EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Krabeva 100mg

Krabeva 400mg

Date: August 2024

Assessment report

Krabeva

Unit: Technical Assessment Unit

Administrative information:

Trade name of the medicinal product:	Krabeva
INN (or common name) of the active substance(s):	Bevacizumab 25 mg/ml
Manufacturer of the finished product	Biocon Biologics Limited Special Economic Zone, Block No. B1, B2, B3, Q13 of Q1 and W20 and Unit S18, 1st Floor, Block B4, Plot No.: 2, 3, 4 and 5, Phase- IV, Bommasandra-Jigani Link Road, Bommasandra Post, Bengaluru, Karnataka - 560099 - India
Marketing Authorization holder	Biocon Biologics Limited Special Economic Zone, Block No. B1, B2, B3, Q13 of Q1 and W20 and Unit S18, 1st Floor, Block B4, Plot No.: 2, 3, 4 and 5, Phase- IV, Bommasandra-Jigani Link Road, Bommasandra Post, Bengaluru, Karnataka - 560099 - India
Applied Indication(s):	• Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum. • Bevacizumab in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. • Bevacizumab in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with bevacizumab in combination with capecitabine. • Bevacizumab, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology. • Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent

	non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations • Bevacizumab in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer. • Bevacizumab, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer • Bevacizumab, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents. • Bevacizumab in combination with paclitaxel, 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 • Bevacizumab, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix
Pharmaceutical form(s) and strength(s):	- Concentrate For Solution For I.V Infusion -Strength:25mg/ml
Route of administration	I.V. Infusion
Approved pack	Carton Box containing one single clear (type I) glass (USP/Ph.Eur.) vial closed with flurotec coated, grey chlorobutyl serum stoppers and the rubber stopper are latex free and sealed with aluminum seal with plastic flip-off cap component with insert leaflet.

List of abbreviations

ATC	Anatomical Therapeutic Chemical
rDNA	recombinant deoxyribonucleic acid

ADCC	antibody-dependent cellular cytotoxicity
MCB	Master Cell Bank
WCB	Working Cell Bank
PPQ	Process Performance Qualification
EURP	European Reference Medicinal Product
USRLD	United State Reference Listed Drug
SOPs	Standard operation procedures
ADA	anti-drug antibodies
ADCC	antibody dependent cellular cytotoxicity
AS	Active substance
DP	Drug Product
DS	Drug substance
CHO	Chinese Hamster Ovary
CDC	complement dependent cytotoxicity
CI	confidence interval
CTD	Common technical document
DCR	Disease control rate
DP	Drug product
EU	European union
Fab	Fragment antigen-binding
FC	Fragment crystallizable region of immunoglobulin
FcRn	Neonatal crystallizable fragment receptor
FcγR	Fc-gamma receptors
GLP	Good Laboratory Practice
HUVEC	Human umbilical vein endothelial cell
I.V	intravenous
MYL-1402O	krabeva
NOAELs	The No Observed Adverse Effect Levels
ORR	Objectives response rate
PDs	Pharmacodynamics
SOP	Standard operating procedure
TKs	toxicokinetic
US	United States
VEGF	Vascular endothelial growth factor
VEGFR-2	Vascular endothelial growth factor receptor-2

Dossier initial submission and evaluation process.

- The product was submitted for registration via 343/2021 ministerial decree.
- The dossier evaluation by the registration administration units was started on 25.7.2023 after providing all the required documents according to "the Checklist for documents of new biological products registration file".
- Full CTD along with detailed SOPs were provided.

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1. **‘General introduction about the product including brief description of the AI, its mode of action and indications:**

-Biocon Biologic’s Bevacizumab is a proposed biosimilar product to Avastin (bevacizumab, Genentech/Roche). Bevacizumab is classified under the Anatomical Therapeutic Chemical (ATC) classification system group antineoplastic agents, subgroup monoclonal antibodies (ATC code: L01X C07). Biocon Biologic’s Bevacizumab is a recombinant humanized IgG1 monoclonal antibody (93% human, 7% murine sequences) manufactured in CHO mammalian cells. This monoclonal antibody, approximately 149 kD in size, selectively binds with high affinity to all isoforms of human vascular endothelial growth factor A (VEGF).
-Once Biocon Biologic’s Bevacizumab is bound to VEGF, it neutralizes VEGF’s biologic activity by sterically hindering the binding of VEGF to its receptors Flt-1 (also known as VEGF receptor-1 [VEGFR-1]) and kinase insert domain receptor (also known as VEGF receptor-2 [VEGFR2]) on the surface of endothelial cells. VEGF is an endogenously expressed protein that stimulates new blood vessel formation. Bevacizumab reduces solid tumor growth by neutralizing the proangiogenic activity of VEGF, thereby reducing the amount of new blood vessel formation in the tumor and facilitating the activity of concomitant chemotherapy.
-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 the market in two presentations: 100 mg/ 4 mL and 400 mg/ 16 mL single-use vials.
-Other ingredients are: α, α-trehalose dihydrate, sodium phosphate (E339), polysorbate 20 (E432) and water for injections
- The product is available in a single clear (type I) glass (USP/Ph.Eur.) vial closed with flurotec coated, grey chlorobutyl serum stoppers and the rubber stopper are latex free and sealed with aluminum seal with plastic flip-off cap component with insert leaflet.
-krabeva 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.

2. Quality aspects:

2.1 Introduction

As mentioned in the aforementioned section

2.2 Drug Substance (Active ingredient)

- **General information**

-Biocon Biologic's Bevacizumab (a proposed biosimilar to bevacizumab) is a recombinant deoxyribonucleic acid (rDNA) derived humanized monoclonal antibody of class immunoglobulin G1 (IgG1) which selectively binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, VEGFR-1 and VEGFR-2, on the surface of endothelial cells.

-The mechanism of action involves the binding of the Fab domain of the monoclonal antibody to the Vascular Endothelial Growth Factors (VEGF) target antigen in the extracellular matrix and preventing it from binding to its receptors (VEGFR-1 and VEGFR2) on the surface of endothelial cells, thereby inhibiting VEGF activities. It also binds to multiple Fcγ receptors and C1q; while Biocon Biologic's Bevacizumab can mediate antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), this is not relevant to its mechanism of action based on binding to VEGF A, a soluble ligand.

- **Manufacture, process controls and characterization:**

➢ **Manufacturer:**

The active substance manufacture, quality control testing are performed at Biocon Biologics -India.

➢ **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.

- **Control of Materials:**

-The raw materials used during the production of 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 fully described in the file. The history and stability of the host cell line has been well established.

-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.

- **Controls of Critical Steps and Intermediates:**

All The critical process parameters and in process controls are illustrated on manufacturing process flow diagram in MA file.

Overall, the proposed controls appear adequate to ensure consistent quality of the DS.

IPC tests have been sufficiently described and validated. In-process data for the Process Performance Qualification (PPQ) batches were presented; all batches met the specifications.

- **Process Validation**

-This section summarizes and discusses the results of process validation data of three full (commercial) scale batches of DS manufactured using the final commercial process.

-The data obtained from assessment of PV batches provides a high degree of assurance that the commercial process, in addition, the results for the supporting studies to justify hold time of intermediates, clearance of process impurities, impurity spiking and resin re-usability have been presented in this section.

- **Manufacturing Process Development**

The manufacturing process development of the active substance was initially based on a manufacturing process which was then optimized 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.

- The details regarding manufacturing process development and the changes made from process A to process B are described in MA file.

- **Characterization**

**Summary of Physico-chemical and Functional Characterization of Biocon Biologic's Bevacizumab (Bevacizumab) DS Compared to Avastin® EURP and USRLD batches:

- **The primary structure:** Intact mass profile and the molecular mass of Biocon's Bevacizumab DS PV batches were consistent, within the theoretical mass range and comparable to Biocon's Bevacizumab IRS and Avastin® EURP and USRLD batches. The light chain and heavy chain molecular mass of Biocon's Bevacizumab DS batches were observed to be consistent within the three DS batches and were comparable with Biocon's Bevacizumab IRS and Avastin® EURP and USRLD batches.

- **Secondary and tertiary structure:** The disulphide bridges in Biocon Biologic's Bevacizumab batches and Avastin® EURP and USRLD batches were found to be conserved and connected, indicative of a folded protein.

- **biological activity:** Biocon Biologic's Bevacizumab PV DS batches and Avastin® EURP and USRLD batches showed similar biological activity in binding to VEGF165 and inhibition of VEGF165 induced proliferation assay which is mechanism of action for bevacizumab.

Specification

-The release specification comprises tests for appearance and description, identity, purity and impurities, process related impurities, potency, quantity, excipient microbial safety, and general tests
-some analytical procedures comply with USP, Ph.Eur and other ones are in-house which is fully validated.

- These specifications have been developed in line with ICH Q6B and pharmacopeia

Recommendations to ensure the product quality and batch-to-batch consistency of final drug substance.
-SOPs were provided with the MA file.

- **Batch analysis**

-The details of the Biocon's Bevacizumab DS several batches manufactured at full scale using different versions of the manufacturing processes are provided in file.

-The results were within the predefined specifications in place at the time of testing and confirm consistency of manufacturing process.

- **Reference Standards or Materials**

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

-All reference standard materials are stored in cryovials at -80°C ± 5°C.

-Characterization & stability protocol for each standard are well described in the MA file and all results have been found to be compliant with the respective acceptance criteria.

- **Container closure system**

-The drug substance (DS) is stored in single-use, sterile bag.

-all the primary packaging components are identified in the file.

-The extractable study report, screening leachable report and a toxicological risk assessment for leachable are provided in MA file.

- **Stability of drug substance**

  Approved Shelf Life: 36 months

  Approved Storage Conditions: Store at -20°C ± 5 °C

i. Drug product:

➢ **Description and Composition of the Drug Product:**

Description of the dosage form:

-The Drug Product (DP) is a sterile, preservative free, clear to slightly opalescent, colorless to pale brown solution in a single dose vial for intravenous use. The drug product is supplied in either 100 mg/4mL or 400 mg/16 mL single dose vial presentation, both containing Bevacizumab concentration at 25 mg/mL.

The drug product is formulated with α, α - trehalose dihydrate, sodium dihydrogen phosphate dihydrate/ sodium phosphate monobasic dihydrate, sodium phosphate dibasic anhydrous/ disodium phosphate anhydrous and polysorbate 20.

Pharmaceutical Development

Formulation Development

The pharmaceutical development for (DP) was focused to develop a formulation that was highly similar to the reference product, Avastin® from a quality and stability perspective.

- The reference product Avastin® in US and EU are available in 2 presentations: 100 mg/4 mL and 400 mg/16 mL as single dose vials. Correspondingly, Mylan has also developed Biocon's Bevacizumab 100 mg/4 mL and 400 mg/16 mL single-dose vials. Both the presentations are intended for commercialization. Biocon's Bevacizumab 100 mg and 400 mg presentations has a same strength, route of administration, dosage form and similar formulation as the reference product Avastin® 100 mg and 400 mg presentation.

Manufacturing Process Development

-The manufacturing process of Krabeva 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 have 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.

Compatibility
- The compatibility of the Biocon Biologic's Bevacizumab solution for intravenous infusion with proposed USP/Ph. Eur. Type I glass vial closed with a chlorobutyl rubber stopper coated with a fluoro polymer laminate has been demonstrated by stability data provided in file.
-Based on the data obtained from this study, the Biocon's Bevacizumab DP is found to be physically, chemically and microbiologically stable for 70 days at 2˚C to 8˚C in PVC and PO bags containing 0.9 % w/v sodium chloride solution (saline) for injection. The relevant data supporting infusion stability is provided in MA file.

- **Manufacture of the drug product:**

- **Description of manufacturing process and process controls along with manufacturers and responsibilities.**
  Manufacturer:
  -The facility involved in the manufacturing and testing of the DP is Biocon Biologics Limited - INDIA;

  - **Control of critical steps and intermediates**

-The manufacturing process for the DP consists of a standard aseptic manufacturing process and is controlled by in-process control (IPC) testing performed during manufacture. Further details on identified critical steps and process controls during manufacturing process of product (DP) are provided in MA file.
***The manufacturing process for Biocon Biologic's Bevacizumab DP does not give rise to pharmaceutical intermediates.

- **Process validation and / or evaluation**

- the DP manufacturing process has been validated at B2 filling line using three consecutive commercial scale batches for each presentation which have been processed in the same manufacturing facilities.
-These validation batches were produced using the validated aseptic manufacturing process in full compliance with cGMP practices at Biocon Biologics India Limited, Bengaluru, India.
-The detailed validation procedures for each manufacturing step is presented in the MA file and found satisfactory.
-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 characterization studies and are considered justified.

- **Product specification:**

-The specifications proposed for release and stability testing of Krabeva finished product comply with Ph. Eur.
- The specifications for the finished product comprise tests for Appearance and Description, identity, purity and impurities, quantity, potency, general attributes and microbial safety.
-Detailed SOPs, validation protocols & reports are provided for the in-house methods
- Justification of the drug product specifications at the release and during stability studies are provided.
-All excipients used for Krabeva drug product are compendial
-No excipients of human or animal origin are used and no novel excipients.

- **Reference Standards or Materials**

-The reference standards for Biocon Biologic's Bevacizumab 100 mg and 400 mg presentation DP are the same as of the Biocon Biologic's Bevacizumab drug substance. No other DP specific reference standards are used in the testing of the DP.

- **Container closure system**

-The Biocon Biologic's Bevacizumab DP is filled in 6R, Type-I clear glass vial (USP/Ph.Eur) for 100 mg presentation and 20 mL, Type-I clear glass vial (USP/Ph.Eur) for 400 mg presentation. Both 6R and 20 mL vials closed with FluroTec coated, chlorobutyl serum stoppers. The rubber stoppers are sealed with an aluminium seal with plastic flip-off cap component. The seal and cap do not come into contact with the drug product.

- **Stability of the drug product**

Based on available stability data

- **Approved Shelf Life: 30 months**
- **Approved Storage Conditions: Store in refrigerator (2-8 ◦C).**
- Do not freeze. Keep the vial in the outer carton in order to protect from light.
- Do not shake the vial
- **Chemical and physical in-use stability:** has been demonstrated for a period of up to 70 days at 2°C to 8°C and a period of up to 15 days at 23°C to 27°C in sodium chloride 9 mg/mL (0.9%) solution for injection
- **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.

- Biosimilarity

-Biocon Biologic's Bevacizumab, a proposed biosimilar to reference drug product Avastin is produced in a Chinese Hamster Ovary (CHO) mammalian cell expression system and is composed of 2 identical heavy chains and 2 identical light chains, which are cross-linked by disulfide bonds. Biocon Biologic's Bevacizumab has approximated molecular weight of 149 kDa and has 214 and 453 amino acids in individual light chain and individual heavy chain respectively. The heavy chain has only one N-linked glycosylation site on asparagine 303. There are no N-linked glycosylation sites in the light chain. Biocon Biologic's Bevacizumab has 16 disulfide bonds which includes 12 intra chain (4 in each heavy chain and 2 in each light chain) and 4 inter chain (2 between each heavy chain and light chain and 2 between two heavy chains).
- The US-Licensed Avastin and EU-Approved Avastin are available in two single dose presentations, 100 mg/vial (4 mL of 25 mg/mL) and 400 mg/vial (16 mL of 25 mg/mL). Proposed biosimilar Biocon's Bevacizumab has also been developed for both presentations with identical formulation buffer. The DS is manufactured as ready-to-fill bulk formulation at the required concentration of 25 mg/mL. Therefore, from a DP manufacturing perspective, the same DS batch can be used to prepare either of these presentations (100 mg or 400 mg). The DP manufacturing process is independent of presentation size, except for the filling step. The final drug product is filled either in (a) a 6R USP/EP type -1 glass vial, stoppered with a 20 mm grey colored, chloro butyl FluroTec™ coated serum rubber stopper and sealed with 20 mm aluminium flip-

off seal for 100 mg presentation, or in (b) a 20 mL USP/EP type -1 glass vial, stoppered with a 20 mm grey colored, chloro butyl FluroTec™ coated serum rubber stopper and sealed with 20 mm aluminium flip-off seal for 400 mg presentation. The material of construct for the container closure system used for both the presentations is similar in nature.

-Stability comparability has been evaluated for the Biocon's Bevacizumab 100 mg/vial and 400 mg/vial drug product presentations at real-time long-term storage condition of 2-8° C to justify pooling the data from both the presentations for assessing the similarity of proposed biosimilar Biocon's Bevacizumab with US-Licensed Avastin and EU-Approved Avastin. Physico-chemical assays like SEC, IEX, CE-SDS (reducing and non-reducing) and functional assay such as inhibition of VEGF165 induced HUVEC proliferation were evaluated for the assessment. These tests were selected as they monitor the quality attributes that may be impacted upon long term storage and thus affect safety and efficacy of the product.

Analytical Method Description

-Extensive evaluation of physicochemical similarity between Biocon's Bevacizumab, US-Licensed Avastin and EU-Approved Avastin has been conducted using sensitive techniques to examine primary structure, secondary structure, tertiary structure, content, charge variants, glycosylated variants, and other post-translational modifications. Additionally, comprehensive evaluation of functional attributes including VEGF binding, inhibition of VEGF induced proliferation in HUVEC, inhibition of VEGF induced VEGFR-2 phosphorylation and Fc receptor binding have been conducted for Biocon's Bevacizumab, US-Licensed Avastin and EU-Approved Avastin lots. Methods used were either validated/qualified or demonstrated to be suitable for their intended use. All data are reported from batches which have met system suitability criteria.

3. Non-clinical and clinical aspects:

In accordance with national and international biosimilar guidelines; the nonclinical development of krabeva was performed, including a comparative battery of in vitro analyses of biological activity and in vivo single and repeated dose toxicity; including toxicokinetics (TKs).

-The toxicology program was conducted in compliance with GLP regulations as claimed by the applicant.

➢ **Pharmacology:**

- The results obtained across the in vitro assays demonstrated that krabeva and its reference Avastin are **highly similar** in terms of primary PDs related to binding to its target vascular endothelial growth factor (VEGF), VEGFR-2 phosphorylation, inhibition of VEGF-induced proliferation of endothelial cells (HUVEC), and secondary PDs related to binding to representative isoforms of the relevant three Fc gamma receptors (FcγRI, FcRII and FcRIII), FcRn and complement (C1q) in addition to Fab-associated functions; and Fc-associated functions (ADCC, CDC and complement activation).
- Minor differences were observed when comparing krabeva to Avastin-US and Avastin-EU in some assays, however, these differences were smaller than the log-order differences generally needed to observe a physiological impact from different binding kinetics. The lack of biologically significant impact of the minor differences in VEGF-121 binding is supported by the data from the functional assay.
- Given the absence of meaningful in vitro biological differences, no in vivo PDs studies have been considered necessary which is in line with national and international biosimilar guidelines.

➢ **Toxicology (including TKs):**

- Generally, krabeva was well tolerated in acute and repeat-dose studies in mice and rabbits, causing no notable toxicity at the highest doses tested in both species. The No Observed Adverse Effect Levels (NOAELs) derived from the repeat dose studies were 445 and ≥ 133.5 mg/kg/dose in mice and rabbits, respectively.
-In the pivotal, comparative repeat-dose study in cynomolgus monkeys, no overt toxicity was observed for krabeva or for its reference Avastin. Findings were limited to those expected from the pharmacology of bevacizumab and were similar between both drugs.
- No dedicated developmental or reproductive toxicology studies were conducted. However, it should be noted that an adverse effect on maturation of ovarian follicles and absence of corpora lutea, decreased uterus weight, and decreased ovarian weight were observed within the repeat-dose toxicity study in cynomolgus monkeys with both krabeva and Avastin.
- No genotoxicity and carcinogenicity toxicity studies have been performed in line with national and international biosimilar guidelines.
- Fundamentally, results from TK analysis indicate a tendency for drug accumulation. Maximum serum concentrations and exposure levels for both krabeva and its reference Avastin were similar in males and females. There were no notable differences in the serum concentrations or the TK parameters between the two compounds.
- It worth mentioning that besides the observed effects reported in the studies conducted by the applicant, preclinical studies conducted by the innovator observed that bevacizumab is associated with reduced wound healing capacity and teratogenicity in rabbit studies. These effects are plausibly linked to the pharmacologic mechanism of action for bevacizumab.

Overall conclusion: Based on the totality of evidence, the results from preclinical in-vitro and in vivo studies demonstrate the biosimilarity between krabeva and the reference drug Avastin.

Therefore, the non-clinical development of krabeva ***is -overall acceptable***

4.Clinical aspect:

- **Pharmacokinetics**

The bevacizumab PK parameters following single dose administration of MYL-1402O, US-Avastin® and EU-Avastin® showed PK equivalence between the three products **PD**

- **Clinical Efficacy conclusion**

There are no concerns regarding similarity of efficacy result between MYL-1402O, US-Avastin® and EU-Avastin® in all submitted studies

As mentioned of pivotal study, the presented ORR analyses indicate similar efficacy between MYL-1402O and EU-Avastin.

- **Clinical Safety conclusion**

The safety profile of MYL-1402O was well tolerated regarding the submitted studies

Overall, the most adverse events were gastrointestinal Perforations that occurred as intra-abdominal abscess constipation and vomiting, wound Healing Complications haemorrhage that including haemoptysis, gastrointestinal bleeding, central nervous systems bleeding, epistaxis, and vaginal bleeding and Eye Disorders,

- **Immunogenicity**

Overall, there were low relative ADA concentration calculated for all ADA positive samples, there was no clinical impact of the observed ADA levels, according to the submitted studies

5. Benefit/ Risk discussion:

- Krabeva 100,400 mg is favorable in the treatment of metastatic carcinoma of the colon or rectum, metastatic breast cancer, unresectable advanced, metastatic or recurrent non-small cell lung cancer, advanced and/or metastatic renal cell cancer, epithelial ovarian, fallopian tube or primary peritoneal cancer, persistent, recurrent, or metastatic carcinoma of the cervix

6. **General Conclusion and Recommendations if any:**

Based on the review of CTD modules and other supplementary documents, the product is approved.