 were provided. All patients with protocol deviations by criteria 1-5 were excluded from the PP set, deviations of criteria 6-10 were decided on a case-by-case basis. Only patients with deviations categorised as major were excluded from the PP set.

Table 21. Number of patients with protocol deviations

No.	Criterion	Category	Number of patients with protocol deviations	Number of patients excluded from PP set due to major protocol deviations
1	No Written Informed Consent provided	Major	0	0
2	Was not randomized in the study but dosed	Major	0	0
3	Did not receive correct treatment as randomized[1]	Major	7	7
4	No measurable disease confirmed by independent review	Major	2	2
5	Did not complete 18 weeks of study and at least 4 doses of chemotherapy plus MYL 1402O or Avastin® and at least one tumor assessment with the exception of progression or death or AE	Major	24	24
6	Forbidden prior therapy/medication	Major/Minor	0/1	0
7	Violation of other inclusion criteria	Major/Minor	2/0	2
8	Violation of other exclusion criteria	Major/Minor	0/0	0
9	Use of prohibited concomitant medication	Major/Minor	3/1	1
10	Previous or current medical conditions	Major/Minor	1/1	1

[1] Patients were randomized but not treated.

Table 22. Assignment of major or minor to protocol deviations

Protocol deviation criteria	Description	Assignment		Missed
		Major	Minor	
#6	Inclusion criteria #9: Prior radiation therapy	-	1 patient	-
#7	Inclusion criteria #6: Performance status of 0 or 1 on ECOF scale	1 patient	-	-
	Inclusion criteria #11: Calculated creatinine clearance ≥45mL/min	1 patient	-	-
#9	Prohibited medication started during study	1 patient (Zoledronic acid from cycle 2 onwards)	1 patient (Zoledronic acid at cycle 6)	2 patients (Zoledronic acid during cycle 2 and Zoledronic acid before cycle 2)
#10	Exclusion criteria #9: Major surgical procedure within 28 days prior to Day 0 of cycle 1	-	1 patient Day 0 of cycle 1 was 25 days after patient's right sided cervical lymphadenectomy due to miscalculation by site	-
	Exclusion criteria #10b: a thoracic, central, mediastinal tumour location in contact with major vessels	1 patient	-	-

Two patients were missed to have major deviations and consequently missed to be excluded from the PP analysis. A sensitivity analysis was provided by excluding these two patients with no controversial results.

Table 23. Current and sensitivity PP set analyses for primary endpoint

	PP set - Current		PP set - Sensitivity	
	MYL-1402O (N=320)	Avastin® (N=314)	MYL-1402O (N=319)	Avastin® (N=313)
Best overall response at Week 18	n (%)	n (%)	n (%)	n (%)
Complete response (CR)	2 (0.6)	3 (1.0)	2 (0.6)	3 (1.0)
Partial response (PR)	137 (42.8)	141 (44.9)	137 (42.9)	140 (44.7)
Stable disease (SD)	134 (41.9)	142 (45.2)	133 (41.7)	142 (45.4)
Non-CR/Non-PD	1 (0.3)	0	1 (0.3)	0
Progressive disease (PD)	22 (6.9)	14 (4.5)	22 (6.9)	14 (4.5)
Not evaluable (NE)	0	0	0	0
Not done (ND)	24 (7.5)	14 (4.5)	24 (7.5)	14 (4.5)
Objective response rate (ORR)	**139 (43.4)**	**144 (45.9)**	**139 (43.6)**	**143 (45.7)**
Ratio of ORR and 90% CI	0.95 (0.82, 1.10)		0.95 (0.82, 1.10)	
Difference in ORR and 95% CI	-2.4 (-10.2, 5.3)		-2.1 (-9.9, 5.6)	

Overall, study drug was administered to 664 patients during the study (335 in the MYL-1402O arm and 329 in the Avastin arm) who completed at least one dose or partial dose of MYL-1402O or Avastin.

The duration of exposure as well as the number of doses administered and the cumulative doses for bevacizumab, carboplatin and paclitaxel are comparable between the treatment arms.

With regard to the duration of IMP exposure, the total number of cycles received was similar between both treatment arms during the induction period (1627 vs 1626 cycles). For the maintenance period, a numerically higher number of treatment cycles was administered in the MYL-1402O arm (1278 vs 1242 cycles). This could be attributed mainly to a higher number of patients having received 7 cycles in the MYL-1402O arm than in the Avastin arm (n=20 vs n=9).

Outcomes and estimation

Primary endpoint

The primary EP was met: the **best ORR during the first 18 weeks** was 41.5% in the MYL-1402O arm and 43.1% in the EU-Avastin arm (independent review, **ITT population**). The difference in ORR between both treatment groups was -1.6 (95% CI -9.0, 5.9), which fully met the pre-specified ± 12.5% equivalence margin.

Table 24. Difference in ORR based on independent review: ITT set

	MYL-1402O (N=337)	Avastin (N=334)	Total (N=671)
Objective Response Rate (ORR) n (%)	140 (41.5)	144 (43.1)	284 (42.3)
95% CI for ORR (%)	(36.3, 46.8)	(37.8, 48.4)	(38.6, 46.1)
DIFF in ORR and 95% CI (%)			-1.6 (-9.0, 5.9)

Difference (DIFF) is calculated as $ORR_{MYL-1402O}$ - $ORR_{AVASTIN}$.
The asymptotic 2-sided 95% confidence interval for the difference in ORRs is calculated based on the Wald confidence interval. The equivalence region is (-12.5%, 12.5%).
Best overall response at any time point during the first 18 weeks, and assessed according to RECIST 1.1.
Source Data: Listing 16.2.6.2.1; Table 14.2.1.2.1

This was supported by sensitivity analyses for the primary endpoint, e.g. **best ORR during 18 weeks** assessed by independent review **in the PP population** (ORR difference of -2.4, with a 95% CI of -

10.2, 5.3), as well as investigator-assessed in the ITT population (ORR difference of -2.2, with a 95% CI of -9.7, 5.3). Here, results were consistent with the primary analysis.

Table 25. Sensitivity analysis – Difference in ORR based on independent review: PP set

Data Source/ Statistics	MYL-1402O (N=320)	Avastin (N=314)	Total (N=634)
Objective Response Rate (ORR) n (%)	139 (43.4)	144 (45.9)	283 (44.6)
95% CI for ORR (%)	(38.0, 48.9)	(40.4, 51.4)	(40.8, 48.5)
Diff of ORR and 95% CI			-2.4 (-10.2, 5.3)

Difference (DIFF) is calculated as $ORR_{MYL-1402O}$ - $ORR_{AVASTIN}$.
The asymptotic 2-sided 95% confidence interval for the difference in ORRs is calculated based on the Wald confidence interval.
Best overall response at any time point during the first 18 weeks and assessed according to RECIST 1.1.
Source Data: Listing 16.2.6.2.2; Table 14.2.1.2.2.

Table 26. Sensitivity analysis – difference in ORR, derived BOR from investigator data – ITT set

Data Source/ Statistics	MYL-1402O (N=337) n (%)	Avastin (N=334) n (%)	Total (N=671) n (%)
Objective Response Rate (ORR) n (%)	152 (45.1)	158 (47.3)	310 (46.2)
95% CI for ORR (%)	(39.8, 50.4)	(42.0, 52.7)	(42.4, 50.0)
DIFF in ORR and 95% CI (%)			-2.2 (-9.7, 5.3)

Difference (DIFF) is calculated as $ORR_{MYL-1402O}$ - $ORR_{AVASTIN}$.
The asymptotic 2-sided 95% confidence interval for the difference in ORRs is calculated based on the Wald confidence interval.
Best overall response at any time point during the first 18 weeks and assessed according to RECIST 1.1.
Source Data: Listing 16.2.6.2.2; Table 14.2.1.2.3.

However, the independent review of the best ORR confirmed at a second time point in the ITT population revealed markably lower ORR rates for both treatment arms (29.1% in the MYL-1402O arm and 30.5% in the EU-Avastin arm). The applicant clarified that the independent review process took place one the patient had completed imaging for the respective review period (here: from Screening through Wk 18 DCO) and no further imaging time points were scheduled. In contrast, the investigator assessed the tumour response upon completion of each imaging time point (i.e. Wk 6, 12, 18), thus on a real-time basis. Within this context, treatment continuation was dependent on the overall tumour response (imaging plus patient´s clinical condition) at a specific time point.

It is acknowledged that this observed difference in the response rates between independent review and investigator assessment is a general limitation that is known and described in literature. Subjective factors such as target-lesion selection as well as different interpretations of non-target or immeasurable lesions are discussed to be of relevance within this context.

With regard to the overall lower confirmed response rate as per independent review (29.8%) compared to investigator assessment (40.4%), the applicant points out that this might be also attributed to limitations of the study design (i.e. the data cut-off defined for the review period for the primary EP). For late responders (i.e. patients with first CR or PR at Week 18), BOR could not be confirmed at a second time point; thus they were assessed as non-responders for this sensitivity analysis. Within this context, the applicant presents an additional analysis for BOR confirmed at a second time point based on independent review, conducted at Week 42. This confirmed response analysis based on Week 42 data provides a higher confirmed mean BOR of 35.0%.

However, this limitation of the DCO time point at Wk 18 for the primary EP in case of late responders and confirmed response analysis would also apply to the investigator-based assessment of confirmed response. Overall, since equivalence was shown between treatment arms in both independent review

and investigator assessment for BOR as well as for confirmed response, the CHMP consider that there is no critical issue with regard to proof of biosimilarity.

Table 27. Sensitivity analysis – difference in ORR – best tumour responses confirmed at a second time point based on independent review: ITT set

Data Source/ Statistics	MYL-1402O (N=337)	Avastin (N=334)	Total (N=671)
Objective Response Rate (ORR) n (%)	98 (29.1)	102 (30.5)	200 (29.8)
95% CI for ORR (%)	(24.2, 33.9)	(25.6, 35.5)	(26.4, 33.3)
Diff of ORR and 95% CI			-1.5 (-8.4, 5.5)

Difference (DIFF) is calculated as $ORR_{MYL-1402O} - ORR_{AVASTIN}$.
The asymptotic 2-sided 95% confidence interval for the difference in ORRs is calculated based on the Wald confidence interval.
Tumor response is based on the best tumor responses confirmed at a second time point, assessed based on RECIST version 1.1
Source Data: Listing 16.2.6.2.1; Table 14.2.1.2.4.

Table 28. Sensitivity analysis – difference in ORR – best tumour responses confirmed at a second time point based on investigator assessment: ITT set

Data Source/ Statistics	MYL-1402O (N=337)	Avastin (N=334)	Total (N=671)
Objective Response Rate (ORR) n (%)	134 (39.8)	137 (41.0)	271 (40.4)
95% CI for ORR (%)	(34.5, 45.0)	(35.7, 46.3)	(36.7, 44.1)
Diff of ORR and 95% CI			-1.3 (-8.7, 6.2)

Difference (DIFF) is calculated as $ORR_{MYL-1402O} - ORR_{AVASTIN}$.
The asymptotic 2-sided 95% confidence interval for the difference in ORRs is calculated based on the Wald confidence interval.
Tumor response is based on the best tumor responses confirmed at a second time point, assessed based on RECIST version 1.1
Source Data: Listing 16.2.6.2.2; Table 14.2.1.2.5.

Secondary endpoints

The analysis of **DCR** revealed no notable differences between the arms (independent review, ITT population). The proportion of patients with disease control at Week 18 in the 2 groups (MYL-1402O: 81.3% versus Avastin 86.2%) was comparable with a DCR difference of -4.9 (95% CI: -10.5, 0.6). This was confirmed by sensitivity analyses, i.e. independent review in the PP population and investigator-based assessment in the ITT population.

updated **PFS** analyses with the Week 42 CSR has been provided. The total number of events on independent review for progression-free survival (PFS) was 184 (54.6%) events in test arm and 156 (46.1%) events in Avastin arm at week 42. Estimated PFS (with corresponding 95% CI) was 7.6 (7.0, 9.5) months in the test arm and 9.0 (7.2, 9.7) months in the Avastin arm. The difference between treatment arms was not statistically significant on 5% significance level based on log-rank test (p-value=0.0906).

When PFS was assessed by the investigator, median PFS was 7.8 (95% CI: 7.0, 9.5) months in the MYL-1402O arm and 7.3 (95% CI: 7.0, 8.9) months in the Avastin arm, with a total number of 190 events (56.4%) in the MYL-1402O arm and 200 events (59.9%) in the Avastin arm.

In a next step, a sensitivity analysis evaluating PFS with new anticancer therapy considered as an event (not reported as PD/ death in the primary analysis) has been conducted. Based on independent review, new anticancer therapy as an event occurred in 34 [10.2%] patients in the Avastin arm compared to 17 [5.0%] patients in the MYL-1402O arm.

Complete **DOR** results with the Week 42 CSR have been submitted. Median DOR was comparable between the MYL-1402O and the Avastin arm (7.7 vs 6.9 months), which thus supports biosimilarity demonstrated in the primary analysis.

Week 42 **Time to First Objective Response** data have been provided. With the full data set, the difference observed between the treatment arms for the Week 0-7 Time to First Objective Response diminishes from 3.5% (Week 18 CSR) to 2.0%.

Updated **OS** data have been provided with the final Week 42 CSR. In the MYL-1402O arm, 236 (70.0%) patients survived through Week 42 compared to 252 (75.4%) patients in the Avastin arm. This difference between the survival curves for both treatment groups was not statistically significant (p=0.1185). The OS HR at Week 42 was 1.26 (0.94, 1.69). In addition, the median OS was not reached in the ITT population at Week 42.

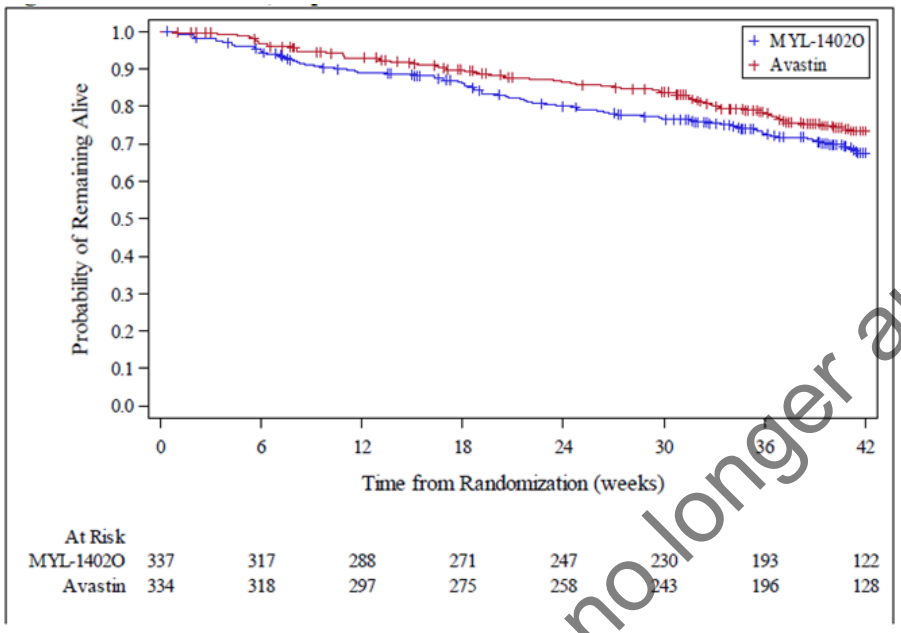


Figure 3. Overall survival, Kaplan-Meier plot ITT set

In addition, additional OS data including data beyond Week 42, which are not part of the Week 42 CSR have been submitted. Those data mainly originate from 274 out of 561 randomised study participants who originally consented to protocol version 1.0 (see also Question 113), implying that OS data were collected as long as patients continued in the study. In addition, data collected beyond Week 42 (until study closure) from 25 out of 110 randomised patients who originally consented to protocol version 2.0 and had a study duration of more than 42 weeks were include for this extended OS analysis. However, the OS analysis including data beyond Week 42 did not show a clearly different picture: median OS was 71.9 weeks (95% CI: 56.71, 90.14) in the MYL-1402O arm compared to 77.3 weeks (95% CI: 67.71, 90.43) in the Avastin arm. The updated OS HR based on all data collected until study closure was 1.21 (0.94, 1.55).

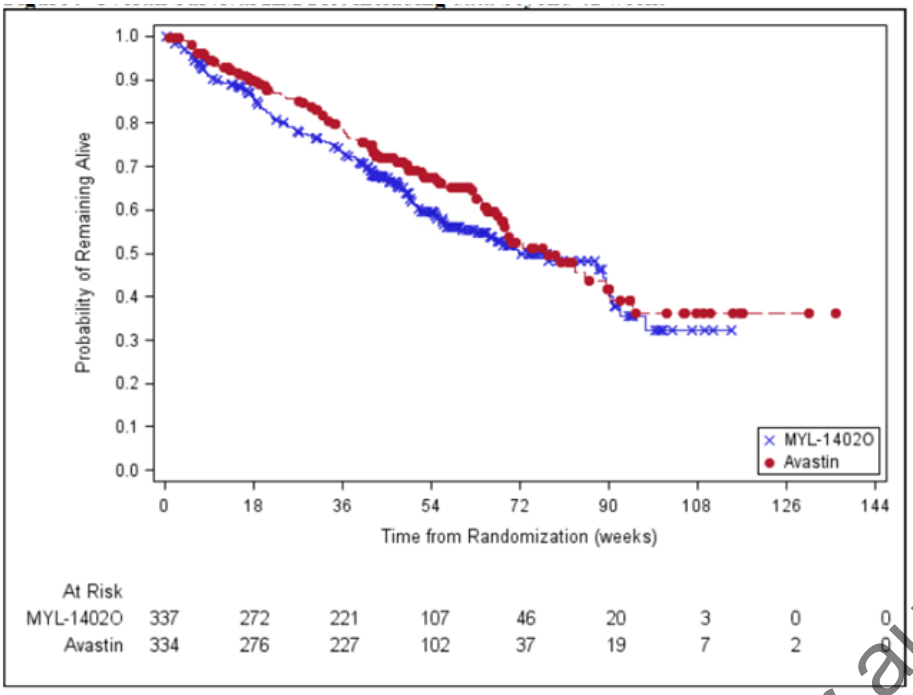


Figure 4. Overall survival KM plot including data beyond 42 weeks

In general, a higher number of patients with disease progression was observed in the Avastin arm than in the MYL-1402O arm in the Week 18 data set (n=56 vs n=50), in the Week 42 data set (n=159 vs n=133), and until study closure (n=192 vs n=165). For those patients with disease progression, subsequent anti-cancer therapy was more frequently reported in the Avastin arm than in the MYL-1402O arm (Wk 18: n=24 vs n=8, Wk 42: n=45 vs n=28, until study closure: n=46 vs n=31), both in absolute and relative numbers. According to the applicant, this higher number of patients in the Avastin arm having received subsequent anti-cancer therapy might have contributed to higher survival rates compared to the MYL-1402O arm.

With regard to the potential impact of deaths within 30 days of the first IMP dose, additional OS analyses excluding the deaths and discontinuations within 30 days of IMP have been conducted. In this subset of patients, the HR (95% CI) improved to 1.15 (0.85, 1.55) in the Week 42 data set and to 1.13 (0.87, 1.45) for data until study closure. To note, the median OS was not reached up to Week 42.

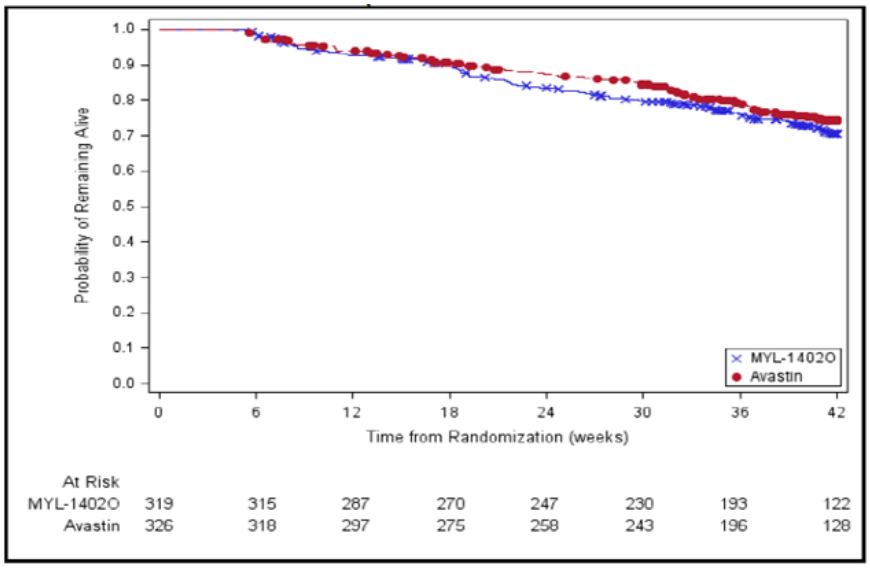


Figure 5. Overall survival KM plot up to week 42 exluding patients who were not treated or discontinued within 30 days after first dose

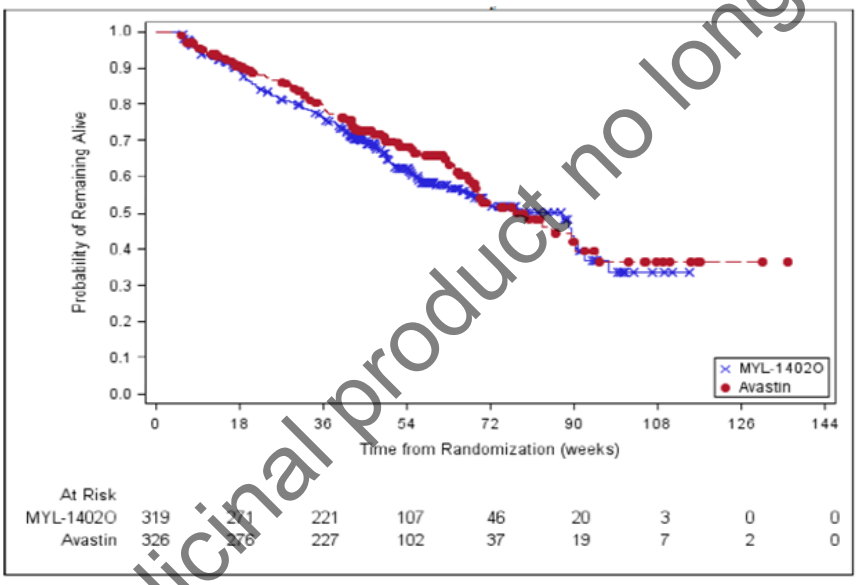
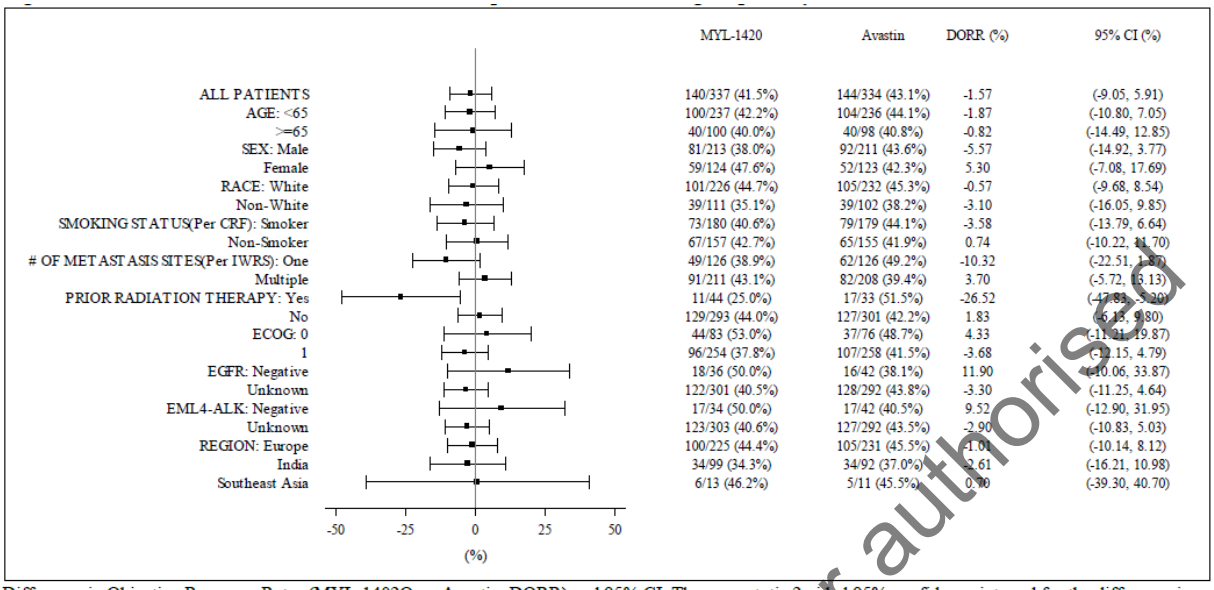


Figure 6. Overall survival KM plot including data beyond 42 weeks excluding patients who were not treated or discontinued within 30 days after first dose

Ancillary analyses

Primary endpoint



Difference in Objective Response Rates (MYL-1402O — Avastin, DORR) and 95% CI. The asymptotic 2-sided 95% confidence interval for the difference in ORRs is calculated based on the Wald confidence interval.
Best overall response at any time point during the first 18 weeks and assessed according to RECIST 1.1
Data Source: Listing 16.2.6.2.1

Figure 7. Difference in ORR, Forest plot, Independent review, subgroup analysis: ITT set

Subgroup analyses have been conducted for the ITT population and revealed no relevant differences for the primary endpoint, except for the subgroup receiving prior radiation therapy. Here the observed difference in best ORR between both treatment arms was -26.25% (95% CI -47.83, -5.20) with a best ORR of 25.0% in the MYL-1402O arm and of 51.2% in the EU-Avastin arm.

Additional subgroup analyses using Forest Plots have been provided for the PP set. No distinct imbalances between treatment arms have been detected for any of the subgroups analysed, except for the subgroup having received prior radiation therapy, consistent with the ITT population.

With regard to subgroup analysis by age, the ORR differences within the age groups <65, ≥65, <75 and ≥75 were comparable between the treatment arms.

Subgroup analysis by geographic region (Europe, India, Southeast Asia) has been performed and revealed no differences or imbalances for the primary endpoint. Additional analyses were presented with regard to EU versus non-EU countries and showed a slightly higher ORR for MYL-1402O compared to Avastin for the region EU-Europe. However, due to the small sample size of this subgroup (n=26 in the MYL-1402O arm vs n=29 in the Avastin arm), this seems to be a chance finding and is not considered to be of relevance.

Secondary endpoints

Subgroup analyses for **DCR** are presented as Forest Plot and reveal no relevant differences between the subgroups.

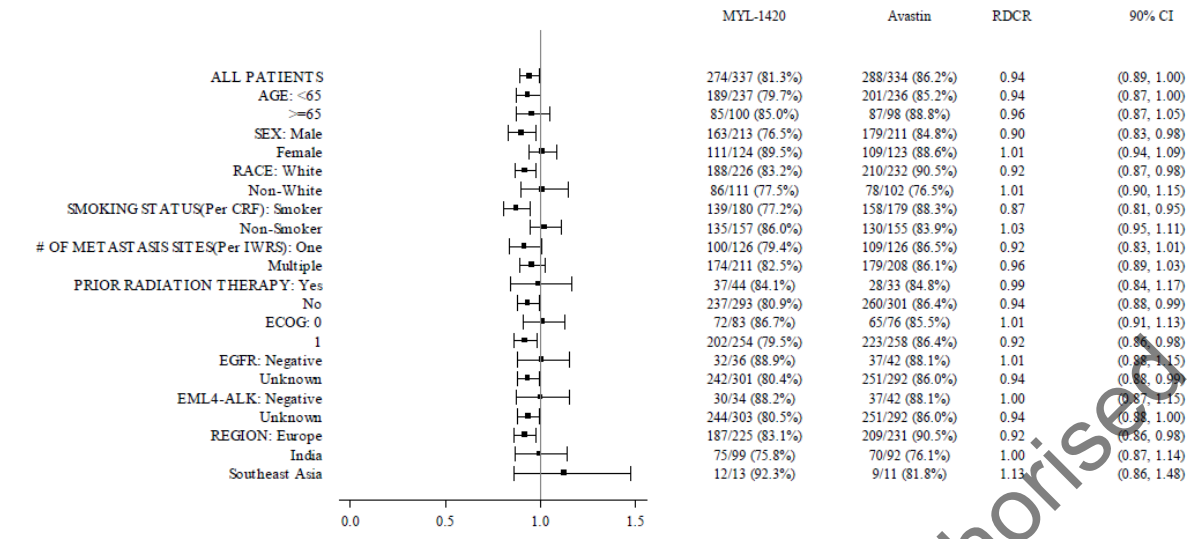
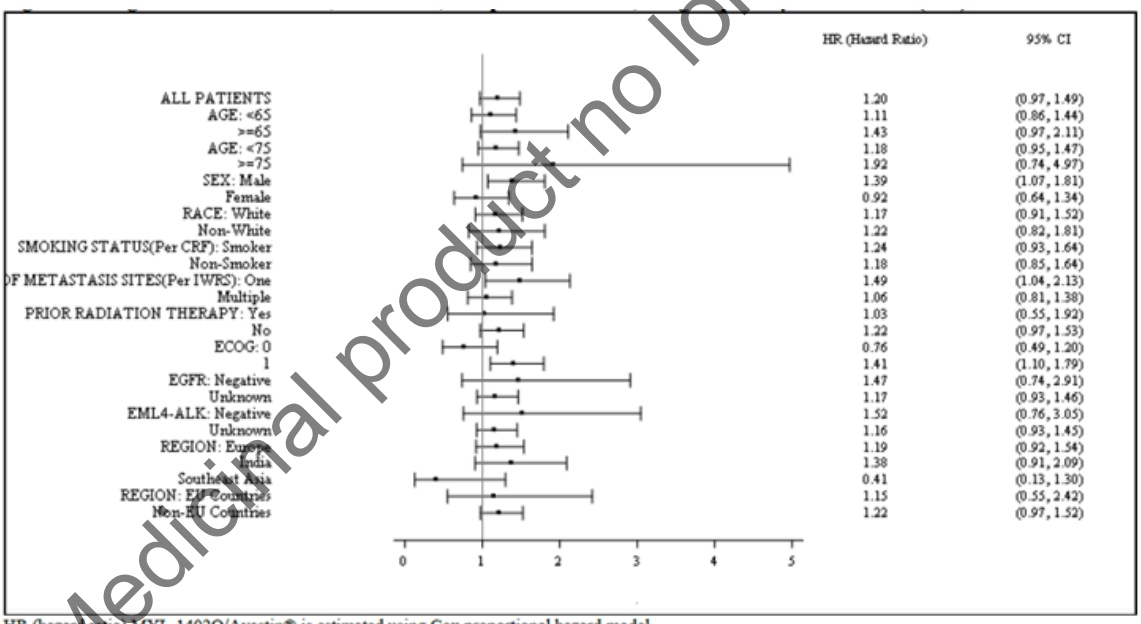


Figure 8. Ratio disease control rates, Forest plot, Independent review, subgroup analysis – ITT set

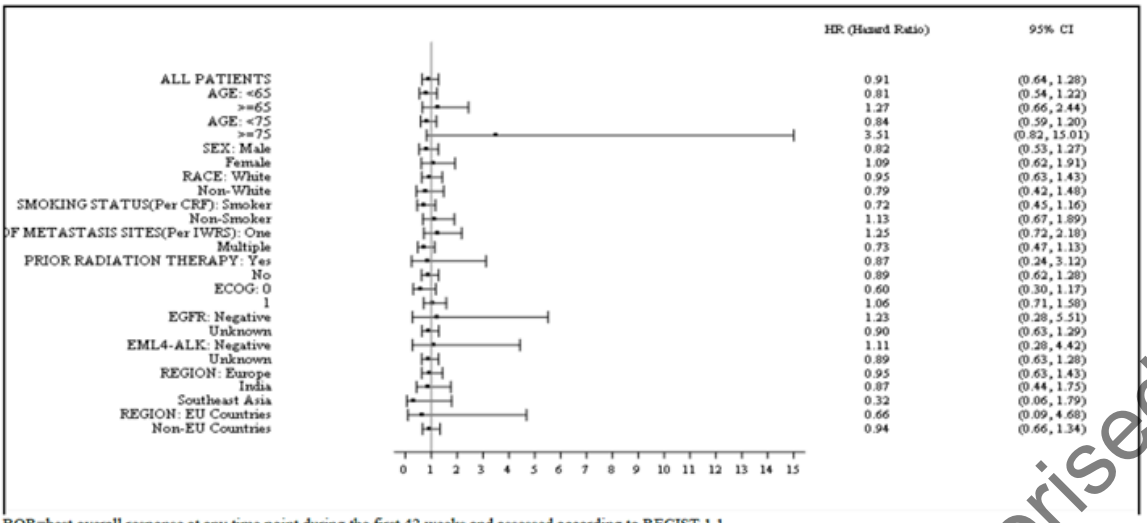
Subgroup analyses have been provided, using Forest Plots, for PFS, DOR and OS for the final Week 42 data, as requested.



HR (hazard ratio) MYL-1402O/Avastin® is estimated using Cox proportional hazard model.
RECIST v1.1
Source data: Figure 05 Appendix II Post CSR Week 42

Figure 9. Progression-free survival, Forest plot, Independent review, subgroup analysis – week 42 (ITT)

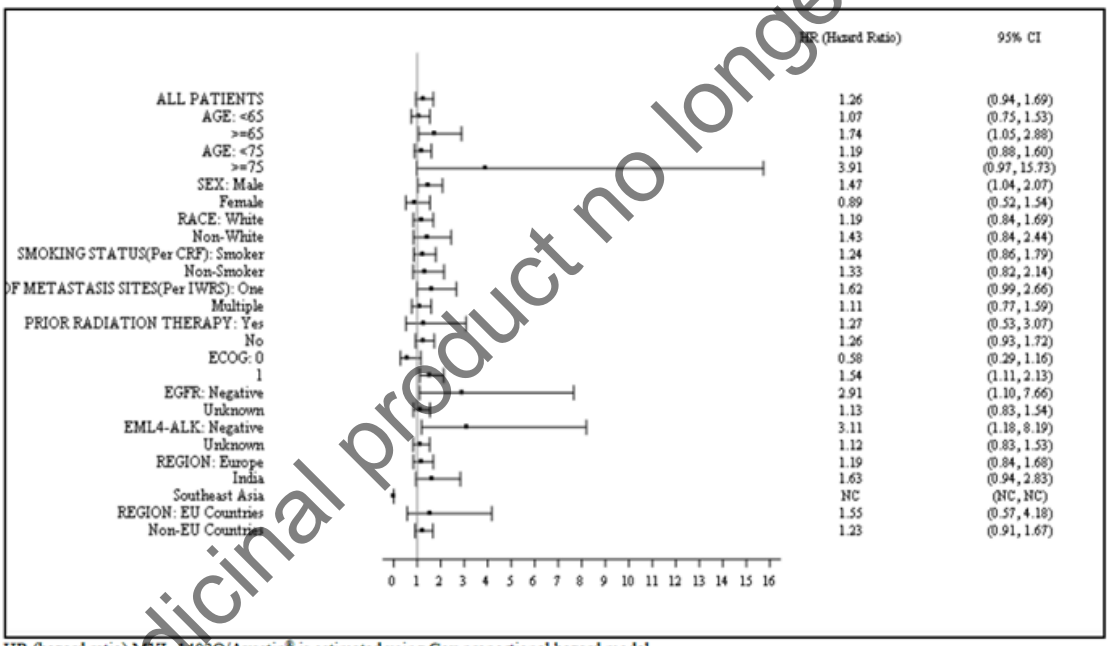
PFS: For the subgroups of males, the number of metastatic sites (one) and ECOG 1, PFS was lower in the MYL-1402O arm compared with Avastin, the 95% CI not including 1.



BOR=best overall response at any time point during the first 42 weeks and assessed according to RECIST 1.1.
HR (hazard ratio) MYL-1402O/Avastin® is estimated using Cox proportional hazard model.
Source data: Figure 06 Appendix II Post CSR Week 42

Figure 10. Duration of response, Forest plot, Independent review, subgroup analysis (ITT patients with BOR of CR or PR) – week 42

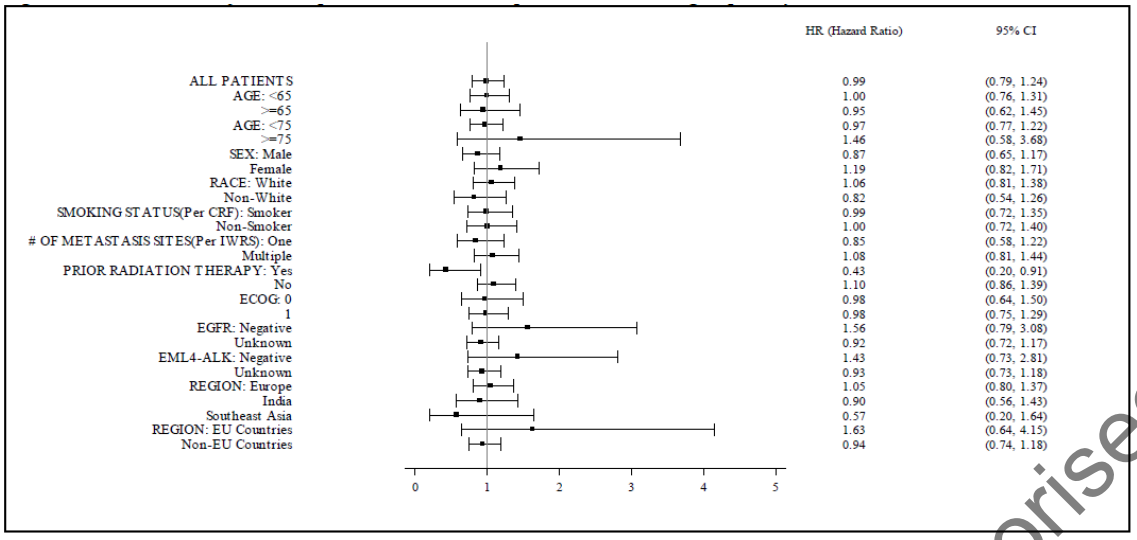
The analyses of **DOR** within each of the subgroups supported equivalence between the treatment arms.



HR (hazard ratio) MYL-1402O/Avastin® is estimated using Cox proportional hazard model
Source data : Figure 08 Appendix II Post CSR Week 42

Figure 11. Overall survival, Forest Plot, subgroup analysis (ITT) – week 42

OS: for the subgroups of males, age ≥65, EGFR negative and EML4-ALK negative, the MYL-1402O arm showed a lower OS than the Avastin arm, the 95% CI not including 1.



First objective response (i.e. partial response or complete response) is determined by an independent, blinded radiologist using RECIST v1.1 at the first time point available.
Subject's first objective response may not necessarily be the subject's best overall response.
HR (hazard ratio) MYL-1402O/Avastin® is estimated using Cox proportional hazard model.
Source data: Figure 07 Appendix II Post CSR Week 42

Figure 12. Time to first objective response, Forest plot, Independent review, subgroup analysis ITT set

Summary of main efficacy results

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

Table 29. Summary of efficacy for trial MYL-1402O-3001

Title: Multicenter, Double-blind, Randomised, Parallel-Group Study to Assess the Efficacy and Safety of MYL-1402O Compared with Avastin®, in the First-line Treatment of Patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer		
Study identifier	EudraCT number: 2015-005141-32 Protocol Number: MYL-1402O-3001	
Design	Randomised, double blind, parallel group, global multicentre study	
	Duration of induction period (Period 1): Duration of maintenance period (Period 2):	18 weeks combination treatment (up to 6 treatment cycles, 21 days per cycle) 24 weeks monotherapy (with up to 8 treatment cycles, 21 days per cycle), until Week 42
Hypothesis	Equivalence	
Treatments groups	MYL-1402O n=337 randomised	MYL-1402O iv infusion, 15 mg/kg Q3W (up to 6 cycles with iv carboplatin AUC of 6 and paclitaxel 200 mg/m^2, followed by up to 8 monotherapy cycles)

	EU-Avastin n=334 randomised		EU-Avastin iv infusion, 15 mg/kg Q3W (up to 6 cycles with iv carboplatin AUC of 6 and paclitaxel 200 mg/m^2, followed by up to 8 monotherapy cycles)
Endpoints and definitions	Primary endpoint	Difference in Best ORR within 18 wks	Proportion of subjects whose best overall response was either CR or PR according to RECIST v1.1 within 18 weeks based on independent review (Period 1)
	Secondary endpoint	DCR within 18 wks	Disease Control Rate (CR, PR, or stable disease) during the first 18 weeks
	Secondary endpoint	PFS	Progression-Free Survival at Weeks 18 and 42
	Secondary endpoint	DOR	Duration of Response defined as the time from start of the first documentation of objective tumour response (CR or PR) to the first documentation of tumour progression
	Secondary endpoint	OS	Overall Survival at Weeks 18 and 42
Database lock	Data cut-off for the Week 18 CSR was the date when the last randomised patient reached or completed the tumour assessment scheduled at Week 18 (i.e. 05 June 2019), for the Week 42 CSR the 22 Nov 2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT set (n=671), Week 18 data (Period 1) for PE, Week 42 date for secondary EP's		
Descriptive statistics and estimate variability	Treatment group	**MYL-1402O**	**EU-Avastin**
	Number of subjects, N	337 (ITT) 320 (PP)	334 (ITT) 314 (PP)
Primary EP (ITT)	**Best ORR within 18 wks, % (n)**	41.5% (140)	43.1% (144)
	Difference (95% CI)	-1.6 (-9.0, 5.9)	
Primary EP (PP)	**Best ORR within 18 wks, % (n)**	43.4% (139)	45.9% (144)
	Difference (95% CI)	-2.4 (-10.2, 5.3)	
Notes	Equivalence has been shown for the primary EP in the ITT assessed by independent review; the two-sided 95% CI was entirely within the pre-defined equivalence margin of ±12.5%. This was supported by sensitivity analyses for the primary EP, i.e. independent review in the PP population (see Table) as well as investigator-assessed in the ITT population (ORR difference of -2.2, 95% CI of -9.7, 5.3). In addition, the results for ORR at Week 18 support equivalence.		

Secondary EP	DCR	81.3% (n=274)	85.6% (n=286)
	Difference (95% CI)	-4.3 (-9.9, 1.3)	
	PFS (median months)	7.6 (7.0, 9.5)	9.0 (7.2, 9.7)
	DOR (median months)	7.7 (95% CI 6.2, 8.3)	6.9 (95% CI 5.8, 8.5)
	OS	NE (median not reached)	NE (median not reached)
Notes	The final CSR has been submitted during the procedure and includes Week 42 data for the analysis of the secondary efficacy endpoints.		

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

N/A

Clinical studies in special populations

N/A

Supportive study

Phase III mCRC Study (BM100-CC-03-I-01)

Supportive efficacy data from study BM100-CC-03-I-01, a comparative PK, efficacy, safety and immunogenicity study of Bmab-100 and Avastin, both in combination with oxaliplatin-capecitabine (XELOX) chemotherapy in patients with metastatic colorectal cancer, have been submitted. Primary objective was to demonstrate PK bioequivalence of Bmab-100 and EU-Avastin. The study was conducted in India.

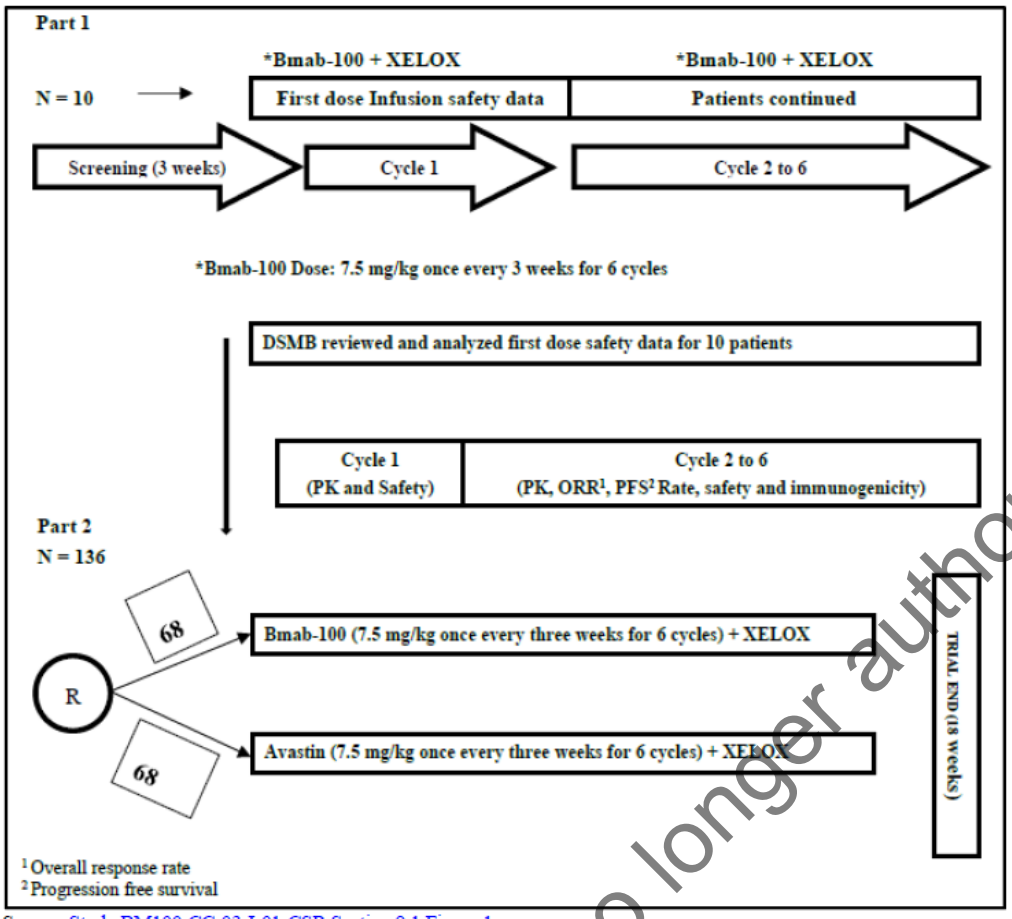
The study was conducted by Biocon, Ltd (Bangalore, India). Bmab-100 is an "earlier version" of as MYL-1402O.

it has been clarified that EU-Avastin was used as reference medicinal product in study BM100-CC-03-I-01. It was confirmed that one EU-Avastin batch was used in this study. The batch certificate for the same batch has also been submitted.

Study design/ Objectives

The study had two parts (1 and 2). The objective of Part 1 of the study was to generate the safety data of infusion-related reactions of the first dose of Bmab-100 when given with XELOX chemotherapy in 10 patients.

The **efficacy objectives of Part 2 of the study** were to evaluate and compare ORR, DCR and PFS rate at 18 weeks.



Source: Study BM100-CC-03-I-01-CSR Section 9.1 Figure 1

Figure 13. Study design for BM100-CC-03-I-01

Part 2 of the study was a double-blind, randomised, active controlled, parallel arm study in patients with mCRC. Part 2 of the study included patients who had not received any treatment for mCRC (i.e. only first line mCRC patients). Patients received Bmab-100 or EU-Avastin at 7.5 mg/kg along with XELOX chemotherapy for up to 6 cycles. Each cycle consisted of a 21-day period. As a whole, the study consisted of 21 days screening period, 15 weeks treatment period, followed by a 3 week follow up. The End of the Study evaluation was performed at the end of 18 weeks. Wherever possible, radiological assessments were performed 4-6 weeks after the EOS (Post EOS) in patients with first documentation of response (PR or CR at EOS).

Study population

For Part 2 of the study, first line mCRC patients were included. For details with regard to Inclusion/ Exclusion criteria, please refer to the D80 Clinical AR.

Efficacy endpoints

Efficacy was the secondary objective of the study. The efficacy objective was to evaluate and compare the effect of Bmab-100 and Avastin, in combination with XELOX chemotherapy on:

- Overall response rate based on RECIST 1.1 criteria

- PFS rate at 18 weeks.

- DCR rate at 18 weeks

The efficacy analyses were performed on the basis of tumour response evaluation by independent, blinded and centralised radiological evaluation according to RECIST 1.1 guidelines for radiological assessment of tumours.

Study treatments

Bevacizumab (Bmab-100 or Avastin) was administered by the investigator/designee at the dose of 7.5 mg/kg by IV infusion over 90 min (in 100 mL of 0.9% sodium chloride injection) on Day 1 of each 3 week cycle along with XELOX chemotherapy for all patients. Up to 6 cycles of bevacizumab in combination with XELOX chemotherapy were administered.

Bmab-100/Avastin was administered as IV infusions using appropriate aseptic technique. All infusions of bevacizumab were to be over 90 min.

Oxaliplatin was administered at a dose 130 mg/m^2 as an IV infusion in 500 mL of 5% dextrose over 2h on Day 1 of each cycle after the completion of Bmab-100/Avastin infusion.

Oral capecitabine 1000 mg/m^2 was administered twice daily on Day 1 through Day 15 (28 doses) of a 21-day cycle. The first dose of capecitabine was started in the evening of Day 1 and the last dose on the morning of Day 15, for each cycle. Patients were instructed to take capecitabine tablets within 30 min after the end of meal with a glass of water (breakfast and dinner).

Disposition of subjects

Part 2: A total of 237 patients were screened, of whom 101 (42.61%) failed screening (most common reasons for screen failure being lack of measurable disease and low hemoglobin/platelet count).

136 patients were randomised (1:1) to either the Bmab-100 or the Avastin arm, of which 135 patients received treatment; one patient in the Avastin arm was randomised but then withdrew consent and was not dosed. Of the randomised patients, 86 (63.24%) patients completed the study and the rest were prematurely discontinued. Overall, the most common reasons for discontinuation were progression of disease, AEs and withdrawal of consent.

Table 30. Disposition of patients (ITT-population) – Part II

Disposition	Bmab-100 N=68 n (%)	Avastin (N=68) n (%)
Total no. of patients Randomised	68	68
Number Randomised but not treated	0 (0.00%)	1[a] (1.47%)
Completed	43 (63.24%)	43 (63.24%)
Discontinued	25 (36.76%)	25 (36.76%)
Reason for Discontinuation		
Adverse event	7 (10.29%)	2 (2.94)
Withdrawal of informed consent	5 (7.35%)	7 (10.29%)
Lost to follow-up	1 (1.47%)	1 (1.47%)
Death	4 (5.88%)	6 (8.82%)
Disease Progression[b]	7 (10.29%)	5 (7.35%)
Other	1 (1.47%)	4 (5.88%)

Note: %=(n/N) 100, N= Total number of Randomised patients, n=number of patients assigned for individual analysis set
Note: 2 patients were dialed in IVRS by error. The patients were screen failures
[a]: a subject was randomised but not dosed, and is included in the discontinued patients in the Avastin arm
[b]: Disease progression also includes clinical progression as per investigator: 3 in Bmab-100 and 2 in Avastin arm

Numbers analysed

Table 31. Analyses set by treatment group (Part II)

Analysis set	Bmab-100 N=68 [n (%)]	Avastin N=68 [n (%)]
Intent to Treat-Analysis set (ITT)	68 (100.00%)	68 (100.00%)
Safety Population	68 (100.00%)	67 (98.53%)
PK population	65 (95.59%)	64 (94.12%)
Per-Protocol population (PP)	63 (92.65%)	60 (88 24%)

Note: %=(n/N)100, N=Total No. of Randomised patients, n-number of patients assigned for individual set

Note: For 2 patients randomisation numbers were dialled in IVRS by error. These patients were considered of screen failures. ITT population includes all randomised patients. Safety population includes all randomised patients who received at least one dose of study medication.

PP population is a subset of the ITT population who met the per protocol criteria

PK population includes all patients who have received at least one dose of Bmab-100 or Avastin treatment and have available serum concentration data evaluable for PK analysis.

1 patient was randomised but not dosed due to consent withdrawal (and hence included in ITT and not in other population)

Reference: Listing 16.2.4

Source: BM100-CC-03-I-01-CSR

Demographics

The demographic profile was similar in the Bmab-100 and Avastin arms with respect to age, height, weight, BSA and survival expectancy. The study included 84 male and 52 female patients of Asian origin; the mean age of patients in the Bmab-100 arm was 50.7±14.0 years and that in the Avastin arm was 51.6±12.8 years. The mean BSA of patients in the Bmab-100 arm was 1.58±0.17 m^2 and in the Avastin arm was 1.60±0.17 m^2. The mean weight of the patients in the Bmab-100 arm was 56.20±11.64 kg and in the Avastin arm was 57.31±11.31 kg. The mean height of patients in the Bmab-100 arm was 160.64±9.67 cm and in the Avastin arm was 161.95±9.20 cm. The mean survival expectancy of patients in the Bmab-100 arm was 9.13 months and in the Avastin arm was 8.57 months (survival expectancy in both arms ranged between 4-24 months).

Tumour history and Baseline characteristics

All parameters evaluated were comparable for both the arms, except the disease burden in terms of sum of diameters of the target lesions, which was numerically higher in the Bmab-100 arm.

Efficacy results

Efficacy of Bmab-100 and Avastin (both in combination with XELOX chemotherapy) was compared in terms of best overall response rate (BORR) over 18 weeks. BORR was determined in the PP as well as the ITT populations. Objective response was defined as a CR or PR.

The ORR observed in the ITT population was 38.24% in the Bmab-100 arm and 48.53% in the Avastin arm. No statistically significant difference was observed between the two arms (p = 0.2258).

Table 32. Summary and analysis of best overall response rate (BORR) (ITT population) – Part II

Over All Response Rate	Bmab-100 (N=68) [n (%)]	Avastin® (N=68) [n (%)]
Complete Response (CR)	1 (1.47%)	1 (1.47%)
Partial Response (PR)	25 (36.76%)	32 (47.06%)
Stable Disease (SD)	36 (52.94%)	27 (39.71%)
Progressive Disease (PD)	3 (4.41%)	2 (2.94%)
In-evaluable	3 (4.41%)	6 (8.82%)
Responders (CR+PR=ORR)	26 (38.24%)	33 (48.53%)
Patient with Clinical Benefit	62 (91.18%)	60 (88.24%)
Difference in Response Rate	10.29%	
P-Value	0.2258	
Note: %=(n/N)100, N= Total number of randomized patients, n= Number of patients assigned for individual analysis set Data Source: rd_frmbestresp.sas7bdat, Listing 16.2.44(a), Generation date: 16FEB2017		

the ORR observed in the ITT population in this study is similar to historically observed ORR of 36.6% when bevacizumab is used in combination with chemotherapy [Zhang et al] and to the ORR of 33.8% [Feliu et al], 38% [Saltz et al], and 44.4% [Bencsikova et al]) when used in combination with XELOX chemotherapy as first-line therapy for mCRC patients.

The ORR observed in the PP population was 41.27% in the Bmab-100 arm and 55.0% in the Avastin arm. No statistically significant difference was observed between the two arms (p = 0.1276).

Table 33. Summary and analysis of best overall response rate (BORR) (PP population) – Part II

Over All Response Rate	Bmab-100 (N=63) [n (%)]	Avastin® (N=60) [n (%)]
Complete Response (CR)	1 (1.59%)	1 (1.67%)
Partial Response (PR)	25 (39.68%)	32 (53.33%)
Stable Disease (SD)	34 (53.97%)	25 (41.67%)
Progressive Disease (PD)	3 (4.76%)	2 (3.33%)
Responders (CR+PR=ORR)	26 (41.27%)	33 (55.00%)
Patient with Clinical Benefit	60 (95.24%)	58 (96.67%)
Difference in Response Rate	13.73%	
P-Value	0.1276	
Note: %=(n/N)100, N= Total number of patients in per-protocol population, n= Number of patients assigned for individual analysis set Data Source: rd_frmbestresp.sas7bdat, Listing 16.2.44(a), Generation date: 16FEB2017		

2.5.3. Discussion on clinical efficacy

Study MYL-1402O-3001, conducted in patients with Stage IV nsNCSLC, was considered pivotal for demonstrating therapeutic equivalence in terms of efficacy between MYL-1402O and EU-Avastin.

Supportive efficacy data were derived from study BM100-CC-03-I-01, conducted by Biocon in metastatic CRC patients in India with Bmab-100, which is an early development version of MYL-1402O. The study BM100-CC-03-I-01 is considered as supportive; and regarding the evaluation of efficacy the results are considered as informative only.

Design and conduct of main study

Demonstration of similarity on efficacy level is based on one pivotal efficacy and safety study. MYL-1402O-3001 is a randomised, double-blind, parallel-group multicentre study to compare the efficacy, safety and immunogenicity between MYL-1402O (proposed bevacizumab biosimilar) and EU-Avastin in subjects with Stage IV unresectable, recurrent or metastatic non-squamous NSCLC with negative or unknown activating EGFR gene mutations or ALK gene translocations.

In total 671 patients were 1:1 randomised to receive either MYL-1402O or EU-sourced Avastin. Gender, smoking status (smoker or <100 cigarettes in entire lifetime) and number of metastasis sites (one site or multiple sites) were used as stratification factors. According to the Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013), section 5.2 "Stratification" states that "(…) *stratification variables, if not solely used for administrative reasons, should usually be included as covariates or stratification variables in the primary analysis regardless of their prognostic value*".

The applicant provided estimated risk difference (RD) with corresponding 95% confidence interval (CI) based on Cochran-Mantel-Haenszel (CMH) test with stratification factors sex, smoking status, number of metastasis sites and newly also with region. RD was -1.57% and corresponding 95% CI was (-9.11%, 5.98%). This was similar to result of CMH test where region factor was not considered which led to RD -1.60% and corresponding 95% CI was (-9.12%, 5.91). This was also similar to unstratified analysis where RD was -1.60% and corresponding 95% CI was (-9.00%, 5.90%).

The study was conducted at 89 sites, including more than 90% of patients from non-EU countries. The applicant states that the study was conducted in accordance with the ethical principles of the Declaration of Helsinki and were consistent with ICH Guidance and the applicable local regulatory requirements and laws. Four patients were excluded from per protocol analysis set due to protocol deviation (2 patients in each arm).

Regarding protocol deviations, it was noted that four patients were excluded from PP set according to major protocol deviations. The deviations were set to be defined in the BDR meeting, which was held after the database lock and before unblinding the data. The applicant provided the number of patients with protocol deviations by 10 categories as defined in SAP, Version 2. All patients with protocol deviations by criteria 1-5 were excluded from the PP set, deviations of criteria 6-10 were decided on a case-by-case basis. Only patients with deviations categorised as major were excluded from the PP set. The applicant confirmed that two patients were missed to have major deviations and consequently missed to be excluded from the PP analysis. A sensitivity analysis was provided by excluding these two patients with no controversial results.

In Period 1 of the study, patients received 15 mg/kg bevacizumab concurrently with CP chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC 6) by iv infusion on Day 1 of every 3-week cycle for up to 6 cycles (18 weeks). In countries where the initial paclitaxel dose was 175 mg/m^2 based on institutional protocols, the investigators were allowed to initiate dosing at 175 mg/m^2. Dose reduction of chemotherapy within predefined dose levels or schedule modifications was permitted for toxicity reasons. If eligible (stable disease or better), patients continued with bevacizumab in Period 2 every 3 weeks as monotherapy until disease progression, treatment discontinuation (for any reason) or

withdrawal of consent. Total duration of Period 2 was 24 weeks; overall study duration was thus 42 weeks.

An Extended Treatment Period provided continued bevacizumab monotherapy to any patient who at Week 42 had stable disease or better response. During the Extended Treatment Period, a patient received bevacizumab until PD, death, unacceptable AE, withdrawal of consent, discontinuation from IMP for any reason, or 42 weeks post last patient randomised (i.e. trial closure).

The general study design was in line with previous scientific advice, except for the study duration. In the EMA Scientific Advice received by the applicant in October 2014 (EMA/CHMP/SAWP/629326/2014), the applicant stated that 1-year data would be generated in the pivotal comparative efficacy and safety study, which was supported by the CHMP. However, EOS was defined as 42 weeks from the randomisation of the last patient or discontinuation of all for study MYL-1402O-3001. Consequently, data up through the Week 42 visit are included in the final CSR for the evaluation of secondary efficacy endpoints and of safety and immunogenicity. This will be further discussed in Section 2.6 (Clinical Safety).

The selected population is considered appropriate to sensitively compare efficacy between EU-Avastin and the proposed biosimilar candidate. The used treatment regimens for bevacizumab and chemotherapy are in line with the Avastin labelling and respective guidances. With regard to the paclitaxel, a dose of 200 mg/m^2 is outlined in the protocol; however, in countries where the initial dose is 175 mg/m^2 based on institutional protocols, the investigators are allowed to initiate dosing at 175 instead of 200 mg/m^2. The majority of patients (69.9%) received the higher initial dose of 200 mg/m^2. In addition, the number of patients with the different paclitaxel doses was balanced between the treatment arms. In- and exclusion criteria are considered appropriate for the chosen population. Baseline demographic and disease characteristics were comparable between treatment arms. Overall, the same number of subjects in each treatment arm (n=9 per arm) discontinued chemotherapy and received bevacizumab monotherapy during the induction period. Up to Cycle 4, there were no subjects who started bevacizumab monotherapy. At Cycles 4, 5 and 6, the proportion of subjects starting maintenance treatment with bevacizumab monotherapy was overall comparable.

The applicant applies for all therapeutic indications currently authorised for the reference product EU-Avastin.

Endpoints:

The primary endpoint was the difference in best overall response rate in the ITT set within 18 weeks, assessed by independent review. Secondary endpoints were DCR, PFS, OS and DOR. An equivalence margin of ±12.5% for the primary endpoint was calculated.

The primary efficacy endpoint ORR assessed according to RECIST 1.1 is appropriate for the intended biosimilarity exercise and is in line with the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) and the Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5). ORR at a specific time point (at 18 weeks) as primary efficacy endpoint was agreed by CHMP during scientific advice.

Efficacy data and additional analyses

The applicant provided the results of the primary efficacy analysis and all other efficacy and safety results up to Week 18 with the initial submission. Final Week 42 data were submitted during the procedure. The data cut-off date was the date when the last randomised patient had reached or completed the tumour assessment scheduled at Week 42.

With regard to the primary EP, assessment is made by an independent central review for primary analysis, in addition to investigator´s analysis, which is supported. The duration of exposure as well as the number of doses administered and the cumulative doses for bevacizumab, carboplatin and paclitaxel were comparable between the treatment arms. With regard to the duration of IMP exposure, the total number of cycles received was similar between both treatment arms during the induction period (1627 vs 1626 cycles). For the maintenance period, a numerically higher number of treatment cycles was administered in the MYL-1402O arm (1278 vs 1242 cycles). This could be attributed mainly to a higher number of patients having received 7 cycles in the MYL-1402O arm than in the Avastin arm (n=20 vs n=9).

The difference in best ORR within 18 wks was -1.6 (-9.0, 5.9) for the ITT population, and -2.4 95% CI of (-10.2, 5.3) for the PP set; the two-sided 95% CI was entirely within the pre-defined equivalence margin of [-12.5%, 12.5%]. Therefore, formally similarity of efficacy regarding the primary efficacy endpoint has been demonstrated. This was supported by sensitivity analyses for the primary EP, e.g. investigator-assessed ORR in the ITT population (ORR difference of -2.2, with a 95% CI of -9.7, 5.3) - the results were consistent with the primary analysis.

However, the applicant has defined the primary efficacy endpoint as the difference of best ORR between MYL-1402O and Avastin during Period 1 by 18 weeks of bevacizumab plus chemotherapy. This implies that a patient who has a response and afterwards a progression in disease or who even dies would still be counted as responder. ORR is considered adequate as primary endpoint, but an evaluation at a specific time point (i.e. week 18) is considered more sensitive in a biosimilar application and would be preferred compared to a best ORR across all time points (e.g., a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). Maximizing the ORR over all tumour assessments might result in the situation to count a subject as responder even if he dies later on in Period 1. The applicant provided analysis of overall response rate (ORR) at week 18 both in ITT and PP set, as requested. Calculations for ITT set and PP set were based 1) on independent review and 2) on the investigator's assessment. Corresponding 95% confidence intervals (CIs) for the estimated differences in ORR between both treatment groups were within equivalence range (-12.5%, 12.5%) in all cases. Namely, 95% CIs for the difference in ORR were 1) (-5.8%, 8.7%) in ITT set and (-6.4%, 8.7%) in PP set for independent review and 2) (-7.4%, 7.3%) in ITT set and (-8.1%, 7.2%) in PP set for the investigator's assessment. Thus, equivalence was concluded. Relevance of equivalence range (-12.5%, 12.5%) for difference in ORR was given by justification that ORR at week 18 was considered to be more conservative than the best overall response (BOR) at any time during the 18-week period. This implied, by the applicant's opinion, that equivalence range for ORR up to week 18 was also suitable for ORR at week 18. Moreover, the observed ORRs at week 18 for MYL-1402O and Avastin were between 35% and 39%. These ORRs were similar to ORR of 38% used for sample size calculation. Here, ORR of 38% was based on results from meta-analysis of 4 studies comparing bevacizumab plus chemotherapy (chemotherapy was either paclitaxel+carboplatin or gemcitabine) to chemotherapy alone.

In addition, it was unclear in how far the primary endpoint has been revised from CSP Version 2.0 to Version 3.0. Here, the applicant clarified that in the revised protocol Version 3.0, the need for BOR to be confirmed at a second time point was deleted for the primary analysis. However, the response rate with confirmation as a second time point was retained and presented as sensitivity analysis. The rationale for this revision was the data cut-off for the primary endpoint at week 18, implying that BOR might not have been confirmed at a second time point in patients having a first objective response at Week 18. Those patients would have been counted as non-responders for PE analysis of confirmed BOR due to the early data cut off.

However, the independent review of the best ORR confirmed at a second time point in the ITT population revealed markably lower ORR rates for both treatment arms (29.1% in the MYL-1402O arm

and 30.5% in the EU-Avastin arm). The applicant clarified that the independent review process took place once the patient had completed imaging for the respective review period (here: from Screening through Wk 18 DCO) and no further imaging time points were scheduled. In contrast, the investigator assessed the tumour response upon completion of each imaging time point (i.e. Wk 6, 12, 18), thus on a real-time basis. Within this context, treatment continuation was dependent on the overall tumour response (imaging plus patient´s clinical condition) at a specific time point.

It is acknowledged that this observed difference in the response rates between independent review and investigator assessment is a general limitation that is known and described in literature. Subjective factors such as target-lesion selection as well as different interpretations of non-target or immeasurable lesions are discussed to be of relevance within this context.

With regard to the overall lower confirmed response rate as per independent review (29.8%) compared to investigator assessment (40.4%), the applicant points out that this might be also attributed to limitations of the study design (i.e. the data cut-off defined for the review period for the primary EP). For late responders (i.e. patients with first CR or PR at Week 18), BOR could not be confirmed at a second time point; thus they were assessed as non-responders for this sensitivity analysis. Within this context, the applicant presents an additional analysis for BOR confirmed at a second time point based on independent review, conducted at Week 42. This confirmed response analysis based on Week 42 data provides a higher confirmed mean BOR of 35.0%.

However, this limitation of the DCO time point at Wk 18 for the primary EP in case of late responders and confirmed response analysis would also apply to the investigator-based assessment of confirmed response.

Overall, since equivalence was shown between treatment arms in both independent review and investigator assessment for BOR as well as for confirmed response, the CHMP considers that there is no critical issue with regard to proof of biosimilarity.

Further results were largely comparable: The number of patients with disease progression (PD), complete response (CR), partial response (PR) and stable disease (SD) was similar between treatment arms and also between independent review and investigator-based assessment.

With regard to secondary efficacy endpoints, DCR at week 18 was comparable between treatment arms (difference of -4.9, with a 95% CI of -10.5, 0.6).

The applicant has provided updated PFS and OS analyses with the Week 42 CSR. Based on independent review, median PFS at 42 weeks was 7.6 (95% CI: 7.0, 9.5) months in the MYL-1402O arm and 9.0 (95% CI: 7.2, 9.7) months in the Avastin arm. This difference was, however, not statistically significant (p-value 0.0906). When PFS was assessed by the investigator, median PFS was 7.8 (95% CI: 7.0, 9.5) months in the MYL-1402O arm and 7.3 (95% CI: 7.0, 8.9) months in the Avastin arm.

With regard to OS, in the MYL-1402O arm 236 (70.0%) patients survived through Week 42 compared to 252 (75.4%) patients in the Avastin arm. This difference between the survival curves for both treatment groups was not statistically significant (p=0.1185). The OS HR at Week 42 was 1.26 (0.94, 1.69). In addition, the median OS was not reached in the ITT population at Week 42.

It is acknowledged that study MYL-1402O-3001 was primarily designed for ORR analysis at Week 18. Although PFS and OS were included as secondary endpoints, the trial was not designed for a mature evaluation and was not powered to demonstrate comparability between MYL-1402O and Avastin based on those time-to-event endpoints.

In general, the primary analysis of an equivalence study should be based on a population that is sensitive to demonstrate equivalence. Protocol violations may tend to bias the results towards a

conclusion of equivalence, see ICH E9. Therefore, the PP set is the preferred analysis set for the primary efficacy analysis. The applicant defined the ITT population to be the primary efficacy population, which is not endorsed.

The applicant has provided additional analyses identifying factors such as imbalances in post treatment anticancer therapies as well as in deaths occurring within 30 days of first IMP dose, which may have contributed to the imbalance in survival rates between the treatment arms.

As stated in the GL on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), data on survival may have to be interpreted with caution due to numerous factors influencing survival beyond the performance of the biosimilar or the reference product. OS may not be sensitive enough for establishing comparability, since there may be influences by factors not attributable to differences between the biosimilar and the reference product, but by factors like tumour burden, performance status, previous lines of treatments, underlying clinical conditions, subsequent lines of treatment, etc.

In addition, the chosen patient population (Stage IV NSCLC patients) may not be ideal for the demonstration of clinical comparability. Especially in NSCLC, the clinical course of the disease varies from slowly progressive to aggressive profile in patients commonly having several comorbidities, increasing the risk of fatal events. This seems to reflect the variable and occasionally unpredictable outcomes seen in clinical practice.

It is acknowledged that, taking into account the results for the primary EP, ORR, supporting efficacy similarity between MYL-1402O and Avastin, this imbalance between the treatment arms in the time-to-event endpoints PFS and OS does not necessarily preclude conclusion of biosimilarity.

The applicant has submitted complete DOR results with the Week 42 CSR. Median DOR was comparable between the MYL-1402O and the Avastin arm (7.7 vs 6.9 months), which thus supports biosimilarity demonstrated in the primary analysis.

Week 42 Time to First Objective Response data have been provided by the applicant. With the full data set, the difference observed between the treatment arms for the Week 0-7 Time to First Objective Response diminishes from 3.5% (Week 18 CSR) to 2.0%. In addition, the applicant stresses that in this patient population, a maximum objective response would not be expected before 3-4 treatment cycles have been administered, which would imply 9-12 weeks. However, the difference of around 2% between the treatment arms with regard to Time to First Objective Response results remains more or less consistent over time. Another explanation provided by the applicant for the observed imbalance between the treatment arms is that for patients who died or discontinued treatment without any post-baseline tumour assessments, Time to First Response could not be determined. These early discontinuations occurred more frequently in the MYL-1402O than in the Avastin arm (11.6% vs 9.3%). Such an imbalance between treatment arms may indeed have contributed to the observed difference of -1% to -2%, persisting throughout the study.

Subgroup analyses revealed no relevant differences for the primary endpoint, except for the subgroup receiving prior radiation therapy. Here the observed difference in best ORR between both treatment arms was -26.25% (95% CI -47.83, -5.20) with a best ORR of 25.0% in the MYL-1402O arm and of 51.2% in the EU-Avastin arm. The applicant has discussed potential explanations for the observed difference in best ORR in the subgroup "prior radiation therapy" between both treatment arms. According to the applicant, the low number of patients in this subgroup along with the differences in baseline disease characteristics, an imbalance in the prior radiation dose and a higher rate of early discontinuations in the MYL-1402O arm may have contributed to the ORR difference observed between treatment arms in this subgroup with prior radiation therapy.

Overall, acknowledging that this is a rather small subgroup as well as that there was no such difference observed between the treatment arms in this subgroup of prior radiation therapy with regard to the other secondary efficacy parameters PFS, DOR, and OS, this ORR difference is regarded to be not of clinical relevance. Additional subgroup analyses using Forest Plots have been provided for the PP set. No distinct imbalances between treatment arms have been detected for any of the subgroups analysed, except for the subgroup having received prior radiation therapy, consistent with the ITT population.

With regard to subgroup analysis by age, the ORR differences within the age groups <65, ≥65, <75 and ≥75 were comparable between the treatment arms.

Subgroup analysis by geographic region (Europe, India, Southeast Asia) has been performed and revealed no differences or imbalances for the primary endpoint. Additional analyses were presented with regard to EU versus non-EU countries and showed a slightly higher ORR for MYL-1402O compared to Avastin for the region EU-Europe. However, due to the small sample size of this subgroup (n=26 in the MYL-1402O arm vs n=29 in the Avastin arm), this seems to be a chance finding and is not considered to be of relevance.

With regard to results for the primary efficacy EP in the ADA-positive subgroup of patients, best ORR by 18 weeks was 44.4% (8/18 patients) in the MYL-1402O arm compared to 27.3% (3/11 patients) in the Avastin arm. However, it is acknowledged that, overall, the post baseline ADA incidence was low for both treatment arms in the NSCLC study (n=18 vs n=11). Importantly, no negative impact of treatment-induced ADA on efficacy in terms of ORR could be observed for MYL-1402O (41.5% ORR in the overall ITT population compared to 44.4% in the subgroup with treatment-induced ADA's).

Supportive study

A supportive study in patients with metastatic Colorectal Cancer (mCRC) was conducted in India with a formulation that has the same drug substance and excipients as the reference formulation, according to the applicant. It is based on an early development version of MYL-1402O, referred to as Bmab-100. Therefore, efficacy data from this study are considered as supportive only.

Study BM100-CC-03-I-01 was a double blind, randomised, active controlled, parallel design, comparative PK, efficacy, safety and immunogenicity study of Bmab-100 and Avastin, both in combination with oxaliplatin-capecitabine (XELOX) chemotherapy in patients with metastatic colorectal cancer. Primary objective was to demonstrate PK bioequivalence of Bmab-100 and Avastin.

The applicant clarified that EU-Avastin was used as reference medicinal product in study BM100-CC-03-I-01. It was confirmed that one EU-Avastin batch was used in this study, as stated in the CSR. The batch certificate for the same batch has also been submitted.

The study had two parts (1 and 2). The objective of Part 1 was to generate the safety data of infusion-related reactions of the first dose of Bmab-100 when given with XELOX chemotherapy in 10 patients.

Part 2 of the study was a double-blind, randomised, active controlled, parallel arm study in patients with mCRC. Only first line mCRC patients were included. Patients received Bmab-100 or Avastin at 7.5 mg/kg along with XELOX chemotherapy for up to 6 cycles. Each cycle consisted of a 21 day period. As a whole, the study consisted of 21 days screening period, 15 weeks treatment period, followed by a 3 week follow up. The End of the Study evaluation was performed at the end of 18 weeks. Wherever possible, radiological assessments were performed 4-6 weeks after the EOS (Post EOS) in patients with first documentation of response (PR or CR at EOS).

Efficacy was the secondary objective of the study. The efficacy objective was to evaluate and compare the effect of Bmab-100 and Avastin, in combination with XELOX chemotherapy on:

- Overall response rate based on RECIST 1.1 criteria

- PFS rate at 18 weeks.

- DCR rate at 18 weeks

The efficacy analyses were performed on the basis of tumour response evaluation by independent, blinded and centralised radiological evaluation according to RECIST 1.1 guidelines for radiological assessment of tumours.

Albeit no statistically significant differences were observed with regard to best ORR within 18 weeks in both the ITT and the PP population, there were higher numbers of subjects with PR in the Avastin arm (n=32) than in the Bmab-100 arm (n=25). Furthermore, considerably more subjects in the Bmab-100 arm had SD (n=36) compared to the Avastin arm (n=27).

Thus, overall no clear conclusion can be drawn from the submitted supportive efficacy data in terms of best ORR within 18 weeks with regard to biosimilarity of Bmab-100 and Avastin or, still less, of MYL-1402O and EU-Avastin.

With regard to the other efficacy endpoints that were evaluated in this study, DCR was comparable between the two study arms (Bmab-100 91.18% versus Avastin 88.24%), as well as the PFS rate at 18 weeks (Bmab-100 61.76% versus Avastin 60.29%).

2.5.4. Conclusions on clinical efficacy

There are no concerns regarding similarity of efficacy.

In the pivotal comparative efficacy study MYL-1402O-3001 in Stage IV nsNSCLC patients, equivalence between MYL-1402O and EU-Avastin was demonstrated for the primary efficacy endpoint, best ORR within 18 weeks, assessed by independent review in the ITT population. This was supported by sensitivity analyses for the primary EP in the PP population, which is the population of interest for a biosimilar.

In addition, post-hoc sensitivity analyses have been provided for ORR at week 18, which is considered a more sensitive endpoint for a biosimilarity exercise than the BOR at any time point during the 18-week induction period. ORR rates at week 18 were similar between the treatment arms, both in the ITT and PP set, based on independent review as well as on investigator assessment. Overall, the presented additional ORR analyses at week 18 indicate similar efficacy between MYL-1402O and EU-Avastin and do thus support the results from the primary analysis.

In summary, biosimilarity on efficacy level can be concluded from the data submitted.

2.6. Clinical safety

Safety of MYL-1402O has been evaluated in 2 clinical comparative studies (studies MYL-1402O-1002 and MYL-1402O-3001). Study MYL-1402O-1002 was completed, whereas for study MYL-1402O-3001, data from Period 1 (up to 18 weeks) were the basis for initial assessment and the final Week 42 data were submitted during the procedure.

Study MYL-1402O-1002 (Phase I PK in healthy volunteers)

The Safety Set consisted of all subjects who were randomised and had received at least 1 dose of bevacizumab (n= 111).

This was a single centre study, conducted in The Netherlands.

Safety Endpoints:

Adverse events (AEs), clinical laboratory, vital signs, 12-lead electrocardiogram (ECG), physical examination, infusion site local tolerance, presence of anti-drug antibodies (ADA) in serum (immunogenicity).

Study MYL-1402O-3001 (Phase III efficacy + safety in nsNSCLC patients)

A multicentre, double-blind, randomised, parallel-group study to assess the efficacy and safety of MYL-1402O compared with Avastin, in the first-line treatment of patients with Stage IV Non-Squamous Non-Small Cell Lung Cancer (nsNSCLC). The Safety Set consisted of all patients who were randomised and had received at least 1 dose of bevacizumab (MYL-1402O or EU-Avastin, n= 664 patients). The whole study duration was 42 weeks.

This multicentre study was conducted at sites in Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Georgia, Hungary, India, Italy, Philippines, Poland, Romania, Russian Federation, Spain, Taiwan, Turkey, Ukraine and Vietnam.

Safety Endpoints:

- Incidence, nature, and severity of AEs including ADRs graded according to CTCAE.

- Detection of antibodies to bevacizumab.

In addition, a supportive clinical study (BM100-CC-03-I-01) was conducted with Bmab-100 by Mylan's development partner Biocon. This study has been completed.

Study BM100-CC-03-I-01 (supportive Phase III study in mCRC patients)

The study had two parts (1 and 2). The objective of Part 1 of the study was to generate safety data on infusion-related reactions of the first dose of Bmab-100 when given with XELOX chemotherapy in 10 patients. The safety objectives were included in Part 2 of the study. The Safety Set consisted of all subjects who were randomised and had received at least 1 dose of bevacizumab (n= 135).

Safety Endpoints:

- Evaluation of comparative safety of Bmab-100 and Avastin (over 18 weeks)

- Evaluation of incidence and titres of ADA for Bmab-100 and Avastin (over 18 weeks)

Safety data from the clinical studies were not pooled.

- The study populations were different. The Phase I PK study MYL-1402O-1002 was conducted in healthy male volunteers, the Phase III efficacy and safety study MYL-1402O-3001 was performed in NSCLC patients.

- Different study protocols and thus, treatment schemes were used in both trials. In the Phase I study one single dose of 1 mg/kg bevacizumab was administered iv to the study participants, in the Phase III study repeated doses (every 3 weeks) of 15 mg/kg bevacizumab were administered iv to the patients, first concomitantly with carboplatin/ paclitaxel during Period 1, then as monotherapy during Period 2 of the trial.

- The two patient-based studies were conducted in patients with different tumour indications and with different chemotherapeutic regimens.

Avastin has a well characterised safety profile and an extensive post-marketing data base. Hence, the sample sizes of the Phase I and Phase III studies are considered acceptable to detect relevant safety signals.

It is noted that the final CSR includes only Week 42 data. This in contrast to the EMA SA received by the applicant in October 2014, where the applicant stated that 1-year data would be generated in the pivotal phase III study, which was supported by the CHMP. The applicant provided justification on the deviation in the context of safety follow-up period for which the data is submitted (42 weeks instead of 1-year data). This is based on the amendment to the study protocol (from version 1.0 to version 2.0). Moreover, the applicant presented data available beyond Week 42 for the patients who entered extended treatment period (i.e. 86 patients from the MYL-1402O group and 84 patients from the Avastin group).

It is stated by the applicant that during the manufacturing of the development batches of MYL-1402O, one formulation buffer component was changed. Instead of sodium dihydrogen phosphate monohydrate, sodium dihydrogen phosphate dehydrate was erroneously used. Since the manufacturing process was based on monohydrate, the buffer quantity was not adjusted for dihydrate (i.e. molecular weight of 137.8 was used instead of 156). This inadvertent change resulted in small differences with regard to pH and osmolality. It was outlined by the applicant that the product quality with dihydrate buffer in terms of stability or other key product attributes were not impacted.

The formulation used in the completed as well as in the ongoing clinical studies (including the supportive study conducted with Bmab-100 in India by Biocon) contained sodium dihydrogen phosphate dihydrate. Also, the commercialised product in India contained the dihydrate salt. Since the product intended to be marketed in the EU is also based on the dihydrate salt, the data submitted are considered relevant for the evaluation of safety and immunogenicity of MYL-1402O.

Patient exposure

Table 34. Overall exposure of the study drug

Study	Study Population	Number of subjects who received MYL-1402O
MYL-1402O-1002	Healthy male volunteers	37
MYL-1402O-3001	nsNSCLC patients	335
BM100-CC-03-I-01	mCRC patients	68

Phase I PK study

The Safety Set consisted of all 111 healthy male subjects who were randomised and who received a single dose of 1 mg/kg bevacizumab. The overall extent of exposure was similar between the three treatment arms (n= 37 per treatment arm). Of the 111 subjects who received the IMP, all completed the trial and no subjects discontinued.

Table 35. Extent of exposure

Total exposure to study treatment per subject	Treatment administered	Number of subjects exposed
1 mg/kg	1 mg/kg MYL-1402O as an iv infusion	N=37
	1 mg/kg US-Avastin as an iv infusion	N=37
	1 mg/kg EU-Avastin as an iv infusion	N=37

iv = intravenous; Source: MYL-1402O-1002 CSR Listing 16.2.5-2

The Phase I study included only healthy male subjects as agreed upon in previous EMA scientific advice. The subjects were aged 18 to 55 years. The majority of healthy volunteers were White. The mean age of study participants was 31 years.

Table 36. Summary of demographic characteristics (SAF set)

Parameter		Statistic / Category	MYL-1402O (N=37)	US-Avastin (N=37)	EU-Avastin (N=37)	Total (N=111)
Gender	– Male	n (%)	37 (100)	37 (100)	37 (100)	111 (100)
Race	– Asian	n (%)	0 (0)	2 (5)	2 (5)	4 (4)
	– Black	n (%)	2 (5)	4 (11)	4 (11)	10 (9)
	– Multiple	n (%)	1 (3)	2 (5)	1 (3)	4 (4)
	– White	n (%)	34 (92)	29 (78)	30 (81)	93 (84)
Ethnicity	– Hispanic or Latino	n (%)	3 (8)	0 (0)	0 (0)	3 (3)
	– Not Hispanic or Latino	n (%)	34 (92)	37 (100)	37 (100)	108 (97)
Age (years)*		mean (SD)	30 (11)	33 (12)	31 (13)	31 (12)
		min - max	18 - 53	20 - 55	18 - 55	18 - 55
Height (cm)*		mean (SD)	182 (6)	181 (7)	181 (8)	181 (7)
		min-max	173 - 196	167 - 194	159 - 197	159 - 197
Weight (kg)*		mean (SD)	79.7 (9.0)	80.7 (9.2)	79.7 (9.3)	80.0 (9.1)
		min-max	61.2 - 99.2	65.5 - 99.5	62.4 - 99.7	61.2 - 99.7
Body Mass Index (kg/m^2)		mean (SD)	24.0 (2.3)	24.7 (2.3)	24.5 (2.9)	24.4 (2.5)
		min-max	20.2 - 29.9	20.4 - 29.0	19.2 - 29.6	19.2 - 29.9

max = maximum; min = minimum; N (n) = number of subjects; SAF set = Safety set SD = standard deviation; * height, body weight and age were determined at screening;
Source: CSR BM100 CC 03 I 01 Table 15.1-2

Phase III NSCLC study

The Safety Set comprised all patients who received bevacizumab (15 mg/kg iv) at least once. Hence, a total of 664 out of the 671 randomised patients were included in the Safety Set (MYL-1402O group: 335 patients [99.4%]; EU-Avastin group: 329 patients [98.5%]).

Table 37. Exposure of investigational medicinal products: safety set

	MYL-1402O (N=335)	Avastin (N=329)	Total (N=664)
Duration of Exposure (weeks)			
n	335	329	664
Mean (SD)	15.6 (5.70)	15.8 (5.32)	15.7 (5.51)
Median	18.1	18.0	18.0
Min, Max	3, 27	3, 25	3, 27
Actual Number of Doses			
n	335	329	664
Mean (SD)	4.9 (1.81)	5.0 (1.68)	5.0 (1.75)
Median	6.0	6.0	6.0
Min, Max	1, 9	1, 8	1, 9
Cumulative Dose (mg/kg)			
n	335	329	664
Mean (SD)	74.8 (27.48)	75.7 (25.32)	75.2 (26.42)
Median	89.6	89.2	89.3
Min, Max	15, 134	15, 123	15, 134

Cumulative dose (mg/kg) is defined as sum of actual dose level.
Planned dose level is 15 mg/kg/cycle for investigational medicinal products.
Source Data: CSR MYL-1402O-3001 Listing 16.2.5.3 and Table 14.1.6.1

The mean duration of exposure to bevacizumab during Period 1 was comparable between MYL-1402O (15.6 weeks) and EU-Avastin (15.8 weeks), as well as the mean number of doses (MYL-1402O 4.9 versus EU-Avastin 5.0) and the mean cumulative doses (MYL-1402O 74.8 versus EU-Avastin 75.7). Based on the full Week 42 data set, the mean duration of exposure to bevacizumab was comparable between MYL-1402O (15.13 weeks) and EU-Avastin (14.65 weeks), as well as the mean number of doses (8.7 for both treatment arms) and the mean cumulative doses (MYL-1402O 131.0 mg/kg versus EU-Avastin 131.8 mg/kg).

In both study periods, a comparable number of cycles was overall administered across all patients in both treatment arms, with a slightly lower number of cycles administered in Period 2 for Avastin (n=1242) than for MYL-1402O (n=1278).

With regard to chemotherapy, the mean duration of exposure to carboplatin during Period 1 was comparable between MYL-1402O (15.3 weeks) and EU-Avastin (15.6 weeks), as well as the mean number of doses (MYL-1402O 4.8 versus EU-Avastin 4.9) and the mean cumulative doses (MYL-1402O 3171.8 versus EU-Avastin 3289.8). The mean duration of exposure to paclitaxel during Period 1 was comparable between MYL-1402O (15.4 weeks) and EU-Avastin (15.6 weeks), as well as the mean number of doses (MYL-1402O 4.9 versus EU-Avastin 4.9) and the mean cumulative doses (MYL-1402O 1641.7 versus EU-Avastin 1732.2).

Table 38. Dose delays of IMP safety set

	MYL-1402O (N=335) n (%)	**Avastin (N=329) n (%)**	**Total (N=664) n (%)**
No Dose Delay	177 (52.8)	182 (55.3)	359 (54.1)
Number of Patients with Dose Delay:			
Any	158 (47.2)	147 (44.7)	305 (45.9)
4-7 Days Delay	68 (20.3)	70 (21.3)	138 (20.8)
≥8 Days Delay	90 (26.9)	77 (23.4)	167 (25.2)

IMP = Investigational medicinal product;
Source Data: Listing 16.2.5.1; Table 14.1.6.3

In the Phase III study in NSCLC patients, the mean age of the patients was 59.3 (SD 9.60) years in the MYL-1402O and 59.2 years (SD 9.73) in the EU-Avastin treatment arm. 70.3% of the patients in

the MYL-1402O and 70.7% of the patients in the EU-Avastin arm were < 65 years old. Both treatment groups were thus comparable with regard to the age of the patients included.

Gender, smoking status, and number of metastasis sites were used for stratification.

In both treatment groups, the majority of the patients was White: 67.1% (226 patients) in the MYL-1402O treatment group and 69.5% (232 patients) in the EU-Avastin group. 111 (32.9%) patients in the MYL-1402O group and 102 (30.5 %) patients in the EU-Avastin group were Asians. No patients were Black or African American. In the MYL-1402O arm, 5 (1.5%) patients were Hispanic or Latino, and 4 (1.2%) in the EU-Avastin arm.

More than 90% of the patients included in the trial were non-EU citizens. Only 8.2% of study participants were EU citizens. 59.8% were recruited from Non-EU countries, and 32.0% were from Asia. The proportion of EU citizens was comparable for both treatment arms.

With regard to medical history, both treatment arms were comparable. The majority of patients had at least 1 medical condition in their history. The most commonly reported medical history disorders (>25% of total) were in the SOC of Respiratory, Thoracic and Mediastinal disorders (MYL-1402O 41.8% and Avastin 42.5%); Vascular disorders (MYL-1402O 39.5% and Avastin 33.5%); and Gastrointestinal disorders (MYL-1402O 28.5% and Avastin 29.9%).

Baseline disease characteristics were comparable between the two treatment arms. However, there were slightly higher proportion of patients with M1C sub stage in the MYL-1402O arm, 125 (37.1%) patients compared to 117 (35.0%) patients in the Avastin arm. However, all the patients were in Stage IV at the time of randomisation into the study, as per protocol requirement.

Supportive Phase III mCRC study

The Safety Set consisted of 135 patients. Overall, 68 mCRC patients were exposed to Bmab-100 and 67 patients were exposed to Avastin.

In both study arms, 63.23% patients completed the study and the rest (36.76%) was prematurely discontinued.

The mean cumulative dose (1.93 g for Bmab-100 versus 2.09 g for Avastin) and the mean duration of exposure (104.9 days versus 109.5 days) were comparable between the treatment arms. In addition, the mean number as well as the median number of cycles received were comparable for both treatment arms.

Table 39. Study drug exposure

Statistics	Bmab-100 (N=68)	Avastin (N=67)
N	68	67
Cumulative Dose (g)		
Mean±SD	1.93±0.79	2.09±0.84
Median	1.98	2.18
Min, Max	(0.41,4.057)	(0.30,3.66)
Duration of Exposure (Mean±SD) days	104.93±(39.96)	109.49±(34.38)
Median	126.00	126.00
Range in days	21.00, 150.00	21.00, 159.00
Mean Number of cycles (SD)	4.76	4.93
Median Number of cycles	6.00	6.00

Note: Cumulative dose is the total amount of dose used by Patient during the treatment period
Source Data: CSR BM100 CC 03 I 01 Table 21

Demographic and baseline disease characteristics as well as the medical history were comparable between the treatment arms.

Adverse events

Phase I PK study

In the Phase I PK study in healthy male subjects, the proportion of subjects who experienced a TEAE, as well as the number of TEAEs, was lower in the EU-Avastin group (29/37 subjects [78%] and 99 TEAEs) and in the US-Avastin group (28/37 subjects [76%] and 98 TEAEs) than in the MYL-1402O arm (33/37 subjects [89%] and 116 TEAEs).

Table 40. Overview of treatment-emergent adverse events during the study

	MYL-1402O (N=37) n (%)	US-Avastin (N=37) n (%)	EU-Avastin (N=37) n (%)
Number of subjects with at least 1 TEAE	33 (89%)	28 (76%)	29 (78%)
Number of subjects with at least 1 related TEAE	17 (46%)	12 (32%)	19 (51%)
Number of subjects with at least 1 TEAE by severity:			
Grade 1 (mild)	33 (89%)	25 (68%)	29 (78%)
Grade 2 (moderate)	3 (8%)	9 (24%)	4 (11%)
Number of subjects withdrawn due to AEs or SAEs:	0 (0%)	0 (0%)	0 (0%)

AE = adverse event; N = the # of subjects exposed to the treatment; n = the # of subjects that experienced the adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event; % is calculated as (n/N)*100
There were no Grade 3 (severe) or higher grade TEAEs
Source: CSR MYL-1402O-1002 Listing 16.2.6-1

All of the TEAEs were Grade 1 (mild) or 2 (moderate) in severity, with a higher number of Grade 1 (mild) TEAEs in the MYL-1402O arm (113 TEAEs) than in the EU-Avastin arm (93 TEAEs) or in the US-Avastin arm (85 TEAEs).

The most frequently reported TEAE was headache in all treatment arms (MYL-1402O 19% [7/37 subjects], US-Avastin 16% [6/37], EU-Avastin 24% [9/37]).

Table 41. Summary of most common (≥5% of subjects) TEAEs by SOC and PT

	MYL-1402O (N=37)			US-Avastin (N=37)			EU-Avastin (N=37)			Total (N=111)		
SYSTEM ORGAN CLASS Preferred Term	E	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)
Total	116	33	(89%)	98	28	(76%)	99	29	(78%)	313	90	(81%)
General Disorders and Administration Site Conditions	30	16	(43%)	14	11	(30%)	18	11	(30%)	62	38	(34%)
Catheter Site Erythema (Blood Sampling Arm)	5	5	(14%)	0	0	(0%)	3	3	(8%)	8	8	(7%)
Catheter Site Pain (Blood Sampling Arm)	3	3	(8%)	1	1	(3%)	3	3	(8%)	7	7	(6%)
Gastrointestinal Disorders	15	9	(24%)	20	11	(30%)	18	12	(32%)	53	32	(29%)
Diarrhoea	3	3	(8%)	4	4	(11%)	2	2	(5%)	9	9	(8%)
Abdominal Pain	2	2	(5%)	1	1	(3%)	5	5	(14%)	8	8	(7%)
Frequent Bowel Movements	1	1	(3%)	2	2	(5%)	2	2	(5%)	5	5	(5%)
Nervous System Disorders	15	8	(22%)	17	10	(27%)	20	13	(35%)	52	31	(28%)
Headache	10	7	(19%)	8	6	(16%)	11	9	(24%)	29	22	(20%)
Dizziness	2	2	(5%)	2	1	(3%)	2	2	(5%)	6	5	(5%)
Paraesthesia	0	0	(0%)	6	2	(5%)	4	3	(8%)	10	5	(5%)
Musculoskeletal and Connective Tissue Disorders	16	11	(30%)	11	10	(27%)	13	9	(24%)	40	30	(27%)

	MYL-1402O (N=37)			US-Avastin (N=37)			EU-Avastin (N=37)			Total (N=111)		
SYSTEM ORGAN CLASS Preferred Term	E	n	(%)	E	n	(%)	E	n	(%)	E	n	(%)
Back Pain	2	2	(5%)	5	5	(14%)	2	2	(5%)	9	9	(8%)
Myalgia	1	1	(3%)	4	3	(8%)	4	3	(8%)	9	7	(6%)
Pain In Extremity	5	4	(11%)	0	0	(0%)	2	2	(5%)	7	6	(5%)
Infections and Infestations	7	6	(16%)	13	8	(22%)	4	4	(11%)	24	18	(16%)
Nasopharyngitis	7	6	(16%)	6	5	(14%)	2	2	(5%)	15	13	(12%)
Respiratory, Thoracic and Mediastinal Disorders	8	7	(19%)	5	3	(8%)	4	4	(11%)	17	14	(13%)
Epistaxis	5	4	(11%)	2	1	(3%)	0	0	(0%)	7	5	(5%)
Vascular Disorders	8	7	(19%)	1	1	(3%)	7	5	(14%)	16	13	(12%)
Haematoma (Infusion Arm)	3	3	(8%)	1	1	(3%)	4	4	(11%)	8	8	(7%)
Haematoma (Blood Sampling Arm)	5	5	(14%)	0	0	(0%)	2	2	(5%)	7	7	(6%)

E = the # of TEAEs; N = the # of subjects exposed to the treatment; n = the # of subjects that experienced the TEAEs; % is calculated as (n/N)*100; Subjects were counted once, per preferred term, of multiple occurrences of a specific MedDRA term. Source: Study MYL-1402O-1002 Listing 16.2.6-1

The most frequently affected SOCs among the treatment groups were Gastrointestinal disorders and Nervous System disorders. The incidence of TEAEs categorised by SOC was overall comparable among the MYL-1402O, EU-Avastin and US-Avastin treatment groups.

However, there were differences in the incidence of TEAEs between the treatment arms for catheter site erythema, pain in extremity, nasopharyngitis and hematoma (blood sampling arm). Notably, there were no PTs with at least a 10% absolute difference between TEAEs in both the EU- or US-Avastin groups vs the MYL-1402O group. The differences in incidence rates between treatment groups are thus not considered of clinical relevance.

No TEAES of Grade 3 (severe) or higher in severity and no discontinuations due to TEAEs during the study occurred in any of the treatment arms.

TEAEs considered to be related to the IMP were reported in 17 subjects in the MYL-1402O treatment group, in 19 subjects in the EU-Avastin treatment group and in 12 subjects in the US-Avastin treatment group.

Table 42. Overall summary of treatment-emergent adverse events by treatment, severity and relationship

	Grade 1 (Mild) Severity			Grade 2 (Moderate) Severity		
	Related	Not Related	Total	Related	Not Related	Total
Treatment	E n (%)	E n (%)	E n (%)	E n (%)	E n (%)	E n (%)
MYL 1402O (N=37)	31 17 (46%)	82 31 (84%)	113 33 (89%)	1 1 (3%)	2 2 (5%)	3 3 (8%)
US-Avastin® (N=37)	28 11 (30%)	57 21 (57%)	85 25 (68%)	1 1 (3%)	12 8 (22%)	13 9 (24%)
EU-Avastin® (N=37)	33 19 (51%)	60 25 (68%)	93 29 (78%)	3 2 (5%)	3 2 (5%)	6 4 (11%)
Total (N=111)	92 47 (42%)	199 77 (69%)	291 87 (78%)	5 4 (4%)	17 12 (11%)	22 16 (14%)

	Total*		
	Related	Not Related	Total
Treatment	E n (%)	E n (%)	E n (%)
MYL 1402O (N=37)	32 17 (46%)	84 31 (84%)	116 33 (89%)
US-Avastin® (N=37)	29 12 (32%)	69 24 (65%)	98 28 (76%)
EU-Avastin® (N=37)	36 19 (51%)	63 25 (68%)	99 29 (78%)
Total (N=111)	97 48 (43%)	216 80 (72%)	313 90 (81%)

E = the # of TEAEs; N = the # of subjects exposed to the treatment; n = the # of subjects that experienced the TEAEs; % is calculated as (n/N)*100

* There were no Grade 3 (severe) or higher grade TEAEs

Adverse events that were assessed as 'possible', 'probable' or 'definite' were considered to be related to the study treatment whereas AEs that were assessed as 'unrelated' or 'unlikely' were considered not to be related to the study treatment.

Source: Listing 16.2.6-1

The most common related TEAEs by PT reported by ≥5% of the subjects were headache (16%; 16% in the MYL-1402O group, 11% in the US-Avastin group and 22% in the EU-Avastin group), diarrhea (5%; 3% in the MYL-1402O group, 11% in the US-Avastin group and 3% in the EU-Avastin group),

abdominal pain (5%; 3% in the MYL-1402O group, 3% in the US-Avastin group and 8% in the EU-Avastin group), and frequent bowel movements (5%; 3% in the MYL-1402O group, 5% in the US-Avastin group and 5% in the EU-Avastin group), all of them being consistent with the SmPC of Avastin except for frequent bowel movements, which however belong to the frequently affected SOC "Gastrointestinal disorders".

Overall, the proportion of patients experiencing TEAEs is deemed comparable between the three treatment arms; no clinically meaningful differences were noticed. No new safety concerns came up. Also the number of subjects with TEAEs as per SOC and PT are largely similar and do not indicate clinically relevant differences in safety between MYL-1402O, EU-Avastin and US-Avastin administered as a single dose of 1 mg/kg iv to healthy subjects.

Phase III NSCLC study

In the Phase III pivotal study in nsNSCLC patients, a total of 605 patients (91.1%) reported 3679 TEAEs at any time after the first dose of the IMP during the overall study period. The overall number of patients experiencing TEAEs in the Phase III study is similar between both treatment groups (n= 306 [91.3%] in the MYL-1402O arm and 90.9% [299] in the EU-Avastin arm). The number of TEAEs reported is, however, higher in the MYL-1402O group (1918 TEAEs), compared to the EU-Avastin group (1761 TEAEs). The overall incidence of TEAEs was markedly lower in Period 2 than in Period 1 (57.1% vs 91.1%).

For Period 2, the incidence of TEAE was numerically higher in the Avastin arm (n=122 patients [61.3] vs n=106 [53.0%]). However, the overall number of events was numerically higher in the MYL-1402 arm (328 events) than in the Avastin arm (319 events). It is acknowledged that overall those numerical imbalances are considered not of clinical relevance, against the background that for the categories treatment-related TEAE, Grade ≥3 TEAEs, SAE, treatment-related SAE, and TEAE leading to discontinuation, and treatment-related TEAE leading to discontinuation the incidences were comparable between the treatment arms in the monotherapy period.

Table 43. Overall incidence of treatment-emergent adverse events: safety population

Category	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)	Total (N=664) n (%)
Number of Patients With			
Any TEAE	306 (91.3)	299 (90.9)	605 (91.1)
Any IMP-Related TEAE	120 (35.8)	115 (35.0)	235 (35.4)
Any Serious TEAE	52 (15.5)	47 (14.3)	99 (14.9)
Any IMP-Related Serious TEAE	17 (5.1)	22 (6.7)	39 (5.9)
Any TEAE Leading to Treatment Discontinuation	30 (9.0)	22 (6.7)	52 (7.8)
Any IMP-Related TEAE Leading to Treatment Discontinuation	13 (3.9)	13 (4.0)	26 (3.9)
Any TEAE Leading to Death	21 (6.3)	13 (4.0)	34 (5.1)
Any IMP-Related TEAE Leading to Death	7 (2.1)	4 (1.2)	11 (1.7)

TEAE = Treatment-emergent adverse event. IMP=Investigational medicinal product
Source Data: Study MYL-1402O-3001 CSR Listing 16.2.7.1.1; Table 14.3.1.1

Table 44. TEAEs by severity in Period 2: safety set

Severity of TEAE	MYL-1402O (N=200)		Avastin® (N=199)		Total (N=399)	
	n (%)	No of events	n (%)	No of events	n (%)	No of events
Any TEAE	106 (53.0)	328	122 (61.3)	319	228 (57.1)	647
Grade 1-2	88 (44.0)	309	100 (50.3)	291	188 (47.1)	600
Grade 3-4	16 (8.0)	17	22 (11.1)	28	38 (9.5)	45
Grade 5	2 (1.0)	2	0	0	2 (0.5)	2
Any Imp-Related TEAE	44 (22.0)	105	43 (21.6)	84	87 (21.8)	189
Any Serious TEAE	5 (2.5)	5	5 (2.5)	5	10 (2.5)	10
Any IMP-Related Serious TEAE	2 (1.0)	2	2 (1.0)	2	4 (1.0)	4
Any TEAE Leading to Treatment Discontinuation	4 (2.0)	4	4 (2.0)	4	8 (2.0)	8
Any Imp-Related TEAE Leading to Treatment Discontinuation	2 (1.0)	2	3 (1.5)	3	5 (1.3)	5
Any TEAE Leading to Death	2 (1.0)	2	0	0	2 (0.5)	2
Any Imp-Related TEAE Leading to Death	1 (0.5)	1	0	0	1 (0.3)	1

Period 2 is defined as from the date of first dose of monotherapy to the end of Week 42. Source Data: Table13; Table 14; Table 15; Table 16; Table 17; Table 18; Table 19; Table 20; Table 25; Table 26 of Appendix II MYL-1402O-3001 Post CSR Week 42

A higher number of fatal TEAEs occurred in the MYL-1402O group compared to the EU-Avastin group. Please refer to Section "SAE and deaths" for further assessment.

Table 45. Treatment-emergent adverse events by severity: safety set

Severity	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)	Total (N=664) n (%)
Total Number of TEAEs	1918	1761	3679
Number of Patients With At Least One TEAE	306 (91.3)	299 (90.9)	605 (91.1)
Grade 1-2	201 (60.0)	196 (59.6)	397 (59.8)
Grade 3-4	84 (25.1)	90 (27.4)	174 (26.2)
Grade 5	21 (6.3)	13 (4.0)	34 (5.1)

The total number of AEs counts all treatment-emergent AEs for patients. At each level of patient summarization, a patient is counted once for the most severe event if the patient reported one or more events. If the severity of an AE is missing, the AE is included for summary at the level of System Organ Class or Preferred Term. Adverse Events were coded using MedDRA, Version 22.0.
Source Data: Listing 16.2.7.1.1, 16.2.7.1.2; Table 14.3.1.3

The most frequently reported TEAEs by SOC were Skin and Subcutaneous Tissue Disorders, reported in 326 (49.1%) patients, Blood and Lymphatic System Disorders reported in 316 (47.4%) patients, Nervous System Disorders reported in 219 (33.0%) patients and Gastrointestinal Disorders reported in 210 (31.6%) patients.

The most frequently occurring TEAEs at PT level were alopecia (MYL-1402O, 148 [44.2%] vs Avastin, 168 [51.1%] patients), followed by anaemia (MYL-1402O, 91 [27.2%] vs Avastin, 77 [23.4 %] patients) and thrombocytopenia (MYL-1402O, 91 [27.2%]. vs Avastin, 77 [23.4%] patients), all of which were expected AEs in patients receiving chemotherapy.

When focussing on the TEAE (by SOC and PT) occurring more frequent in the MYL-1402O arm than in the Avastin arm, the imbalances between the treatment arms were observed for the SOCs General disorders and administration site conditions, Gastrointestinal disorders, and Metabolism and Nutrition Disorders during Period 1. However, there was no clear pattern or clustering by any SOC/PT detectable.

During Period 2 (i.e. monotherapy with bevacizumab), no distinct differences between the treatment arms with regard to TEAE incidences sorted by SOCs could be detected.

Table 46. Treatment-emergent adverse events (≥3% of the patients by PT) by system organ class and preferred term: safety set

System Organ Class Preferred Term	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)	Total (N=664) n (%)
Total Number of TEAEs	1918	1761	3679
Number of Patients with At Least One TEAE	306 (91.3)	299 (90.9)	605 (91.1)
Skin and Subcutaneous Tissue Disorders	154 (46.0)	172 (52.3)	326 (49.1)
Alopecia	148 (44.2)	168 (51.1)	316 (47.6)
Blood and Lymphatic System Disorders	163 (48.7)	152 (46.2)	315 (47.4)
Anaemia	108 (32.2)	99 (30.1)	207 (31.2)
Thrombocytopenia	91 (27.2)	77 (23.4)	168 (25.3)
Neutropenia	60 (17.9)	70 (21.3)	130 (19.6)
Leukopenia	34 (10.1)	36 (10.9)	70 (10.5)
Nervous System Disorders	113 (33.7)	106 (32.2)	219 (33.0)
Peripheral Sensory Neuropathy	67 (20.0)	61 (18.5)	128 (19.3)
Hypoaesthesia	12 (3.6)	18 (5.5)	30 (4.5)
Headache	14 (4.2)	11 (3.3)	25 (3.8)
Gastrointestinal Disorders	117 (34.9)	93 (28.3)	210 (31.6)
Nausea	52 (15.5)	48 (14.6)	100 (15.1)
Vomiting	51 (15.2)	36 (10.9)	87 (13.1)
Diarrhoea	43 (12.8)	31 (9.4)	74 (11.1)
Stomatitis	22 (6.6)	6 (1.8)	28 (4.2)
Constipation	11 (3.3)	6 (1.8)	17 (2.6)
General Disorders and Administration Site Conditions	79 (23.6)	69 (21.0)	148 (22.3)
Asthenia	45 (13.4)	25 (7.6)	70 (10.5)
Pyrexia	29 (8.7)	19 (5.8)	48 (7.2)
Fatigue	23 (6.9)	22 (6.7)	45 (6.8)
Pain	13 (3.9)	10 (3.0)	23 (3.5)
Investigations	68 (20.3)	63 (19.1)	131 (19.7)
Alanine Aminotransferase Increased	16 (4.8)	21 (6.4)	37 (5.6)
Aspartate Aminotransferase Increased	15 (4.5)	14 (4.3)	29 (4.4)
Weight Decreased	17 (5.1)	4 (1.2)	21 (3.2)
Blood Alkaline Phosphatase Increased	12 (3.6)	7 (2.1)	19 (2.9)
Respiratory, Thoracic and Mediastinal Disorders	55 (16.4)	64 (19.5)	119 (17.9)
Dyspnoea	22 (6.6)	13 (4.0)	35 (5.3)
Cough	8 (2.4)	15 (4.6)	23 (3.5)
Epistaxis	5 (1.5)	17 (5.2)	22 (3.3)
Musculoskeletal and Connective Tissue Disorders	46 (13.7)	55 (16.7)	101 (15.2)
Arthralgia	15 (4.5)	17 (5.2)	32 (4.8)
Pain in Extremity	12 (3.6)	9 (2.7)	21 (3.2)
Myalgia	5 (1.5)	12 (3.6)	17 (2.6)
Metabolism and Nutrition Disorders	56 (16.7)	36 (10.9)	92 (13.9)
Decreased Appetite	35 (10.4)	27 (8.2)	62 (9.3)
Vascular Disorders	22 (6.6)	17 (5.2)	39 (5.9)
Hypertension	12 (3.6)	11 (3.3)	23 (3.5)

The total number of AEs counts all treatment-emergent AEs for patients. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Adverse Events were coded using MedDRA, Version 22.0.

TEAEs related to study treatment were similar between the two treatment groups with regard to the proportion of patients who experienced these events (MYL-1402O n=120 [35.8%], Avastin n=115 [35.0%] and the number of events reported (377 in the MYL-1402O arm versus 382 in the Avastin arm).

Table 47. Related TEAEs (in ≥3 patients by PT) – safety set

System Organ Class Preferred Term	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)	Total (N=664) n (%)
Total Number of Related TEAEs	377	382	759
Number of Patients with At Least One Related TEAEs	120 (35.8)	115 (35.0)	235 (35.4)
Blood and Lymphatic System Disorders	45 (13.4)	39 (11.9)	84 (12.7)
Anaemia	22 (6.6)	22 (6.7)	44 (6.6)
Thrombocytopenia	21 (6.3)	18 (5.5)	39 (5.9)
Neutropenia	15 (4.5)	16 (4.9)	31 (4.7)
Leukopenia	10 (3.0)	13 (4.0)	23 (3.5)
Febrile Neutropenia	0	3 (0.9)	3 (0.5)
Gastrointestinal Disorders	37 (11.0)	28 (8.5)	65 (9.8)
Diarrhoea	20 (6.0)	12 (3.6)	32 (4.8)
Vomiting	8 (2.4)	6 (1.8)	14 (2.1)
Nausea	2 (0.6)	8 (2.4)	10 (1.5)
Stomatitis	5 (1.5)	2 (0.6)	7 (1.1)
Constipation	3 (0.9)	3 (0.9)	6 (0.9)
Nervous System Disorders	29 (8.7)	23 (7.0)	52 (7.8)
Peripheral Sensory Neuropathy	10 (3.0)	10 (3.0)	20 (3.0)
Headache	12 (3.6)	6 (1.8)	18 (2.7)
Hypoaesthesia	4 (1.2)	3 (0.9)	7 (1.1)
Paraesthesia	1 (0.3)	3 (0.9)	4 (0.6)
Respiratory, Thoracic and Mediastinal Disorders	13 (3.9)	27 (8.2)	40 (6.0)
Epistaxis	5 (1.5)	15 (4.6)	20 (3.0)
Pulmonary Embolism	4 (1.2)	4 (1.2)	8 (1.2)
Dyspnoea	5 (1.5)	2 (0.6)	7 (1.1)
Haemoptysis	0	4 (1.2)	4 (0.6)
General disorders and Administration Site Conditions	15 (4.5)	21 (6.4)	36 (5.4)
Asthenia	8 (2.4)	6 (1.8)	14 (2.1)
Fatigue	3 (0.9)	4 (1.2)	7 (1.1)
Pain	2 (0.6)	4 (1.2)	6 (0.9)
Pyrexia	3 (0.9)	3 (0.9)	6 (0.9)
Investigations	13 (3.9)	12 (3.6)	25 (3.8)
Alanine Aminotransferase Increased	3 (0.9)	2 (0.6)	5 (0.8)
Aspartate Aminotransferase Increased	2 (0.6)	3 (0.9)	5 (0.8)
Neutrophil Count Decreased	0	3 (0.9)	3 (0.5)
Weight Decreased	3 (0.9)	0	3 (0.5)
Vascular Disorders	15 (4.5)	9 (2.7)	24 (3.6)
Hypertension	8 (2.4)	7 (2.1)	15 (2.3)
Deep Vein Thrombosis	3 (0.9)	1 (0.3)	4 (0.6)
Skin and Subcutaneous Tissue Disorders	6 (1.8)	15 (4.6)	21 (3.2)
Alopecia	5 (1.5)	12 (3.6)	17 (2.6)
Musculoskeletal and Connective Tissue Disorders	13 (3.9)	7 (2.1)	20 (3.0)
Muscular Weakness	5 (1.5)	2 (0.6)	7 (1.1)
Myalgia	3 (0.9)	1 (0.3)	4 (0.6)
Pain in Extremity	3 (0.9)	1 (0.3)	4 (0.6)
Arthralgia	3 (0.9)	0	3 (0.5)
Metabolism and Nutrition Disorders	7 (2.1)	6 (1.8)	13 (2.0)
Decreased Appetite	5 (1.5)	5 (1.5)	10 (1.5)

TEAE = Treatment-Emergent Adverse Events; The total number of AEs counts all treatment-emergent AEs for patients. Related is defined as a relationship of Possible, Probable, or Definite. If the relationship of an AE is

There were minor differences in the related TEAEs by PT: diarrhea occurred in 20 (6.0%) patients in the MYL-1402O arm compared with 12 (3.6%) patients in Avastin arm, and epistaxis occurred in 5 (1.5%) patients in MYL-1402O arm compared with 15 (4.6%) patients in Avastin arm. Both diarrhea and epistaxis are commonly reported known ADRs with bevacizumab. The isolated numerical differences in incidences between the treatment groups are not considered to be of clinical relevance.

A total of 52 (7.8%) patients discontinued treatment due to TEAE; 30 (9.0%) and 22 (6.7%) in the MYL-1402O and Avastin arms, respectively, during Period 1. The number of patients who reported treatment-related TEAE leading to treatment discontinuation was comparable in both arms, 13 (3.9%) in MYL-1402O arm versus 13 (4.0%) in Avastin arm. In Period 2, there were 2 patients in the MYL-

1402O group (1.0%) and 3 patients in the Avastin group (1.5%) who discontinued treatment due to treatment-related TEAE.

Of note, for the MYL-1402O, there were 2 concerned events which are not considered "listed" for the known safety profile of bevacizumab, i.e. cardiorespiratory arrest and acute angle closure glaucoma. Based on the submitted narrative, one patient who experienced cardiorespiratory arrest came from India and was 57 years old. He received only one dose of study drug (720 mg), paclitaxel (259 mg) and carboplatin (702 mg). On Day 4, he had severe bone marrow toxicity (leukopenia, thrombocytopenia) and there were likely multiple contributing factors (e.g. carboplatin dose was too high considering the patient weight of 49 kg, "late effects" from radiation). According to the Investigator, thrombocytopenia and leukopenia could have led to a cardiovascular accident leading to terminal cardiorespiratory arrest. Another patient who experienced angle closure glaucoma also came from India and was 51 years old. This patient also received only one dose of study drug (660 mg), paclitaxel (229 mg) and carboplatin (612 mg). On Day 7, she was diagnosed with conjunctivitis (grade 2) and on Day 9 she experienced blurring of vision of the left eye, redness and pain in both eyes. The eye examination showed acute angle closure glaucoma with conjunctivitis (grade 3) and CT scan showed brain lesions, therefore, the patient was discontinued from the study. In view of the provided information, no impact on safety of MYL-1402O and related conclusions on safety profile can be detected.

The number of patients with AESI by SMQ was comparable between the treatment arms (16.1% in the MYL-1402O vs 20.1% in the EU-Avastin arm) in Period 1. The number of patients with Grade ≥3 AESI and serious AESI was also comparable between the treatment arms.

There were differences between the study arms with regard to the AESIs epistaxis and haemoptysis: a lower number of patients experienced epistaxis as an AESI in the MYL-1402O arm (5 [1.5%]) compared with the Avastin arm (17 [5.2%]), as well as haemoptysis (2 [0.6%]) in the MYL-1402O arm and 6 [1.8%] in the Avastin arm). Most of the reported AEIs were of Grade 1-2 only.

Table 48. Adverse events of interest by SMQ and PTs – safety set reported in ≥ 2 patients by PT

SMQ Preferred Term	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)	Total (N=664) n (%)
Number of Patients With At Least One Event	54 (16.1)	66 (20.1)	120 (18.1)
Haemorrhage Terms (excl Laboratory Terms) (SMQ)	13 (3.9)	29 (8.8)	42 (6.3)
Epistaxis	5 (1.5)	17 (5.2)	22 (3.3)
Haemoptysis	2 (0.6)	6 (1.8)	8 (1.2)
Pulmonary Haemorrhage	3 (0.9)	3 (0.9)	6 (0.9)
Hypertension (SMQ)	15 (4.5)	11 (3.3)	26 (3.9)
Hypertension	12 (3.6)	11 (3.3)	23 (3.5)
Essential Hypertension	2 (0.6)	0	2 (0.3)
Hypertensive Crisis	2 (0.6)	0	2 (0.3)
Embolic and Thrombotic Events, Venous (SMQ)	8 (2.4)	9 (2.7)	17 (2.6)
Pulmonary Embolism	5 (1.5)	5 (1.5)	10 (1.5)
Deep Vein Thrombosis	3 (0.9)	3 (0.9)	6 (0.9)
Proteinuria (SMQ)	5 (1.5)	9 (2.7)	14 (2.1)
Proteinuria	5 (1.5)	9 (2.7)	14 (2.1)
Hypersensitivity (SMQ)	8 (2.4)	5 (1.5)	13 (2.0)
Dermatitis Allergic	5 (1.5)	1 (0.3)	6 (0.9)
Drug Hypersensitivity	2 (0.6)	0	2 (0.3)
Osteonecrosis (SMQ)	3 (0.9)	5 (1.5)	8 (1.2)
Bone Pain	3 (0.9)	4 (1.2)	7 (1.1)
Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous (SMQ)	4 (1.2)	1 (0.3)	5 (0.8)
Cerebrovascular Accident	2 (0.6)	1 (0.3)	3 (0.5)
Cardiac Failure (SMQ)	2 (0.6)	2 (0.6)	4 (0.6)
Oedema Peripheral	2 (0.6)	1 (0.3)	3 (0.5)
Gastrointestinal Perforation (SMQ)	2 (0.6)	2 (0.6)	4 (0.6)
Peritonitis	0	2 (0.6)	2 (0.3)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
Adverse Events were coded using MedDRA, Version 22.0.
Source Data: Study MYL-1402O-3001 CSR Listing 16.2.7.1.1, 16.2.7.1.2; Table 14.3.1.9

All Grade ≥3 AEIs, including the AESI haemoptysis, were comparable between the treatment arms.

Table 49. Grade ≥3 adverse events of interest by SMQ and PTs for safety set

SMQ ..Preferred Term	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)	Total (N=664) n (%)
Number of Patients With At Least One Event	23 (6.9)	23 (7.0)	46 (6.9)
Embolic and Thrombotic Events, Venous (SMQ)	4 (1.2)	7 (2.1)	11 (1.7)
Pulmonary Embolism	4 (1.2)	5 (1.5)	9 (1.4)
Deep Vein Thrombosis	1 (0.3)	1 (0.3)	2 (0.3)
Pulmonary Thrombosis	0	1 (0.3)	1 (0.2)
Haemorrhage Terms (excl Laboratory Terms) (SMQ)	5 (1.5)	6 (1.8)	11 (1.7)
Pulmonary Haemorrhage	3 (0.9)	3 (0.9)	6 (0.9)
Haemoptysis	1 (0.3)	1 (0.3)	2 (0.3)
Cystitis Haemorrhagic	0	1 (0.3)	1 (0.2)
Gastric Ulcer Haemorrhage	1 (0.3)	0	1 (0.2)
Peptic Ulcer Haemorrhage	0	1 (0.3)	1 (0.2)
Hypertension (SMQ)	8 (2.4)	2 (0.6)	10 (1.5)
Hypertension	5 (1.5)	2 (0.6)	7 (1.1)
Hypertensive Crisis	2 (0.6)	0	2 (0.3)
Essential Hypertension	1 (0.3)	0	1 (0.2)
Gastrointestinal Perforation (SMQ)	2 (0.6)	2 (0.6)	4 (0.6)
Peritonitis	0	2 (0.6)	2 (0.3)
Gastric Perforation	1 (0.3)	0	1 (0.2)
Ileal Perforation	0	1 (0.3)	1 (0.2)
Large Intestine Perforation	0	1 (0.3)	1 (0.2)
Peptic Ulcer Perforation	0	1 (0.3)	1 (0.2)
Rectal Abscess	1 (0.3)	0	1 (0.2)
Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous (SMQ)	2 (0.6)	1 (0.3)	3 (0.5)
Cerebrovascular Accident	2 (0.6)	1 (0.3)	3 (0.5)
Cardiac Failure (SMQ)	1 (0.3)	1 (0.3)	2 (0.3)
Cardiac Failure Acute	0	1 (0.3)	1 (0.2)
Pulmonary Oedema	1 (0.3)	0	1 (0.2)
Hypersensitivity (SMQ)	1 (0.3)	1 (0.3)	2 (0.3)
Anaphylactic Reaction	0	1 (0.3)	1 (0.2)
Hypersensitivity	1 (0.3)	0	1 (0.2)
Osteonecrosis (SMQ)	1 (0.3)	1 (0.3)	2 (0.3)
Bone Pain	1 (0.3)	1 (0.3)	2 (0.3)
Interstitial Lung Disease (SMQ)	0	1 (0.3)	1 (0.2)
Acute Respiratory Distress Syndrome	0	1 (0.3)	1 (0.2)
Proteinuria (SMQ)	0	1 (0.3)	1 (0.2)
Proteinuria	0	1 (0.3)	1 (0.2)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
Adverse Events were coded using MedDRA, Version 22.0.
Source Data: Study MYL-1402O-3001 CSR Listing 16.2.7.1.1, 16.2.7.1.2; Table 14.3.1.11

Also the number of patients with serious AESIs by SMQ was comparable between the study arms; 17 (5.1%) in MYL-1402O arm and 19 (5.8%) in Avastin arm All serious AESIs, including haemoptysis, were comparable between the treatment arms.

In Period 2, the incidence of AESI was lower compared to Period 1 (overall n=37 vs n=120 subjects with at least one event). Importantly, the AESI incidence was comparable between the treatment arms in the monotherapy period (n=21 [10.5%] in MYL-1402O vs n=16 [8.0%] in Avastin arm), also with regard to Grade ≥3 AESI (n=4 [2.0%] in the MYL-1402O vs n=5 [2.5%] in Avastin arm).

According to the Avastin SmPC, the incidence of hypersensitivity reactions and infusion reactions is reported to be common in clinical trials where Avastin was given in combination with chemotherapy (up to 5% incidence in bevacizmab-treated patients). The applicant clarified that infusion-related reactions were captured under the MedDRA SMQ of Hypersensitivity, which had been defined as AESI for study MYL-1402O 3001. Overall, up to Week 42, the incidence of Hypersensitivity AESI was low and comparable between treatment arms (reported in overall n=15 [2.3%] of patients, n=9 in MYL-1402O and n=6 in Avastin arm).

Most of the Hypersensitivity AESI occurred during Period 1 (in n=13 patients [2.0%]). Here, 8 events were reported for the MYL-1402O arm and 5 events for the Avastin arm. Most events (n=6) were captured under the PT Dermatitis allergic. Only 1 PT of Hypersensitivity was reported in the MYL-1402O arm, and 1 PT of Anaphylactic reaction was reported in the Avastin arm; both were Grade ≥3. During Period 2, Hypersensitivity AESI occurred only in 2 patients (1 PT of Dermatitis allergic in the MYL-1402O arm and 1 PT of Swelling face in the Avastin arm).

Supportive Phase III mCRC study

In the supportive Phase III study in mCRC patients, the overall incidence of TEAEs was slightly higher in the Avastin arm as compared to Bmab-100 arm. 54 (79.41%) patients in the Bmab-100 arm and 60 (89.55%) patients in the Avastin arm reported at least one TEAE. Most of the TEAEs were Grade 1 or Grade 2 in severity.

Table 50. Summary of patients with TEAEs by treatment group

Description	Bmab-100 (N=68) n (%)	Avastin (N=67) n (%)
Number of patients with at least one TEAE	54 (79.41%)	60 (89.55%)
Number of patients with at least one TEAE related to Bmab-100/Avastin	6 (8.82%)	12 (17.91%)
No of patients with at least one Severe/Grade 3 or above TEAE	18 (26.47%)	18 (26.87%)
Number of patients with at least one Severe/Grade 3 or above TEAE related to Bmab- 100/Avastin	3 (4.41%)	2 (2.99%)
Number of patients with at least one Treatment Emergent SAE	16 (23.53%)	15 (22.39%)
Number of patients with at least one Treatment Emergent SAE related to Bmab-100/Avastin	2 (2.94%)	3 (4.48%)
Number of patients with dose temporarily stopped at least once because of a TEAE	11 (16.18%)	11 (16.42%)
Number of patients with TEAE related to the study drug leading to temporarily stopping of the study drug	0 (0.00%)	1 (1.49%)
Number of patients with dose permanently stopped because of a TEAE	7 (10.29%)	2 (2.99%)
Number of patients with TEAE related to the study drug leading to permanently stopping the study drug	1 (1.47%)	2 (2.99%)
Number of patients with Fatal TEAEs	5 (7.35%)	8 (11.94%)
Number of patients with Fatal AEs related to study drug	1 (1.47%)	1 (1.49%)

Note 1: TEAE are defined as any AE which started or deteriorated at or after first dose of study treatment
Note 2: n=number of subjects with AEs
Note 3: System Organ Class and Preferred Term coded as per MedDRA version 17.1
Reference: BM100-CC-03-1401 CSR Table number 14.3.1.1 (b)

Table 51. Overview of treatment emergent adverse events by severity

Severity	Bmab-100 (N=68) [n (%)]	e	Avastin (N=67) [n (%)]	e
Grade 1 – Mild	35 (51.47%)	107	50 (74.63%)	131
Grade 2 - Moderate	31 (45.59%)	62	30 (44.78%)	70
Grade 3 - Severe	13 (19.12%)	19	14 (20.90%)	26
Grade 4 - Life threatening	1 (1.47%)	1	1 (1.49%)	1
Grade 5 – Death	5[a] (7.35%)	6	7 (10.45%)	7[b]

Most of the TEAEs were considered not related to study drug and instead related to chemotherapy (XELOX) or underlying disease or progression. Six (8.82%) patients in the Bmab-100 arm and 12 (17.91%) patients in the Avastin arm had at least 1 TEAE related to Bmab-100/Avastin.

Overall, the most commonly reported TEAE in the study was diarrhea, reported in 11 (16.17%) patients (17 events, including one bacterial diarrhea) in the Bmab-100 arm and 22 (32.84%) patients (35 events) in the Avastin arm. The other frequently reported TEAEs (> 10% incidence) were palmar-plantar erythrodysesthesia syndrome, vomiting and asthenia.

In the CSR for study Bm100-CC-03-I-01, it is stated that diarrhoea was reported in 11 patients (16.17%) in the Bmab-100 arm (16 events). However, it is depicted that 10 patients (14.71%) experienced 16 events of diarrhoea. The applicant has clarified that, overall, there were 17 events of diarrhoea occurring in study BM100-CC-03-I-01. However, one event of bacterial diarrhea was not included, since this table presented TEAE's occurring in >5% by treatment group. Therefore, the event of bacterial diarrhoea, captured under the SOC 'Infection and infestation' instead of 'Gastrointestinal disorders', fell under the cut-off of 5% and thus was not included.

The most frequently reported drug-related TEAE in the study was anemia reported by 4 (5.88%) patients in the Bmab-100 arm and 3 (4.48%) patients Avastin arm.

Altogether, across both treatment groups, the incidences, types and severities of TEAE are considered comparable and thus supportive for the MYL-1402O MAA.

Serious adverse events and deaths

Phase I PK study

There were no serious AEs or deaths reported in the study.

Phase III NSCLC study

From the data provided, it seems that across both treatment groups, the incidences and types the SAEs were generally comparable, with no clinically meaningful differences noticed between both treatment groups.

Overall, 142 SAEs were reported, all of which were treatment-emergent (i.e. serious TEAEs). The proportion of patients experiencing SAEs was comparable between both treatment groups. Hence, in the MYL-1402O treatment arm, 75 SAEs were reported in 52/335 (15.5%) subjects and in the EU-Avastin arm, 67 SAEs were reported in 47/329 (14.3%) subjects. However, SAE with fatal outcome were more frequent in the MYL-1402O arm (n=22) compared to the Avastin arm (n=13).

Most of the SAE (82 out of 142 events) recovered or resolved – 40 in the MYL-1402O arm and 42 in the Avastin arm. The majority of those SAE resolved without any action taken. However, 10 SAE required study drug interruption (8 in the MYL-1402O arm vs 2 in the Avastin arm), 14 SAE resulted study drug discontinuation (7 in each arm). 8 SAE recovered with sequelae (3 in the MYL-1402O arm vs 5 in the Avastin arm). 17 SAE were reported as not recovered or resolved at the end of Week 42 (10 in the MYL-1402O arm and 7 in the Avastin arm) - 14 patients died (due to another SAE or disease progression; 10 vs 4), 3 SAE in the Avastin arm were reported as ongoing at last follow up (events of Grade 3 pulmonary thrombosis, Grade 4 pulmonary embolism, and Grade 3 anaemia).

In addition, there were another 17 SAE (9 in the MYL-1402O arm versus 8 in the Avastin arm) in 13 patients (5 vs 8) that occurred during Period 1 after the DCO for the Week 18 CSR. 5 of those SAE in overall 3 patients (2 in MYL-1402O arm and 1 in Avastin arm) had fatal outcome. 6 SAE resolved without any action taken. 3 SAE required study drug interruption. 1 SAE recovered with sequelae, and 2 SAE were reported as not recovered (1 leading to treatment discontinuation, 1 in which death was reported).

For Period 2, a total of 10 SAE was reported, 5 in each study arm. 2 SAE in the MYL-1402O arm (one of cardiac arrest and one of pulmonary haemorrhage, both assessed as treatment-related) had fatal outcome. The majority of 7 events recovered during Period 2. 2 SAE, one in each treatment arm, required study drug interruption. 3 SAEs (1 in MYL-1402O arm, 2 in Avastin arm) resulted in permanent discontinuation of treatment. 1 event was reported as not recovered in the Week 42 CSR. However, this event recovered after the DCO for the CSR.

Overall, a distinctly higher incidence of SAE was observed during Period 1 (i.e. bevacizumab in combination with ChT) than during the monotherapy period with bevacizumab treatment alone (142 [+ 17] vs. 10 events). Here, the applicant discusses underlying comorbidities as well as ChT-induced toxicity during the combination therapy period as possible explanations. This is acknowledged.

Importantly, during the monotherapy period, SAE incidence was low and similar for MYL-1402O and for Avastin.

The most frequently affected SOCs for SAEs were Respiratory, Thoracic and Mediastinal Disorders (5.7% in the MYL-1402O and 4.6% in the EU-Avastin arm), followed by Blood and Lymphatic System Disorders (5.1% and 4.0%, respectively, and Infections and Infestations (3.9% and 2.7%, respectively). The most frequently occurring SAEs at the PT level were Febrile Neutropenia (1.8% and 1.5%, respectively), Thrombocytopenia (1.5% in both treatment arms), and Pulmonary Embolism (1.2% in both treatment arms). This is generally in line with the known safety profile of bevacizumab.

Table 52. Serious treatment-emergent adverse events (≥2 patients per PT) by SOC and PT – safety set

System Organ Class Preferred Term	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)	Total (N=664) n (%)
Total Number of Serious TEAEs	75	67	142
Number of Patients with At Least One Serious TEAEs	52 (15.5)	47 (14.3)	99 (4.9)
Respiratory, Thoracic and Mediastinal Disorders	19 (5.7)	15 (4.6)	34 (5.1)
Pulmonary Embolism	4 (1.2)	4 (1.2)	8 (1.2)
Pulmonary Haemorrhage	3 (0.9)	3 (0.9)	6 (0.9)
Dyspnoea	4 (1.2)	1 (0.3)	5 (0.8)
Haemoptysis	1 (0.3)	2 (0.6)	3 (0.5)
Pneumothorax	2 (0.6)	1 (0.3)	3 (0.5)
Pleural Effusion	2 (0.6)	0	2 (0.3)
Blood and Lymphatic System Disorders	17 (5.1)	13 (4.0)	30 (4.5)
Febrile Neutropenia	6 (1.8)	5 (1.5)	11 (1.7)
Thrombocytopenia	5 (1.5)	5 (1.5)	10 (1.5)
Anaemia	5 (1.5)	1 (0.3)	6 (0.9)
Neutropenia	4 (1.2)	2 (0.6)	6 (0.9)
Leukopenia	2 (0.6)	1 (0.3)	3 (0.5)
Infections and Infestations	13 (3.9)	9 (2.7)	22 (3.3)
Gastroenteritis	3 (0.9)	0	3 (0.5)
Sepsis	2 (0.6)	1 (0.3)	3 (0.5)
Peritonitis	0	2 (0.6)	2 (0.3)
Pneumonia	2 (0.6)	0	2 (0.3)
Gastrointestinal Disorders	4 (1.2)	8 (2.4)	12 (1.8)
Diarrhoea	1 (0.3)	3 (0.9)	4 (0.6)
Vomiting	2 (0.6)	0	2 (0.3)
General Disorders and Administration Site Conditions	1 (0.3)	6 (1.8)	7 (1.1)
Pyrexia	1 (0.3)	3 (0.9)	4 (0.6)
Vascular Disorders	3 (0.9)	2 (0.6)	5 (0.8)
Hypertensive Crisis	2 (0.6)	0	2 (0.3)
Nervous System Disorders	2 (0.6)	1 (0.3)	3 (0.5)
Cerebrovascular Accident	2 (0.6)	1 (0.3)	3 (0.5)

The total number of SAEs counts all treatment-emergent SAEs for patients. At each level of patient summarization, a patient is counted once if the patient reported one or more events. TEAE = Treatment emergent adverse event. Adverse Events were coded using MedDRA, Version 22.0; Source Data: Study MYL-1402O-3001 CSR Listing 16.2.7.2; Table 14.3.1.5

With regard to treatment-related SAEs, there was a higher number of patients in the Avastin arm (n=22) than in the MYL-1402O arm (n=17) during Period 1 reporting a higher number of treatment-related SAEs (30 vs 21 events). The most frequently reported treatment-related SAEs by PT were pulmonary embolism (n=4 in each treatment arm), thrombocytopenia (n=3 in the Avastin arm, n=1 for MYL-1402O), and febrile neutropenia (n=3 in the Avastin arm).

In Period 2, the number of patients experiencing treatment-related SAE was similar between the treatment groups (n=2 patients per treatment arm). Furthermore, the incidence of related SAE was overall low and similar (n=2 events per group). Here, the following events (by PT) were reported: coronary artery disease, myocardial infarction, pulmonary haemorrhage, and hypertension.

Overall, there were 183 deaths reported during the study, with 101 deaths in the MYL-1402O arm and 82 deaths in the Avastin arm.

Importantly, the imbalance with regard to the number of deaths remained rather stable between the treatment arms throughout the study. The numerical difference in deaths between the treatment arms increased slightly from n=16 (Week 18 CSR, with 50 versus 34 deaths for the MYL-1402O arm vs Avastin) to n=19 (Week 42 CSR, with 101 versus 82 deaths for MYL-1402O vs Avastin).

Table 53. Overview of deaths including Period 1, Period 2 and survival follow up through week 42-safety set

Study Phase	Period 1 (Induction)			Period 2 (Maintenance)			Treatment Period	Survival Follow up			Overall Deaths		
Treatment Arm	MYL-1402O N=335 n (%)	Avastin N=329 n (%)	Total N=664 n (%)	MYL-1402O N=200 n (%)	Avastin N=199 n (%)	Total N=399 n (%)	Total N=664 n (%)	MYL-1402O N=335 n (%)	Avastin N=329 n (%)	Total N=664 n (%)	MYL-1402O N=335 n (%)	Avastin N=329 n (%)	Total N=664 n (%)
Any cause of Death	**38 (11.3)**	**25 (7.6)**	**63 (9.5)**	**6 (3.0)**	**3 (1.5)**	**9 (2.6)**	**72 (10.8)**	**57 (17.0)**	**54 (16.4)**	**111 (16.7)**	**101 (30.1)**	**82 (24.9)**	**183 (27.6)**
Disease progression	10 (3.0)	10 (3.0)	20 (3.0)	4 (2.0)	2 (1.0)	6 (1.5)	26 (3.9)	43 (12.8)	44 (13.4)	87 (13.1)	57 (17.0)	56 (17.0)	113 (17.0)
TEAE	20 (6.0)	12 (3.6)	32 (4.8)	2 (1.0)	0	2 (0.5)	34 (5.1)	3 (0.9)	2 (0.6)	5 (0.8)	25 (7.5)	14 (4.3)	39 (5.9)
Other*	1 (0.3)	0	1 (0.1)	0	0	0	1 (0.2)	2 (0.6)	1 (0.3)	3 (0.5)	3 (0.9)	1 (0.3)	4 (0.6)
Unknown	7 (2.1)	3 (0.9)	10 (1.5)	0	1 (0.5)	1 (0.3)	11 (1.7)	9 (2.7)	7 (2.1)	16 (2.4)	16 (4.8)	11 (3.3)	27 (4.1)
IMP Related TEAEs	**7 (2.1)**	**[$]5 (1.5)**	**12 (1.8)**	**1 (0.5)**	**0**	**1 (0.3)**	**13 (2.0)**	**0**	**0**	**0**	**8 (2.4)**	**5 (1.5)**	**13 (2.0)**
Non cancer deaths (TEAE and unknown)	**27 (8.1)**	**15 (4.6)**	**42 (6.3)**	**2 (1.0)**	**1 (0.5)**	**3 (0.8)**	**45 (6.8)**	**12 (3.6)**	**9 (2.7)**	**21 (3.2)**	**41 (12.2)**	**25 (7.6)**	**66 (9.9)**

Source data: listing 16.2.7.4b
[$] Including TEAE Sepsis (Related to IMP) with fatal outcome in 1 patient (Avastin arm) during period 1 after data cut for week 18 CSR
* Other – In period 1, 1 patient in MYL-1402O died due to suspected clinical progression. During survival follow up in MYL-1402O arm. 1 patient died due to suspected disease progression and 1 patient due to suicide, 1 patients in Avastin arm died at home with dyspnoea as the only symptom reported at the time of death

The majority of the deaths was due to disease progression. Here, no imbalance was observed between the treatment arms (n=57 in the MYL-1402O arm vs n=56 in the Avastin arm)

The number of non-cancer related deaths (i.e. due to TEAE and unknown) was, however, higher in the MYL-1402O arm (n=41) than in the Avastin arm (n=25).

25 patients in the MYL-1402O arm compared to 14 patients in the Avastin arm experienced TEAE leading to death. However, most of these TEAE leading to death were not classified as treatment-related – only 8 deaths in the MYL-1402O arm and 5 deaths in the Avastin arm were associated with a treatment-related TEAE, most of them (n=11) occurred during Period 1. These drug related TEAEs which occurred in the MYL-1402O group were the following: pulmonary embolism (in 2 patients), pulmonary haemorrhage (in 2 patients), cardiorespiratory arrest, acute coronary syndrome, gastric perforation and cerebrovascular accident. With the exception of cardiorespiratory arrest and acute coronary syndrome, the reported events are listed in the product information for Avastin. In case of the event of acute coronary syndrome, the Investigator assessed this event as possibly related to study drug, paclitaxel and carboplatin. The patient received the only dose of study drug (690 mg), paclitaxel (254 mg) and carboplatin (480 mg) and died by Day 30. The immediate cause of death was assessed as lung cancer with metastases, acute coronary syndrome with severe left ventricular dysfunction as antecedent cause and hypertension as other significant condition contributing to the fatal outcome. The patient who experienced cardiorespiratory arrest received only one dose of study drug (720 mg), paclitaxel (259 mg) and carboplatin (702 mg). On Day 4, he had severe bone marrow toxicity (leukopenia, thrombocytopenia) and there were likely multiple contributing factors (e.g. carboplatin dose was too high considering the patient weight of 49 kg, "late effects" from radiation). According to the Investigator, thrombocytopenia and leukopenia could have led to a cardiovascular accident leading to terminal cardiorespiratory arrest.

During Period 2 (i.e. monotherapy with bevacizumab), only 1 treatment-related TEAE of pulmonary haemorrhage leading to death was reported in the MYL-1402O arm.

Since a significantly higher number of IMP-related TEAEs leading to death occurred during the combination therapy, it is acknowledged that this might be attributed to chemotherapy-induced toxicity rather than bevacizumab-induced toxicity alone.

This is supported by the fact that most of the reported Grade 5 TEAEs are known to occur in the setting of advanced NSCLC as well as with the combination of ChT and bevacizumab (e.g. pulmonary embolism, pulmonary hemorrhage, cardiorespiratory arrest, acute coronary syndrome, febrile neutropenia, gastric perforation, sepsis, cerebrovascular accident).

Furthermore, following a review on a case by case basis, no trend or significant safety-related concern with regard to the study drug could be identified.

Table 54. Treatment related TEAEs leading to death by SOC and PT in Period 1 – safety set

System Organ Class Preferred Term	MYL-1402O (n=335) n (%)	Avastin® (n=329) n (%)	Total (n=664) n (%)
Total Number of TEAEs Leading to Death	**7**	**4**	**11**
Number of Patients pith at Least one TEAE Leading to Death	**7 (2.1)**	**4 (1.2)**	**11 (1.7)**
Respiratory, Thoracic and Mediastinal Disorders	**3 (0.9)**	**2 (0.6)**	**5 (0.8)**
Pulmonary Embolism	2 (0.6)	0	2 (0.3)
Pulmonary Haemorrhage	1 (0.3)	1 (0.3)	2 (0.3)
Acute Respiratory Distress Syndrome	0	1 (0.3)	1 (0.2)
Cardiac Disorders	**2 (0.6)**	**0**	**2 (0.3)**
Acute Coronary Syndrome	1 (0.3)	0	1 (0.2)
Cardio-Respiratory Arrest	1 (0.3)	0	1 (0.2)
Blood and Lymphatic System Disorders	**0**	**1 (0.3)**	**1 (0.2)**
Febrile Neutropenia	0	1 (0.3)	1 (0.2)
Gastrointestinal Disorders	**1 (0.3)**	**0**	**1 (0.2)**
Gastric Perforation	1 (0.3)	0	1 (0.2)
Infections and Infestations	**0**	**1 (0.3)**	**1 (0.2)**
Sepsis	0	1 (0.3)	1 (0.2)
Nervous System Disorders	**1 (0.3)**	**0**	**1 (0.2)**
Cerebrovascular Accident	1 (0.3)	0	1 (0.2)

The total number of AEs counts all treatment-emergent AEs for patients. At each level of patient summarisation, a patient is counted once if the patients reported one or more events. Related is defined as a relationship of possible. Probable, or definite. If the relationship of an AE is missing, the AE is reported as "related".
Adverse events were coded using MedDRA, version 22.0.
Period 1 is defined as from the date of first dose of induction therapy up to data cut off for week 18 CSR.
1 patient in Avastin arm reported an TEAE sepsis (Related to IMP) with fatal outcome during period 1 after data cut for week 18 CSR and is not included in above table
Source table: Week 18 CSR MYL-1402O-3001 Listing 16.2.7.1.1, 16.2.7.1.2, Table 14.3.1.14

Table 55. Treatment related TEAE leading to death by SOC and PT in Period 2 – safety set

System Organ Class Preferred Term	MYL-1402O (N=200) N (%)	Avastin® (N=199) N (%)	Total (N=399) N (%)
Total number of TEAEs leading to Death	**1**	**0**	**1**
Number of patients with at least OneTEAE leading To Death	**1 (0.5)**	**0**	**1 (0.3)**
Respiratory, Thoracic and MediastinalDisorders	**1 (0.5)**	**0**	**1 (0.3)**
Pulmonary Haemorrhage	1 (0.5)	0	1 (0.3)

Period 2 is defined as from the date of first dose of monotherapy to the end of Week 42.
Source Data: Week 42 CSR MYL-1402O-3001 Listing 16.2.7.1.1b, 16.2.7.1.2b, Appendix II MYL-1402O-3001 Post week 42 CSR, Table 26

Table 56. Occurrence of deaths by study day

Deaths by Study Day	MYL-1402O	Avastin	Total
Day ≤30	13	3	16
Day 31-60	17	15	32
Day 61-90	6	5	11
Day >90	14	11	25
Total Deaths	50	34	84

Source: Listing 16.2.7.4

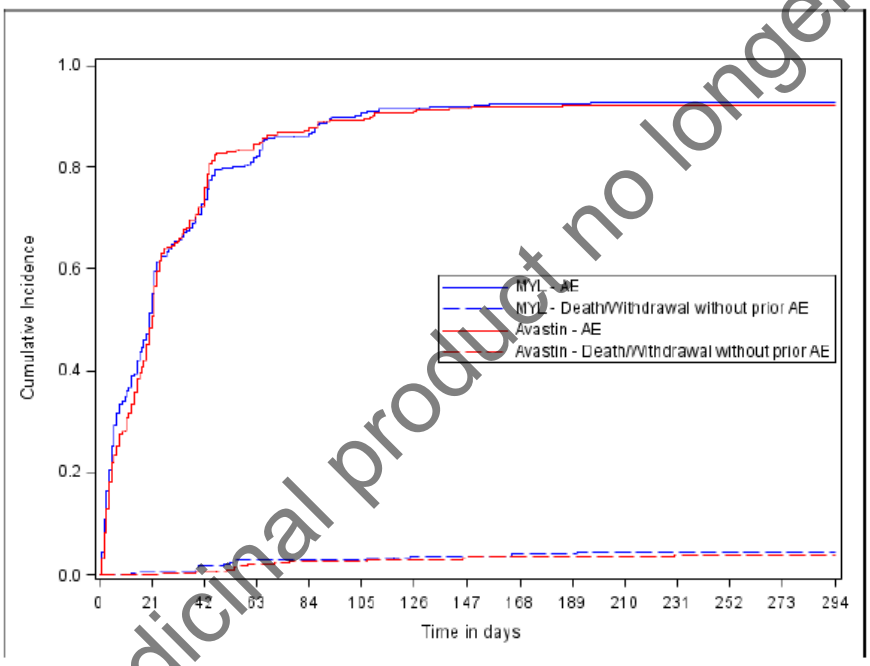


Figure 14. First TEAE – Aalen-Johansen estimator of the cumulative incidence function

The incidence of AESI leading to death was similar in both the arms, 11 (3.3%) patients in the MYL-1402O arm and 8 (2.4%) patients in Avastin arm.

Table 57. AEIs leading to death by SMQ (SOC and PT) (includes Period 1 and Period 2 through week 42)

Standard Medical Query (SMQ) Preferred Term	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)	Total (N=664) n (%)
Number of Patients With At Least One Event	11 (3.3)	8 (2.4)	19 (2.9)
Haemorrhage Terms (Excl Laboratory Terms) (SMQ)	4 (1.2)	5 (1.5)	9 (1.4)
Pulmonary Haemorrhage	4 (1.2)	3 (0.9)	7 (1.1)
Haemoptysis	0	1 (0.3)	1 (0.2)
Peptic Ulcer Haemorrhage	0	1 (0.3)	1 (0.2)
Cardiac Failure (SMQ)	2 (0.6)	1 (0.3)	3 (0.5)
Cardiac Failure Acute	0	1 (0.3)	1 (0.2)
Cor Pulmonale Acute	1 (0.3)	0	1 (0.2)
Pulmonary Oedema	1 (0.3)	0	1 (0.2)
Embolic and Thrombotic Events, Venous (SMQ)	2 (0.6)	0	2 (0.3)
Pulmonary Embolism	2 (0.6)	0	2 (0.3)
Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous (SMQ)	2 (0.6)	0	2 (0.3)
Cerebrovascular Accident	2 (0.6)	0	2 (0.3)
Gastrointestinal Perforation (SMQ)	1 (0.3)	1 (0.3)	2 (0.3)
Gastric Perforation	1 (0.3)	0	1 (0.2)
Peritonitis	0	1 (0.3)	1 (0.2)
Interstitial Lung Disease (SMQ)	0	1 (0.3)	1 (0.2)
Acute Respiratory Distress Syndrome	0	1 (0.3)	1 (0.2)

At each level of patient summarization, a patient is counted once if the patient reported one or more events.
Adverse Events were coded using MedDRA, Version 22.0. Source Data: Listing 16.2.7.1.1b, Listing 16.2.7.1.2b; Table 14.3.1.15b

Supportive Phase III mCRC study

In the supportive Phase III study in mCRC patients, 42 SAEs were reported in 31 patients, of which 5 were related to the study drug. 16 (23.53%) patients in the Bmab-100 arm reported 18 treatment-emergent SAEs, and 15 (22.39%) patients in the Avastin arm reported 24 treatment-emergent SAEs. The SAEs constituted events expected from the known safety profile of Avastin. Most were assessed to be related to other confounding factors like XELOX chemotherapy and underlying disease.

Thirteen deaths were reported (Bmab-100 arm: 5 and Avastin arm: 8). Of these, 2 deaths were attributed to TEAEs related to study drug (1 event in each arm).

Table 58. Listing of patients with fatal TEAEs, by treatment group (safety population)

Treatment	Age/Gender	TEAE Preferred Term	Relationship to Bmab-100/Avastin	Alternative Etiology
Part 1				
Bmab-100	65/Male	Metastases to Meninges	Unrelated	Disease progression
Part 2				
Bmab-100	37/Male	Death	Unrelated	Disease progression
Bmab-100	37/Female	Intestinal obstruction, sepsis, respiratory failure	Unlikely Unlikely Unlikely	Disease progression
Avastin	64/Female	Cardiac arrest	Unlikely	Secondary to mCRC
Bmab-100	63/Male	Sepsis	Unrelated	Sepsis with MOF
Bmab-100	27/Male	Sudden cardiac arrest	Possible	Sudden cardiac death secondary to underlying disease
Avastin	52/Male	Death	Possible	Thromboembolism and disease progression
Avastin	50/Female	Disease progression	Unrelated	Bone metastasis causing severe marrow suppression
Avastin	75/Male	Diarrhoea, Metabolic acidosis	Unrelated, Unrelated	Capecitabin included diarrhoea leading to metabolic acidosis and cardiorespiratory arrest
Avastin	51/Female	Abdominal pain	Unrelated	Unknown
Avastin	55/Male	Diarrhoea	Unrelated	Capecitabine
Bmab-100	61/Female	Death	Unrelated	Unknown
Avastin	31/Female	Death	Unrelated	Unknown
Avastin	69/Male	Diarrhoea	Unrelated	Acute respiratory failure and acute renal failure

Laboratory findings

there was no evidence of clinically relevant differences in any laboratory parameter between the three treatment groups over time in the Phase I study, between the two treatment arms in the Phase III nsNSCLC study, and between the three treatment arms in the supportive Phase III mCRC study.

For study MYL-1402O-3001, no clinically significant differences between treatment groups were observed in hematology, serum chemistry, urinalysis results, vital signs, physical examination findings, or ECOG status from baseline through Week 18.

With regard to liver function parameters, there were elevations in post-baseline values detected for ALT and for total bilirubin in a higher number of patients in the MYL-1402O arm than in the Avastin arm.

Overall, 2 patients in the MYL-1402O arm as well as 1 patient in the Avastin arm had concurrent elevation of ALT ≥3 and bilirubin ≥2ULN. The 2 patients in the MYL-1402O arm had Stage IV NSCLC with liver metastasis at baseline, whereas the patient in the Avastin arm had Stage IV NSCLC without liver metastasis at baseline. All patients were discontinued from treatment due to PD. Since the study population comprised patients with other comorbidities for which they were receiving concomitant medications, it is acknowledged that it is rather difficult to attribute liver enzyme elevations or clinically apparent liver injury to any of the IMPs.

When comparing the number of patients by treatment arm who showed CTCAE grade shift in ALT from baseline to worst post-baseline during the study, an imbalance between the treatment arms was observed: 15 patients in the MYL-1402O arm versus 7 patients in the Avastin arm showed a post-baseline shift to Grade 2 ALT. With regard to post-BL shifts to Grade 3 ALT, there was no distinct difference between the treatment arms. Furthermore, no patients had post-BL shifts to Grade 4 ALT in either treatment arm.

With regard to bilirubin post-baseline shifts, there were no distinct imbalances observed between the treatment arms, except for post-BL shift to Grade 3 bilirubin from baseline, which occurred in 3 patients in the MYL-1402O arm and in 1 patient in the Avastin arm.

With regard to the overall study population at baseline, a higher number of patients in the MYL-1402O arm had Grade 1 ALT elevation (n=44) compared to Avastin (n=38).

Since, however, incidence of liver-related TEAE was overall comparable between the treatment arms (MYL-1402O: 16 patients with 41 events, Avastin: 15 patients with 27 events) and since the majority of events occurred during the combination therapy period (i.e. when patients were on background ChT), the overall conclusion of the applicant that those differences in elevated ALT and bilirubin are not considered to be of clinical relevance is considered acceptable.

Regarding haematology, number of patients experienced shifts in performed tests, however, most of them were not serious and similar across treatment arms. There were reported CTCAE grade shifts to Grade 3-4 for parameters including haemoglobin, white blood cell counts, neutrophil and platelet count, however, with similar incidence in both arms. The presented data did not indicate any new safety patterns related to MYL-1402O.

No clinically relevant differences between treatment arms were observed for serum chemistry parameters. The observed shifts with increase of 1-2 grades or to higher Grade 3-4 were comparable between treatment arms. The clinically significant chemistry abnormalities reported as TEAEs consisted of anaemia, thrombocytopenia, neutropenia, leukopenia, febrile neutropenia, blood creatinine increased, hyperkalaemia, hyponatremia, hypokalaemia. Majority of these events were of Grade 1-2 and incidences were in overall comparable between treatment arms.

The clinically significant vital signs reported as TEAEs included PTs (in >1% of patients) hypertension, decreased weight and pyrexia which were mainly of CTCAE Grade 1-2. The incidence of observed PTs was comparable between arms except for PT 'Decrease of weight', which was more pronounced in the MYL-1402O arm (22 patients [6.6%] vs 7 patients [2.1%]). Notwithstanding this evidence, the treatment-related decrease of weight was shown in few patients only.

In addition, a performed analysis of few reported TEAEs related to laboratory and vital signs abnormalities leading to discontinuation of treatment did not show any specific patterns. Overall, the collected results of haematology and serum chemistry parameters and vital signs did not reveal any

clinically significant differences between treatments. Thus, the safety profile related to laboratory findings is concluded as comparable to Avastin without observation of any new safety risks.

Safety in special populations

No specific safety studies in special populations have been conducted. This is acceptable for a biosimilar application.

No cases of pregnancies were reported in any of the studies.

Immunological events

Refer to Section 2.2 for the discussion on immunogenicity.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to AES

Phase I PK study

There were no AEs resulting in premature discontinuation from the study.

Phase III NSCLC study

Overall, 64/664 patients (9.6%) discontinued study treatment due to a total of 66 TEAEs. A slightly higher number of patients withdrew from treatment in the MYL-1402O group (36/335 patients, 10.7%; 38 events) compared to the EU-Avastin group (28/329 patients; 8.5%; 28 events).

Table 59. TEAEs leading to treatment discontinuation (in ≥2 patients by PT in either arms) – safety set (includes Period 1 and Period 2 through week 42)

System Organ Class Preferred Term	MYL-1402O (N=335) n (%)	Avastin (N=329) n (%)	Total (N=664) n (%)
Total Number of TEAEs Leading to Treatment Discontinuation	38	28	66
Number of patients with at least one TEAE leading to treatment discontinuation	36 (10.7)	28 (8.5)	64 (9.6)
Respiratory, thoracic and mediastinal disorders	15 (4.5)	11 (3.3)	26 (3.9)
Pulmonary embolism	5 (1.5)	5 (1.5)	10 (1.5)
Pulmonary haemorrhage	3 (0.9)	1 (0.3)	4 (0.6)
Haemoptysis	0	3 (0.9)	3 (0.5)
Dyspnoea	2 (0.6)	0	2 (0.3)
Infections and infestations	6 (1.8)	4 (1.2)	10 (1.5)
Sepsis	1 (0.3)	2 (0.6)	3 (0.5)
Pneumonia	2 (0.6)	0	2 (0.3)
Nervous system disorders	4 (1.2)	1 (0.3)	5 (0.8)
Cerebrovascular accident	2 (0.6)	1 (0.3)	3 (0.5)
Vascular disorders	3 (0.9)	2 (0.6)	5 (0.8)
Hypertensive crisis	2 (0.6)	0	2 (0.3)

The total number of AEs counts all treatment-emergent AEs leading to treatment discontinuation for patients. At each level of patient summarization, a patient is counted once if the patient reported one or more events.
Adverse Events were coded using MedDRA, Version 22.0.
Source Data: Listing 16.2.7.3b; Table 14.3.1.07b

With regard to the number of patients who discontinued treatment due to drug related TEAEs, during Period 1, there were 13 of such patients in both treatment arms (MYL-1402O: 3.9%; Avastin: 4.0%). In Period 2, there were 2 patients in the MYL-1402O group (1.0%) and 3 patients in the Avastin group (1.5%).

Of note, for the MYL-1402O, there were 2 concerned events which are not considered "listed" for the known safety profile of bevacizumab, i.e. cardiorespiratory arrest and acute angle closure glaucoma. The patient experiencing cardiorespiratory arrest was 57 years old. Please refer to the Section on SAE and deaths for further details. Another patient who experienced angle closure glaucoma was 51 years old. This patient also received only one dose of study drug (660 mg), paclitaxel (229 mg) and carboplatin (612 mg). On Day 7, she was diagnosed with conjunctivitis (grade 2) and on Day 9 she experienced blurring of vision of the left eye, redness and pain in both eyes. The eye examination showed acute angle closure glaucoma with conjunctivitis (grade 3) and CT scan showed brain lesions, therefore, the patient was discontinued from the study. In view of the provided information, no impact on safety of MYL-1402O and related conclusions on safety profile can be detected.

Supportive Phase III mCRC study

TEAEs resulted in permanent discontinuation in 7 (10.29%) patients in the Bmab-100 and 2 (2.99%) patients in the Avastin arm. Out of these, 1 (1.47%) patient in the Bmab-100 arm and both patients in the Avastin arm had study drug-related TEAEs.

Table 60. TEAE leading to study drug discontinuation by system organ class and preferred term (safety population) – part 2

System Organ Class(SOC) Preferred Term(PT)	Bmab-100 (N=68) [n (%)]	e	Avastin (N=67) [n (%)]	e
No of patients with at least one TEAE leading to study drug discontinuation	7 (10.29%)	8	2 (2.99%)	4
Blood and lymphatic system disorders	0 (0.00%)	0	1 (1.49%)	1
Thrombocytopenia	0 (0.00%)	0	1 (1.49%)	1
Cardiac disorders	1 (1.47%)	1	0 (0.00%)	0
Myocardial ischaemia	1 (1.47%)	1	0 (0.00%)	0
Gastrointestinal disorders	4 (5.88%)	4	1 (1.49%)	1
Ascites	1 (1.47%)	1	0 (0.00%)	0
Intestinal obstruction	3 (4.41%)	3	0 (0.00%)	0
Stomatitis	0 (0.00%)	0	1 (1.49%)	1
General disorders and administration site conditions	0 (0.00%)	0	1 (1.49%)	1
Death	0 (0.00%)	0	1 (1.49%)	1
Hepatobiliary disorders	1 (1.47%)	1	0 (0.00%)	0
Hyperbilirubinaemia	1 (1.47%)	1	0 (0.00%)	0
Infections and infestations	0 (0.00%)	0	1 (1.49%)	1
Pneumonia	0 (0.00%)	0	1 (1.49%)	1
Investigations	1 (1.47%)	1	0 (0.00%)	0
Blood bilirubin increased	1 (1.47%)	1	0 (0.00%)	0
Respiratory, thoracic and mediastinal disorders	1 (1.47%)	1	0 (0.00%)	0
Pleural effusion	1 (1.47%)	1	0 (0.00%)	0

Note 1: TEAE are defined as any AE which started or deteriorated at or after first dose of study treatment
Note 2: n=number of subjects with AEs.
Note 3: e=number of events. Percentages are based on the number of subjects in safety population (N).
Note 4: System Organ Class and Preferred Term coded as per MedDRA version 17.1
Reference: Table number 14.3.1.7 (b)

Post marketing experience

The bevacizumab biosimilar MYL-1402O has not been approved or marketed yet in any country worldwide. However, Bmab-100, which is an "earlier version" of MYL-402O, received marketing authorisation approval in India in 2017 and is currently marketed in four non-European countries.

From these post approval safety data, no new safety signals were detected so far.

2.6.1. Discussion on clinical safety

The applicant has provided safety data from a pivotal single-dose PK study in healthy male volunteers (study MYL-1402O-1002) and from a Phase III efficacy and safety study in male and female nsNSCLC patients (MYL-1402O-3001). In addition, supportive safety data from a Phase III study in male and female mCRC patients (BM100-CC-03-I-01) have been submitted. This study was conducted with Bmab-100, an early development version of MYL-1402O. Here, the same drug product formulation was used as for MYL-1402O.

It is stated by the applicant that during the manufacturing of the development batches of MYL-1402O, one formulation buffer component was changed. Instead of sodium dihydrogen phosphate monohydrate, sodium dihydrogen phosphate dehydrate was erroneously used. Since the manufacturing process was based on monohydrate, the buffer quantity was not adjusted for dihydrate (i.e. molecular weight of 137.8 was used instead of 156). This inadvertent change resulted in small differences with regard to pH and osmolality. It was outlined by the applicant that the product quality with dihydrate buffer in terms of stability or other key product attributes were not impacted.

According to the applicant, the formulation used in the completed as well as in the ongoing clinical studies (including the supportive study conducted with Bmab-100 in India by Biocon) contained sodium dihydrogen phosphate dihydrate. Also, the commercialised product in India contained the dihydrate salt. Since the product intended to be marketed in the EU is also based on the dihydrate salt, the data submitted are considered relevant for the evaluation of safety and immunogenicity of MYL-1402O.

Study MYL-1402O-1002 and study BM100-CC-03-I-01 have been completed. For the pivotal Phase III study MYL-1402O-3001, data from Period 1 (up to 18 weeks) were the basis for initial assessment. In addition, during the procedure the final CSR including Week 42 data has been submitted.

It was noted that the final CSR will include only Week 42 data. This in contrast to the EMA SA received by the applicant in October 2014, where the applicant stated that 1-year data would be generated in the pivotal phase III study, which was supported by the CHMP. The applicant provided justification on the deviation in the context of safety follow-up period for which the data is submitted (42 weeks instead of 1-year data). This is based on the amendment to the study protocol (from version 1.0 to version 2.0). Moreover, the applicant presented data available beyond Week 42 for the patients who entered extended treatment period (i.e. 86 patients from the MYL-1402O group and 84 patients from the Avastin group). This is acceptable in this instance, since the pivotal Phase III study was conducted in an end-stage oncology indication in patients with a rather poor prognosis. Hence, a relevant "drop-out" of patients would have been expected over a period of 1 year.

Furthermore, 42-week data are considered acceptable against the background that immunogenicity is not so much a topic for bevacizumab and its biosimilars.

The clinical studies were designed to rule out clinically relevant differences in safety between the biosimilar and the reference product and to confirm biosimilarity. The overall approach for the assessment of safety profile is considered acceptable, as it allows to capture relevant safety findings.

Exposure data:

In the pivotal PK study, the safety population consisted of 111 healthy male subjects aged 18 to 55 years who were randomised to one of three treatment arms and exposed to a single dose of 1 mg/kg bevacizumab iv (MYL-1402O: 37 subjects; EU-Avastin: 37 subjects; US-Avastin: 37 subjects). In the pivotal Phase III study in nsNSCLC patients, the safety population consisted of all NSCLC patients who received bevacizumab (either MYL-1402O or EU-Avastin) at a dose of 15 mg/kg iv at least once. Hence, a total of 663 out of the 671 randomised patients were included in the safety set (MYL-1402O group: 335 patients [99.4%]; EU-Avastin group: 329 patients [98.5%]). In the supportive mCRC study, the safety set consisted of all subjects who had received at least 1 dose of bevacizumab at a dose of 7.5 mg/kg iv (n= 135; Bmab-100: 68 patients, Avastin 67 patients). The overall safety population is considered sufficiently large to detect relevant safety signals in this comparability exercise.

In the pivotal efficacy study MYL-1402O-3001, patients were randomised in a 1:1 ratio to receive either an iv dose of 15 mg/kg of MYL-1402O or EU-Avastin plus carboplatin and paclitaxel (every three weeks) for up to 6 cycles (induction treatment phase/ Period 1). Patients who responded to treatment continued with bevacizumab Q3W as monotherapy in the maintenance treatment phase (Period 2) until progression of disease (PD) or discontinuation of interventional therapy (for any reason), or withdrawal of consent, whichever occurred first.

Due to the heterogeneity of the study populations and the different treatment doses/ schemes used in the clinical studies, no pooled safety analysis was applicable. This is considered adequate.

For the pivotal NSCLC study, based on the full Week 42 data set, the mean duration of exposure to bevacizumab was comparable between MYL-1402O (15.13 weeks) and EU-Avastin (14.65 weeks), as well as the mean number of doses (8.7 for both treatment arms) and the mean cumulative doses (MYL-1402O 131.0 mg/kg versus EU-Avastin 131.8 mg/kg). In both study periods, a comparable number of cycles was overall administered across all patients in both treatment arms, with a slightly lower number of cycles administered in Period 2 for Avastin (n=1242) than for MYL-1402O (n=1278).

With regard to chemotherapy, the mean duration of exposure as well as the mean number of doses received and the mean cumulative doses were comparable for both carboplatin and paclitaxel between both treatment arms.

There was a higher number of patients with dose delays, especially with a delay of 8 or more days, observed in the MYL-1402O arm (n= 90 compared to n= 77 in the EU-Avastin arm). The applicant states that treatment delays ≤6 weeks were permitted as per protocol in case of documented toxicity related to bevacizumab or ChT. If ChT was withheld due to toxicity, the bevacizumab dose was also put on hold. However, the reasons for dose delays were not recorded systematically in the CRF.

At Week 18, 217 (64.4%) patients in the MYL-1402O arm and 225 (67.4%) in the Avastin arm had their treatment ongoing. 118 patients in the MYL-1402O arm and 104 patients in the Avastin arm had discontinued treatment. The main reasons for discontinuation were disease progression, AEs or withdrawal in both groups.

Adverse events:

In the Phase I PK study, the proportion of subjects who experienced a TEAE was higher in the MYL-1402O arm (89%) as compared to the EU-Avastin (78%) and US-Avastin group (76%) arms. All of the TEAEs were however, Grade 1 (mild) or 2 (moderate) in severity. No TEAES of Grade 3 (severe), 4 (life threatening) or 5 (death) in severity and no discontinuations due to TEAEs or other safety issues occurred during the study in any of the groups. No systemic hypersensitivity or infusion reactions were reported in this study.

The most frequently affected SOCs among the treatment groups were Gastrointestinal disorders and Nervous System disorders. There were differences in the incidence of TEAEs by PT between the treatment arms for catheter site erythema, pain in extremity, nasopharyngitis and hematoma (blood sampling arm). Notably, there were no PTs with at least a 10% absolute difference between TEAEs in both the EU- or US-Avastin groups vs the MYL-1402O group. The differences in incidence rates between treatment groups are thus not considered of clinical relevance.

The most frequently reported TEAE by PT was headache in all treatment arms (MYL-1402O 19% [7/37 subjects], US-Avastin 16% [6/37], EU-Avastin 24% [9/37]). This is consistent with the SmPC of Avastin, where headache is listed among the most frequently observed AE.

The number of subjects experiencing TEAEs related to IP was overall comparable between the three treatment arms (MYL-1402O n=17, EU-Avastin n= 19, US-Avastin n=12).

In the Phase III NSCLC study, the majority of patients (91.1%) experienced at least one TEAE (91.3% in the MYL-1402O arm; 90.9% in the EU-Avastin group), most of the TEAEs being grade 1 and grade 2 in severity in both treatment groups. The number of TEAEs reported is, however, numerically higher in the MYL-1402O group (1918 TEAEs), compared to the EU-Avastin group (1761 TEAEs).

In general, across both treatment arm, the incidences, types and severities of TEAEs seem similar and the distribution is in line with the safety profile for bevacizumab (SmPC Avastin). No new safety signals were identified.

The overall number of patients experiencing TEAEs in the Phase III study is similar between both treatment groups (n= 306 [91.3%] in the MYL-1402O arm and 90.9% [299] in the EU-Avastin arm). The number of TEAEs reported is, however, higher in the MYL-1402O group (1918 TEAEs), compared to the EU-Avastin group (1761 TEAEs). The overall incidence of TEAEs was markedly lower in Period 2 than in Period 1 (57.1% vs 91.1%). It is acknowledged that this might be explained by the combination with ChT during Period 1, implying the occurrence of TEAE due to chemotherapy-associated toxicities.

TEAEs related to study treatment were similar between the two treatment groups with regard to the proportion of patients who experienced these events (MYL-1402O n=120 [35.8%], Avastin n=115 [35.0%] and the number of events reported (377 in the MYL-1402O arm vs 382 in the Avastin arm).

The number of patients with AESI by SMQ was comparable between the treatment arms (16.1% in the MYL-1402O vs 20.1% in the EU-Avastin arm). The number of patients with Grade ≥3 AESI and serious AESI was also comparable between the treatment arms. Most of the reported AEIs were of Grade 1-2 only. Also the number of patients with serious AESIs by SMQ was comparable between the study arms; 17 (5.1%) in the MYL-1402O arm and 19 (5.8%) in the Avastin arm.

Across both treatment groups, the incidences, types and severities of AESI seem comparable, and the distribution is in line with the safety profile for bevacizumab (SmPC Avastin). The number of patients with AESI by SMQ was comparable between the treatment arms (16.1% in the MYL-1402O vs 20.1% in the EU-Avastin arm) in Period 1. The number of patients with Grade ≥3 AESI and serious AESI was also comparable between the treatment arms. In Period 2, the incidence of AESI was lower compared to Period 1 (overall n=37 vs n=120 subjects with at least one event). Importantly, the AESI incidence was comparable between the treatment arms in the monotherapy period (n=21 [10.5%] in MYL-1402O vs n=16 [8.0%] in Avastin arm), also with regard to Grade ≥3 AESI (n=4 [2.0%] in the MYL-1402O vs n=5 [2.5%] in Avastin arm).

Overall, up to Week 42, the incidence of Hypersensitivity AESI was low and comparable between treatment arms (reported in overall n=15 [2.3%] of patients, n=9 in MYL-1402O and n=6 in Avastin arm).

Most of the Hypersensitivity AESI occurred during Period 1 (in n=13 patients [2.0%]). Here, 8 events were reported for the MYL-1402O arm and 5 events for the Avastin arm. Most events (n=6) were captured under the PT Dermatitis allergic. Only 1 PT of Hypersensitivity was reported in the MYL-1402O arm, and 1 PT of Anaphylactic reaction was reported in the Avastin arm; both were Grade ≥3. During Period 2, Hypersensitivity AESI occurred only in 2 patients (1 PT of Dermatitis allergic in the MYL-1402O arm and 1 PT of Swelling face in the Avastin arm).

In the supportive Phase III study in mCRC patients, the overall incidence of TEAEs was slightly higher in the Avastin arm as compared to Bmab-100 arm. 54 (79.41%) patients in the Bmab-100 arm and 60 (89.55%) patients in the Avastin arm reported at least one TEAE. Most of the TEAEs were Grade 1 or Grade 2 in severity.

Most of the TEAEs were considered not related to study drug and instead related to chemotherapy (XELOX) or underlying disease or progression. Six (8.82%) patients in the Bmab-100 arm and 12 (17.91%) patients in the Avastin arm had at least 1 TEAE related to Bmab-100/Avastin.

The most commonly reported TEAE in the study was diarrhea, reported in 11 (16.17%) patients (17 events, including one bacterial diarrhea) in the Bmab-100 arm and 22 (32.84%) patients (35 events) in the Avastin arm.

Overall, across both treatment groups, the incidences, types and severities of TEAE are considered comparable and thus supportive for the MYL-1402O MAA.

Serious adverse events and deaths:

There were no serious AEs or deaths reported in the Phase I PK study.

The incidences and types of the SAEs reported in the Phase III NSCLC study were in line with the known safety profile of bevacizumab, generally comparable between the groups and with no clinically meaningful differences noticed. The incidence of SAE was similar between treatment arms, 59 (17.6%) patients in MYL-1402O arm and 55 (16.7%) in Avastin arm. Overall, 142 SAEs were reported, all of which were treatment-emergent (i.e. serious TEAEs). However, SAE with fatal outcome were more frequent in the MYL-1402O arm (n=22) compared to the Avastin arm (n=13). Most of the SAE (82 events) recovered or resolved – 40 in the MYL-1402O arm and 42 in the Avastin arm. The majority of those SAE resolved without any action taken.

With regard to treatment-related SAEs, there was a higher number of patients in the Avastin arm (n=22) than in the MYL-1402O arm (n=17) during Period 1 reporting a higher number of treatment-related SAEs (30 vs 21 events). The most frequently reported treatment-related SAEs by PT were pulmonary embolism (n=4 in each treatment arm), thrombocytopenia (n=3 in the Avastin arm, n=1 for MYL-1402O), and febrile neutropenia (n=3 in the Avastin arm).

In Period 2 of the study, the number of patients experiencing treatment-related SAE was similar between the treatment groups (n=2 patients per treatment arm). Furthermore, the incidence of related SAE was overall low and similar (n=2 events per group). Here, the following events (by PT) were reported: coronary artery disease, myocardial infarction, pulmonary haemorrhage, and hypertension.

Overall, there were 183 deaths reported during the study, with 101 deaths in the MYL-1402O arm and 82 deaths in the Avastin arm.

Importantly, the imbalance with regard to the number of deaths remained rather stable between the treatment arms throughout the study. The numerical difference in deaths between the treatment arms increased slightly from n=16 (Week 18 CSR, with 50 versus 34 deaths for the MYL-1402O arm vs Avastin) to n=19 (Week 42 CSR, with 101 versus 82 deaths for MYL-1402O vs Avastin).

When focusing on the imbalance in the number of deaths, it was noted that death due to disease progression was similar between the treatment arms - 57 (17.0%) in the MYL-1402O arm vs 56 (17.0%) in the Avastin arm. The observed imbalance in deaths between the treatment arms could be attributed mainly to Non-Cancer deaths (i.e. deaths due to TEAE and due to Unknown reasons).

Overall, more deaths occurred during the Induction phase (combination with ChT) than during the Maintenance phase (bevacizumab monotherapy). Here, the additional toxicity by the chemotherapy components might have played a role.

25 patients in the MYL-1402O arm compared to 14 patients in the Avastin arm experienced TEAE leading to death. However, most of these TEAE leading to death were not classified as treatment related.

Treatment-related TEAEs leading to death were reported in 8 (2.4%) patients in the MYL-1402O arm and in 5 (1.5%) patients in the Avastin arm, respectively. These drug-related TEAE that occurred in the MYL-1402O group were the following: pulmonary embolism (in 2 patients), pulmonary haemorrhage (in 2 patients), cardiorespiratory arrest, acute coronary syndrome, gastric perforation and cerebrovascular accident. With the exception of cardiorespiratory arrest and acute coronary syndrome, the reported events are listed in the product information for Avastin.

The not IMP-related deaths were considered possibly related to underlying disease, chemotherapy, cardiac medical history, comorbidities and concurrent illnesses.

The incidence of AESI leading to death was similar in both the arms, 11 (3.3%) patients in the MYL-1402O arm and 8 (2.4%) patients in Avastin arm.

Unknown reasons leading to death were reported in 16 patients (4.8%) in the MYL-1402O arm and in 11 patients (3.3%) in the Avastin arm. 11 deaths due to unknown reason occurred during the treatment period. Causes of death, upon further clinical evaluation, were likely due to underlying disease, comorbidities, clinical progression or concurrent chemotherapy. Another 16 deaths due to unknown reason were reported by phone during Follow-Up.

To note, a comparatively higher incidence of deaths was observed during the induction period especially within the first 30 days of IMP administration (n=13 for MYL-1402O vs n=3 for Avastin).

In those patients who died during 30 days of the first IMP dose in the MYL-1402O arm, various baseline and disease related factors increasing the risk of death during anti-cancer treatments were observed, i.e. age ≥65 years, ECOG 1, smoking, advanced substage M1c and significant comorbid conditions.

It is acknowledged that this early difference in death numbers between the treatment arms cannot be conclusively attributed to a lack of IMP efficacy, since a steady state concentration for bevacizumab is reported to be reached after approx. 100 days in the NSCLC population. In addition, the mean Cmax after the first treatment cycle was similar between the treatment arms, thus IMP-related toxicity is considered unlikely.

Overall, it is concluded by the applicant that a "carry-over" effect of the higher number of early deaths may, at least in part, be responsible for the overall imbalance in deaths between the treatment arms. Furthermore, the types of deaths were rather variable including treatment-related and non-treatment-related deaths, with no clear pattern or clustering by any SOC/PT in the TEAE leading to death in the MYL-1402O arm. This is acknowledged.

The different numbers of death in the treatment groups at early time points lead to different follow-up times for adverse events, and probably to bias in incidence proportions of adverse events. The

provided cumulative incidence functions (Aalen-Johansen estimator) show that the bias due to early deaths that lead to an underestimation of adverse event rates were negligible.

In the supportive Phase III study in mCRC patients, 42 SAEs were reported in 31 patients, of which 5 were related to the study drug. 16 (23.53%) patients in the Bmab-100 arm reported 18 treatment-emergent SAEs, and 15 (22.39%) patients in the Avastin arm reported 24 treatment-emergent SAEs. The SAEs constituted events expected from the known safety profile of Avastin. Most were assessed to be related to other confounding factors like XELOX chemotherapy and underlying disease. Across both treatment groups, the incidences and types of SAES are considered comparable and thus supportive for the MYL-1402O MAA.

Thirteen deaths were reported in the mCRC study (Bmab-100 arm: 5 and Avastin arm: 8). Of these, 2 deaths were attributed to TEAEs related to study drug (1 event in each arm).

Laboratory findings:

According to the applicant, there was no evidence of clinically relevant differences in any laboratory parameter between the three treatment groups over time in the Phase I study, between the two treatment arms in the Phase III nsNSCLC study, and between the three treatment arms in the supportive Phase III mCRC study.

In the pivotal Phase III NSCLC study, the collected results of haematology and serum chemistry parameters and vital signs did not reveal any clinically significant differences between treatments. Thus, the safety profile related to laboratory findings is concluded comparable to Avastin without observation of any new safety risks.

Immunogenicity:

Refer to the discussion on immunogenicity.

Study discontinuation due to AEs:

In the Phase I PK study in healthy volunteers, no AE resulted in premature discontinuation from the study.

In the Phase III NSCLC trial, a slightly higher number of patients withdrew from treatment in the MYL-1402O group (36/335 patients, 10.7%; 38 events) compared to the EU-Avastin group (28/329 patients; 8.5%; 28 events). With regard to the number of patients who discontinued treatment due to drug related TEAEs, during Period 1, there were 13 of such patients in both treatment arms (MYL-1402O: 3.9%; Avastin: 4.0%). In Period 2, there were 2 patients in the MYL-1402O group (1.0%) and 3 patients in the Avastin group (1.5%).

In the supportive Phase III study in mCRC patients, TEAEs resulted in permanent discontinuation in 7 (10.29%) patients in the Bmab-100 and 2 (2.99%) patients in the Avastin arm. Out of these, 1 (1.47%) patient in the Bmab-100 arm and both patients in the Avastin arm had study drug-related TEAEs.

2.6.2. Conclusions on clinical safety

The provided Week 42 safety and immunogenicity data support the overall conclusion that a comparable safety profile has been demonstrated between MYL-1402O and Avastin. Furthermore, no new safety signals have been identified.

The provision of 42 week (instead of 1-year data, as requested by ICH E1) is considered acceptable in this instance, since the pivotal Phase III study was conducted in an end-stage oncology indication in

patients with a rather poor prognosis. Hence, a relevant "drop-out" of patients would have been expected over a period of 1 year.

Moreover, the applicant presented data available beyond Week 42 for the patients who entered extended treatment period (i.e. 86 patients from the MYL-1402O group and 84 patients from the Avastin group). Furthermore, 42-week data are considered acceptable against the background that immunogenicity is not so much a topic for bevacizumab and its biosimilars.

With regard to the observed imbalance in death/ survival rates between the treatment arms, a review of BL characteristics showed higher incidence of vascular and cardiac disorders in the MYL-1402O arm, as well as a higher proportion of M1c substage patients. Types of deaths were rather variable with no clear pattern or clustering by any SOC/PT. Even though the present underlying conditions make an assessment of causal association more difficult, following a review on a case by case basis, no trend or significant safety-related concern in view of the study drug could be identified.

In addition, it is noted that the chosen NSCLC patient population may not be ideal for demonstration of clinical comparability, due to the fact that the course of disease may vary from slowly progressive to aggressive profile in patients having several comorbidities, increasing the risk of fatal events.

Taken together, the numerical difference in deaths between study arms can be explained by several confounding factors and is not considered a difference in biosimilarity.

2.7. Risk Management Plan

Safety concerns

No safty concerns have been identified.

This is in line with the reference medicinal product.

Pharmacovigilance plan

No additional pharmacovigilance activities were identified for Lextemy.

Routine pharmacovigilance activities are sufficient to mitigate the risks of Lextemy.

Risk minimisation measures

No additional risk minimisation measures were identified for Lextemy.

Routine risk minimisation activities are sufficient to minimise the risks of Lextemy.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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

2.9. New Active Substance

The applicant declared that bevacizumab has not been previously authorised in a medicinal product in the European Union.

2.10. Product information

2.10.1. User consultation

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

2.10.2. Labelling exemptions

A request to display minimum particulars on the 16 mL vial label as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reason: the vial label is too small to accommodate full particulars without compromising its readability.

2.10.3. Additional monitoring

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

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Lextemy (working name MYL-1402O) is developed as a biosimilar to Avastin. The approval is sought for intravenous use in the proposed therapeutic indications identical to the currently approved indications for Avastin:

- Lextemy in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.
- Lextemy in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer.
- Lextemy in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracyclinecontaining regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Lextemy in combination with capecitabine.
- Lextemy, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.
- Lextemy, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.
- Lextemy in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer.
- Lextemy, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- Lextemy, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor targeted agents.
- Lextemy in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.
- Lextemy, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix).

Summary of analytical similarity

For the biosimilarity exercise, the quality attributes of the reference medicinal product in terms of its physicochemical and functional properties were characterised. The identified quality attributes were

ranked according to (a) their risk to potentially impact activity, PK/PD, safety, efficacy, and immunogenicity, and (b) the degree of uncertainty surrounding a certain quality attribute.

The number of batches of EU-Approved Avastin and US-Licensed Avastin as well as of Abevmy were considered adequate for the analytical similarity assessment.

To support the known mechanism of action, binding to VEGF and inhibition of cell proliferation was assessed by functional and binding assays in the scope of the biosimilarity exercise. Assays include binding to VEGF (VEGF-165 and VEGF-121 and VEGF-189), inhibition of VEGF (VEGF-165, VEGF-121 and VEGF-189) induced proliferation of endothelial cells (HUVECs), and inhibition of VEGF-165 induced VEGFR-2 phosphorylation.

In addition to Fab-associated antigen binding, MYL1402O binding to Fc receptors and complement factor C1q were evaluated in the scope of the biosimilarity exercise using *in vitro* assays. C1q binding was assessed via ELISA and binding kinetics with FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb and FcRn were assessed via surface plasmon resonance. Furthermore, antibody dependent cellular cytotoxicity and complement dependent cytotoxicity assays were included as part of the comparability exercise - even though bevacizumab is not known to act through either of these mechanisms.

Furthermore, primary structure, higher order structure, protein concentration, high and low molecular weight impurities, charge heterogeneity, glycosylation and other amino acid modifications were assessed using a variety of methods.

Overall, the applicant followed relevant guidelines and performed an extensive biosimilarity exercise using sensitive orthogonal state-of-the-art analytical methods. All relevant quality attributes were addressed.

Summary of non-clinical data

For global development, the toxicological profile of the proposed biosimilar candidate was determined in several *in vivo* acute and repeat-dose studies in mice, rabbits and cynomolgus monkeys. Two of the studies are comparative in nature. In a repeat-dose study in mice (Study 9335), Bmab-100 (an older version of MYL-1402O) was compared to US-Avastin. In a repeat-dose study in cynomolgus monkeys, MYL-1402O and US-Avastin were compared. Overall, studies 9335 and TOX-070-002 seem to demonstrate biosimilarity of MYL-1402O and Avastin. The results of the studies are regarded supportive and do not add further value for the demonstration of biosimilarity.

Summary of clinical data

The clinical development programme consists of two studies:

- a 3-arm pivotal Phase I PK study (**MYL-1402O-1002**), comparing MYL-1402O to EU-sourced and US-sourced Avastin in 111 healthy male subjects, investigating PK, safety and immunogenicity, and
- a global multi-centre parallel group Phase III efficacy/safety study (**MYL-1402O-3001**) in 671 patients with Stage IV non-squamous NSCLC to comparatively investigate efficacy, safety, immunogenicity and PK of MYL-1402O compared to EU-Avastin.

In addition, supportive data were submitted from a comparative PK, efficacy, safety and immunogenicity study (**BM100-CC-03-I-01**) conducted by Mylan's partner Biocon in 135 mCRC patients in India with Bmab-100, an early development version of MYL-1402O.

In general, the applicant followed EMA guidelines and former CHMP advice. However, it is noted that - in contrast to the EMA SA received by the applicant in October 2014, where it was agreed that 1-year data would be generated in the pivotal phase III study - the final CSR will include only Week 42 data.

Overall, the data from the clinical studies that have been submitted with the MAA support biosimilarity of MYL-1402O and EU-Avastin.

The pharmacokinetics of MYL-1402O are considered similar to that of EU-Avastin.

In the pivotal Phase III study MYL-1402O-3001 in NSCLC patients, equivalence between MYL-1402O and EU-Avastin was demonstrated for the primary efficacy endpoint, best ORR within 18 weeks, assessed by independent review in the ITT population. This was supported by sensitivity analyses for the primary EP in the PP population, which is the population of interest for a biosimilar.

An imbalance in death rates was observed between treatment arms (n=101 [30.1%] vs n=82 [24.9%]), disfavoring MYL-1402O. A thorough review of BL characteristics showed higher incidence of vascular and cardiac disorders in the MYL-1402O arm, as well as a higher proportion of M1c substage patients. Types of deaths were rather variable with no clear pattern or clustering by any SOC/PT.

The applicant has provided analyses identifying factors such as imbalances in post-treatment anticancer therapies as well as in deaths occurring within 30 days of first IMP dose, which may have contributed to this imbalance ("carry-over" effect of higher number of early deaths).

In addition, it is noted that the chosen NSCLC patient population may not be ideal for demonstration of clinical comparability, due to the fact that the course of disease may vary from slowly progressive to aggressive profile in patients having several comorbidities, increasing the risk of fatal events.

3.2. Results supporting biosimilarity

Quality

In summary, the presented analytical data show similarity of the proposed biosimilar MYL-1402O and the reference medicinal product EU-Avastin. Quality attributes related to the mechanism of action of bevacizumab were highly similar. The analytical differences observed for several quality attributes have been appropriately addressed by the applicant and justified with regard to their potential impact on clinical performance of the product.

Clinical

Pharmacokinetics:

The pharmacokinetics of MYL-1402O are considered similar to that of EU-Avastin.

Efficacy:

In the pivotal comparative efficacy study MYL-1402O-3001 in Stage IV nsNSCLC patients, equivalence between MYL-1402O and EU-Avastin was demonstrated for the primary efficacy endpoint, best ORR within 18 weeks, assessed by independent review both in the ITT and in the PP population. The difference in best ORR within 18 wks was -1.6 (-9.0, 5.9) for the ITT population and -2.4 95% CI of (-10.2, 5.3) for the PP set; the two-sided 95% CI was entirely within the pre-defined equivalence margin of [-12.5%, 12.5%]. This was supported by sensitivity analyses for the primary EP, e.g. investigator-assessed ORR in the ITT population (ORR difference of -2.2, with a 95% CI of -9.7, 5.3) - the results were consistent with the primary analysis.

In addition, post-hoc sensitivity analyses have been provided for ORR at week 18, which is considered a more sensitive endpoint for a biosimilarity exercise than the BOR at any time point during the 18-week induction period. ORR rates at week 18 were similar between the treatment arms, both in the ITT and PP set, based on independent review as well as on investigator assessment. Overall, the presented additional ORR analyses at week 18 indicate similar efficacy between MYL-1402O and EU-Avastin and do thus support the results from the primary analysis.

Safety:

Based on Week 42 safety and immunogenicity data from the pivotal comparative efficacy and safety study in NSCLC patients, on the data of the Phase I PK study in healthy volunteers as well as of the supportive Phase III mCRC study conducted by Biocon, the incidences, types and severities of TEAEs, AESI and SAE seem comparable between MYL-1402O and EU-Avastin and are in line with the safety profile for bevacizumab (SmPC Avastin). No new safety signals have been identified so far.

3.3. Uncertainties and limitations about biosimilarity

No uncertainties considering the biosimilarity remain as outlined below.

Quality

The similarity assessment of MYL-1402O and the EU reference medicinal product showed highly similar biological activity of both the Fab and Fc-based functionality. Minor differences in the levels of aggregates, fragments, charged species and the glycosylation pattern were observed for MYL-1402O and EU-Avastin. However, it was concluded that these differences have no impact on PK, activity, safety and immunogenicity. From a quality perspective, MYL-1402O is regarded similar to its reference medicinal product EU-Avastin.

Clinical

Efficacy:

Phase III NSCLC study:

Overall, equivalence between MYL-1402O and EU-Avastin was convincingly demonstrated for the primary efficacy endpoint, best ORR within 18 weeks.

Safety:

Phase III NSCLC study:

Safety and immunogenicity data support the conclusion that a comparable safety profile has been demonstrated between MYL-1402O and Avastin. Furthermore, no new safety signals have been identified.

42-week data have been submitted, instead of 1 year data, as advised by ICH E1 and the CHMP GL on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues. In this instance, this is considered acceptable, since the pivotal Phase III study was conducted in an end-stage oncology indication in patients with a rather poor prognosis. Hence, a relevant "drop-out" of patients would have been expected over a period of 1 year.

Moreover, the applicant presented data available beyond Week 42 for the patients who entered extended treatment period (i.e. 86 patients from the MYL-1402O group and 84 patients from the

Avastin group). Furthermore, 42-week data are considered acceptable against the background that immunogenicity is not so much a topic for bevacizumab and its biosimilars.

3.4. Discussion on biosimilarity

Overall, the design of the analytical similarity exercise is considered adequate. The results of the analytical similarity exercise between MYL-1402O and EU-Avastin demonstrate similarity. Analytical differences observed between MYL-1402O and the reference product have been adequately justified with regard to their potential impact on clinical efficacy and safety. From an analytical perspective, MYL-1402O is regarded similar to its reference medicinal product.

The pharmacokinetics of MYL-1402O are considered similar to that of EU-Avastin.

In the pivotal comparative efficacy study MYL-1402O-3001 in Stage IV nsNSCLC patients, equivalence between MYL-1402O and EU-Avastin was demonstrated for the primary efficacy endpoint, best ORR within 18 weeks, assessed by independent review in the ITT population. This was supported by sensitivity analyses for the primary EP in the PP population, which is the population of interest for a biosimilar. ORR is considered adequate as primary endpoint, and ORR analysis at Week 18 supported equivalence between MYL-1402O and the reference product.

42-week data have been submitted, instead of 1-year data, as advised by ICH E1 and the CHMP GL on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues. In this instance, this is considered acceptable, since the pivotal Phase III study was conducted in an end-stage oncology indication in patients with a rather poor prognosis. Hence, a relevant "drop-out" of patients would have been expected over a period of 1 year.

Moreover, the applicant presented data available beyond Week 42 for the patients who entered extended treatment period (i.e. 86 patients from the MYL-1402O group and 84 patients from the Avastin group). Furthermore, 42-week data are considered acceptable against the background that immunogenicity is not so much a topic for bevacizumab and its biosimilars.

Overall, safety and immunogenicity data support the conclusion that a comparable safety profile has been demonstrated between MYL-1402O and Avastin. Furthermore, no new safety signals have been identified.

With regard to the observed imbalance in death/ survival rates between the treatment arms, a review of BL characteristics showed higher incidence of vascular and cardiac disorders in the MYL-1402O arm, as well as a higher proportion of M1c substage patients. Types of deaths were rather variable with no clear pattern or clustering by any SOC/PT.

Even though the present underlying conditions make an assessment of causal association more difficult, following a review on a case by case basis, no trend or significant safety-related concern in view of the study drug could be identified.

In addition, it is noted that the chosen NSCLC patient population may not be ideal for demonstration of clinical comparability, due to the fact that the course of disease may vary from slowly progressive to aggressive profile in patients having several comorbidities, increasing the risk of fatal events.

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

3.5. Extrapolation of safety and efficacy

The primary mechanism of action of bevacizumab is the inhibition of tumour vessel growth by blocking VEGF. The mode of action of bevacizumab is considered the same across all approved cancer indications.

Extrapolation to all approved indications authorised for the bevacizumab reference product Avastin is considered acceptable, provided that similarity of MYL-1402O/ Lextemy to EU-Avastin has been convincingly demonstrated.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Lextemy (also referred to as MYL-1402O) is considered biosimilar to Avastin. Therefore, a benefit/risk balance is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

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

Outcome

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

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

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

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

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

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

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

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

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

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

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

Not applicable.

New Active Substance Status

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