EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2022
EMA/CHMP/636045/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vegzelma

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/005534/0000

Note

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

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Administrative information

Name of the medicinal product:	Vegzelma
Applicant:	Celltrion Healthcare Hungary Kft. Westend Office Building B Torony Vaci Ut 1-3 1062 Budapest HUNGARY
Active substance:	Bevacizumab
International Non-proprietary Name/Common Name:	bevacizumab
Pharmaco-therapeutic group (ATC Code):	other antineoplastic agents, (L01FG01)
Therapeutic indication(s):	Vegzelma in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum. Vegzelma 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. Vegzelma 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 Vegzelma in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1. Vegzelma, 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 (NSCLC) other than predominantly

	squamous cell histology. Vegzelma, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSCLC with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1). Vegzelma, in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer. Vegzelma, 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). Vegzelma, 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 vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents. Vegzelma 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 (see section 5.1). Vegzelma, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see section 5.1).

Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	25 mg/ml
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial and 10 vials

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List of abbreviations

ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ASAT	aspartate aminotransferase
ATE	arterial thromboembolism
AUC	area under the curve
AUC0-72	area under the concentration time curve from 0 hour to 72 hours
BLA	biologics license application
BOR	best overall response
BSA	body surface area
C1q	complement component 1, Q subcomponent
CDC	complement-dependent cytotoxicity
CELISA	cellular enzyme-linked immunosorbent assay
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
CHF	congestive heart failure
CI	confidence interval
Cmax	maximum serum concentration
CMC	Chemistry, Manufacturing and Control
CNS	central nervous system
COVID	Coronavirus disease
CPK	creatine phosphokinase
CR	complete response
CrCl	creatinine clearance
CSR	clinical study report
CT	computerised tomography
CTCAE	common terminology criteria for adverse events
CTD	common technical document
Ctrough	trough serum concentration
CV	coefficient of variation
DKMA	Danish medicines agency
DP	drug product
DRM	data review meeting
DSMB	data safety monitoring board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMA	European medicines agency
EMEA	Europe, Middle East, and Africa
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life
EOT	end of treatment
EU	European Union
Fc	fragment crystallizable

FcRn	neonatal Fc receptor
FcγRI	Fc-gamma receptor I
FcγRIIa	Fc-gamma receptor II a
FcγRIIb	Fc-gamma receptor II b
FcγRIIIa	Fc-gamma receptor III a
FcγRIIIa-F	Fc-gamma receptor III a-F
FcγRIIIa-V	Fc-gamma receptor III a-V
FcγRIIIb	Fc-gamma receptor III b
FDA	Food and Drug Administration
FTIR	Fourier transformed Infrared spectroscopy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	host cell proteins
HIV	human immunodeficiency virus
HMW	high molecular weight
HPLC	high performance liquid chromatography
HUVEC	human umbilical vein endothelial cells
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IEC-HPLC	ion exchange HPLC
IPC	in-process control
IRB	institutional review board
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
KDR	kinase insert domain receptor
kg	kilogram(s)
LLOQ	lower limit of quantification
LMW	low molecular weight
MAA	marketing authorisation application
MCB	Master Cell Bank
mCRC	metastatic carcinoma of the colon or rectum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
MNAR	missing not at random
MoA	mechanism of action
MPA	medical products agency (Sweden)
MRI	magnetic resonance imaging
NAb	neutralising antibody
NCI	National Cancer Institute
NE	inevaluable
NSCLC	non-small cell lung cancer
nsNSCLC	non-squamous non-small cell lung cancer

OECD	Organisation for Economic Co-operation and Development
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PlGF	placental growth factor
PP	per protocol
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PT	preferred term
PVG	pharmacovigilance
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-LC13	Quality of Life Questionnaire Lung Cancer-specific module
QoL	quality of life
QTPP	quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumors
RH	relative humidity
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SEC-HPLC	size exclusion HPLC
SmPC	summary of product characteristics
SOC	system organ class
SPR	surface plasmon resonance
TEAE	treatment-emergent adverse event
TEAESI	treatment-emergent adverse event of special interest
TESAE	treatment-emergent serious adverse event
TK	toxicokinetic(s)
TSE	Transmissible Spongiform Encephalopathy
TTP	time to progression
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VTE	venous thromboembolism
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celltrion Healthcare Hungary Kft. submitted on 8 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Vegzelma, 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:

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

Vegzelma 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.

Vegzelma 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 Vegzelma in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1.

Vegzelma, 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 (NSCLC) other than predominantly squamous cell histology.

Vegzelma, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSCLC with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1).

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

Vegzelma, 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).

Vegzelma, 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 vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents.

Vegzelma 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 (see section 5.1).

Vegzelma, 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).

1.2. Legal basis and dossier content

The legal basis for this application refers to:

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

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

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Avastin, 100 mg and 400 mg, 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, EU/1/04/300/002

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

- Product name, strength, pharmaceutical form: Avastin, 100 mg and 400 mg, 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, EU/1/04/300/002

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

- Product name, strength, pharmaceutical form: Avastin, 100 mg and 400 mg, 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, EU/1/04/300/002

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

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

Date	Reference	SAWP co-ordinators
21 July 2016	EMA/CHMP/SAWP/476333/2016	Ira Palminger Hallen; Kirstine Moll Harboe

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Physico-chemical and biological testing approach to demonstrate comparability of CT-P16 to the reference product Avastin.
- Release specifications of CT-P16 active substance and drug product.
- Assessment of potency of CT-P16 active substance and drug product by vascular endothelial growth factor (VEGF) blockade assay using kinase insert domain receptor (KDR) HEK293 cell line.
- Adequacy of CT-P16 non-clinical development to support clinical development programme.
- Design of an in vivo xenograft study in mice to compare the inhibition of tumour growth between CT-P16 and the reference product.
- Design of Phase 1, randomised, double-blind, three-arm, parallel group, single-dose study in healthy male subjects to compare CT-P16 to EU- and US-approved Avastin including study population, dose, primary PK endpoints, sampling duration, sample size, equivalence margin, necessity of VEGF-A evaluation.
- Design of Phase 3, randomised, double-blind clinical study to compare efficacy, safety, and immunogenicity of CT-P16 and Avastin in patients with not squamous non-small cell lung cancer and metastatic colorectal cancer including study population, primary, secondary, and tertiary endpoints, statistical plan, sample size, statistical power.
- Extrapolation of clinical study results to all indication of the reference product.
- Size of safety and immunogenicity database.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Andrea Laslop

The application was received by the EMA on	8 October 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	25 April 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	19 May 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	8 June 2022
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 Vegzelma on	23 June 2022
The CHMP adopted a report on similarity of Vegzelma with Zejula on	23 June 2022

2. Scientific discussion

2.1. Problem statement

About the product

Vegzelma has been developed as a biosimilar to the reference product Avastin (bevacizumab). The applicant is claiming all of the approved indications for Avastin.

The active substance (bevacizumab) is a recombinant humanised monoclonal IgG1 antibody. The mechanisms of action (MoA) of bevacizumab is known as Fab-mediated neutralizing activity. The Fab region of CT-P16 has the ability to bind and neutralise VEGF to block its binding to VEGF receptors (VEGFR1 and VEGFR2) thereby inhibiting the process of angiogenesis in tumours.

The applicant is seeking marketing authorisation for CT-P16 in accordance with Article 10(4) of Directive 2001/83/EC, as amended. The reference biological medicinal product Avastin was originally approved in the US in February 2004 and in the EU in January 2005 (EMEA/H/C/000582).

2.2. Quality aspects

2.2.1. Introduction

Vegzelma has been developed as biosimilar to the reference medicinal product Avastin. The finished product is presented as concentrate for solution for infusion containing 25 mg/mL of bevacizumab as active substance. The finished product is supplied in two presentations, i.e. 100 mg /4 mL and 400 mg/16 mL in single-use vials and are the same as approved for the reference product.

Other ingredients are: trehalose dihydrate, sodium phosphate, polysorbate 20 and water for injections.

The finished product is available in Type I glass a vial with a chlorobutyl rubber stopper and aluminum flip-off seal.

2.2.2. Active Substance

2.2.2.1. General information

The active substance (AS) is bevacizumab, a recombinant humanised monoclonal IgG1 antibody (referred by the applicant as CT-P16). Like other IgG of IgG1 subclass, CT-P16 is a glycoprotein with one N-linked glycosylation site in the CH2 domain of each heavy chain. The detected oligosaccharides consist mostly of G0F and G1F structures. The molecular weight is 146,306 g/mol and formulae for the light and heavy chains are $C_{1034}H_{1595}N_{273}O_{338}S_6$ and $C_{2229}H_{3409}N_{583}O_{677}S_{16}$, respectively. Each heavy chain consists of 453 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. Each heavy chain contains an N-linked oligosaccharide at glycosylation site at N303. All cysteines in the heavy and light chain are involved in either intra- chain or inter-chain disulfide bonding.

The mechanisms of action (MoA) of bevacizumab is known as Fab-mediated neutralizing activity. The Fab region of CT-P16 has the ability to bind and neutralise VEGF to block its binding to VEGF receptors (VEGFR1 and VEGFR2) thereby inhibiting the process of angiogenesis in tumours.

2.2.2.2. Manufacture, process controls and characterisation

CT-P16 is produced and release tested at Celltrion Plant II Korea. The process setup is a standard monoclonal technology. Upstream process consists of several cell expansion steps, harvest, clarification and finally filtration. In the downstream process the clarified harvest is purified using a series of purification steps. Purification includes virus inactivation and removal steps (low-pH hold and nanofiltration) and final filtration.

Information on the source of the cell substrate and analysis of the expression construct used to develop the Master Cell Bank is described in satisfactory detail. Chinese hamster cells were used to generate the transfected cell line. Selection process of production cell line is described adequately. A common two-tiered cell banking system consisting of a Master Cell Bank (MCB) and Working Cell Bank (WCB), is used. Overall, the cell banking system, including characterisation and testing is adequately described.

Critical parameters include AS-related attributes, process/material-related impurities, general requirements and formulation-related attributes. Relevant process parameters are set to control the manufacturing process. Process characterisation and validation studies support the established process parameters.

Process validation studies were performed at commercial scale. Overall, there were no batch failure during validation, and all AS results met acceptance criteria. Some deviations were observed during the process validation studies. In general, observed deviations are adequately discussed and relevant adjustments were applied.

Characterisation studies were performed using several batches of AS manufactured using the current process and several lots of finished product (FP) manufactured using AS from the current process. The characterisation studies include determination of primary and higher order structure, charge variants, N-linked glycans, purity, and biological activity. Overall, the performed characterisation studies are considered relevant and cover a wide variety of physicochemical and biological characterisation studies. Justification of the identification and classification of the product-related impurities can be agreed.

The development of the manufacturing process and the comparability studies conducted were adequately described. Generally, comparability assessment covers all necessary tests to conclude the similarity of the AS before and after the manufacturing changes between earlier processes and current one. Description of changes and reasons for changes (justification) with respect to the impact on quality was provided and is acceptable.

2.2.2.3. Specification

The release specification includes tests for general attributes, microbial, identity, glycosylation, purity and impurities, content, and potency.

Overall, the proposed test parameters are considered relevant and cover variety of physicochemical test methods and one parameter for biological activity. The proposed acceptance criteria are agreeable.

The stability specification test items are identical to that employed at release with the exception of parameters, for which no change is expected; this is acceptable.

Analytical methods were sufficiently described including system suitability testing and assay acceptance criteria of the methods and listing of key materials and equipment. Qualification of used standards and antigen for HCP and residual host cell DNA was described in section S.5. Representative chromatograms were provided for relevant methods. The Validation for the used analytical methods has been adequately performed.

The reference standards used during the product development and for routine batch release use, have been adequately described. A two-tiered reference standard system is used for commercial manufacturing including primary reference standard (PRS) and working reference standards (WRS). The WRS is used for routine lot release and stability testing, as well as other quality activities such as investigations and method transfers/validation.

The active substance is filled into pre-sterilised, pyrogen free polycarbonate bottles. Representative certificates of analysis provided by the vendor are provided. The CHMP made a recommendation (REC) to the applicant to submit the final report for the leachables studies for the active substance container closure in H1/2026. In summary, the container closure system is considered suitable.

2.2.2.4. Stability

Stability data at long-term (-40 ± 5°C), intermediate (5 ± 3ºC) and at accelerated (25 ± 2ºC / 60 ± 5% RH) stability conditions was provided. All stability batches were manufactured at CELLTRION Plant II (CLT2) at commercial batch scale. Batches manufactured by the previous process were used to manufacture product for clinical studies. For these batches, real-time stability data is completed and available for 60 months at long-term conditions, 12 months at intermediate conditions and for accelerated conditions for 6 months. Stability data for batches manufactured with the commercial process is available for 12 months at long-term conditions. For studies under intermediate and accelerated conditions (study completed), 12 months and 6 months data is available, respectively. In addition, photostability study results for one batch (commercial process) were provided. Shelf-life of 60 months at −40±5°C is being proposed.

Long-term stability results demonstrate that all quality attributes studied were within the acceptance criteria through 60 months for all clinical lots with minor exception; all long-term results available for the current process batches (i.e. up to 12 months) comply as well. Intermediate stability study results comply with specifications and are completed for batches manufactured with the current process. Accelerated stability study results revealed a downward trend and OOS results in some parameters and an upward trend others.

The applicant has conducted photostability studies and concluded, that the AS should be protected from light as changes in some quality attributes were observed in the AS when stored without light protection.

Overall, the provided stability data support the proposed shelf-life for the AS packaged in the proposed container closure (polycarbonate bottles) and stored at the recommended storage condition.

2.2.3. Finished Medicinal Product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is a sterile liquid solution containing 400 mg or 100 mg of bevacizumab active substance. Each vial is designed to deliver a single dose of 400 mg or 100 mg active ingredient in 16 mL or 4 mL of solution at a nominal concentration of 25.0 mg/mL. The finished product contains the active

substance (bevacizumab), di-sodium hydrogen phosphate, anhydrous, sodium dihydrogen phosphate monohydrate, α, α - trehalose, dihydrate, polysorbate 20, and water for injection.

The development strategy of Vegzelma focused on developing a similar biological medicinal product comparable to EU-approved reference product Avastin. To this end, the CT-P16 formulation used in non-clinical, clinical development and commercial supply are identical to that of Avastin with respect to pharmaceutical form, concentration and composition.

Since the CT-P16 formulation is identical to the reference product, the applicant performed only limited qualitative and quantitative formulation studies, the purpose of which was to demonstrate that the formulation is robust in terms of product stability and quality, and comparable with the reference product. Five formulation parameters were varied as part of this study. The two presentations are comparable and representative of one another in that the AS and formulated bulk product used to make the finished product is identical for the two presentations.

An extensive characterisation of CT-P16 was conducted including physicochemical and biological analysis. The results show that CT-P16 AS and FP have the expected primary, secondary and higher order structure of bevacizumab, acceptable levels of protein content and purity, and the biological activities expected of bevacizumab. The physicochemical and biological comparability program undertaken indicate that CT-P16 AS and FP are comparable with respect to primary structure and post-translational modifications; charge variants; glycation / glycosylation; purity; higher-order structure; content and biological activities as confirmed using a number of orthogonal techniques.

Based on the results of EU approved (and US-licensed) reference product Avastin 100 mg, an overfill is applied during filling of the 100 mg presentation into vials to ensure similarity in protein content and extractable volume. Similarly, based on the results of the 400 mg Avastin, an overfill is applied during filling of the 400 mg presentation into vials to ensure similarity of protein content and extractable volume.

Manufacturing process development

The manufacturing process development has been described in sufficient detail. The production scale, manufacturing site and details of the material usage from each facility were adequately presented. Changes were introduced to the manufacturing process for process validation of the commercial manufacture of both 400 mg and 100 mg presentations with modification of in-process controls. To demonstrate that the change in scale of manufacture of CT-P16 finished product has not adversely impacted product quality, an extensive comparability study has been performed between processes. In addition, during CT-P16 development, changes to the FP manufacturing process for CT-P16 100 mg and CT-P16 400 mg presentations were introduced. A summary of the comparability studies undertaken was provided and sufficiently demonstrated the comparability of each product presentation manufactured with the previous and current process.

Container closure system

The primary container closure system for CT-P16 finished product is composed of a type I borosilicate glass vial, a rubber stopper and a cap. Each CT-P16 finished product vial is packed individually in an outer carton box to prevent exposure to UV light and to protect the vial from any potential physical damage during handling, shipping, and storage.

The glass vials and rubber stoppers comply with the appropriate Ph. Eur. monographs for primary containers and closures.

Results of the leachable studies for vial and stopper indicate that no leachables of toxicological concern are present, which is compatible with vial and stopper. The leachable study will be continued. The vials used for CT-P16 400 mg and 100 mg presentations are manufactured with same type glass vial and the stoppers used are identical.

The CHMP recommended that the leachables study should be continued up to the end of shelf-life. The final study report of the leachables study should be submitted by July of 2026. Furthermore, the Agency should be informed in the event that any compound of toxicological concern is identified in the study at 5 ± 3°C prior to 48 months (REC).

2.2.3.2. Manufacture of the product and process controls

Finished product manufacture is performed at CELLTRION, Inc., Plant II (CLT2), 20 Academy-ro 51 beon-gil, Yeonsu-gu, Incheon, 22014, Republic of Korea.

Three sites are responsible for the physical importation and batch release of the FP to Europe: Millmount Healthcare Ltd., Block 7, City North Business Campus, Stamullen, Co. Meath K32 YD60, Ireland; Nuvisan GmbH, Wegenerstraße 13, 89231 Neu Ulm, Germany and Nuvisan France SARL, 2400, Route des Colles 06410, Sophia Antipolis, France.

The applicant has provided a brief description and a flow chart of the manufacturing process. The 400 mg/16 mL and 100 mg/4 mL (both 25 mg/mL) presentations are manufactured using the same process steps and controls. The only differences between the presentations are the fill volume. All other manufacturing steps and process parameters are the same. The manufacturing process is described with sufficient details.

Appropriate critical process steps and IPCs are described in the dossier. The commercial manufacturing process has been validated. Validation of the finished product manufacturing process included consecutive performance qualifications lots; covering both presentations. The validation lots met the proposed release specifications. Sufficient information is provided on media fills, filter validation and shipping validation

The data gathered during the FP process validation show that the manufacturing process of CT-P16 meets the predetermined quality characteristics and the process validation is acceptable. Moreover, the defined set of process parameters have been shown to be suitable for monitoring the manufacturing process. In addition, ranges and values chosen for the processing parameters are acceptable to support the commercial manufacture of the product.

2.2.3.3. Product specification

The specification for the finished product, include tests for general attributes, microbial safety, identity, purity and impurities, SEC, content, potency.

The methodology for preparation of the specification was in compliance with ICH Q6B. the specification includes the critical quality attributes (CQA) of the product that can affect the safety and efficacy of the finished product and defines the acceptable range of the physicochemical and biological characteristics of the FP. The specification was established based on development data, a reasonable range of expected analytical and manufacturing variability, and reference information including literature, regulatory guidelines, and pharmacopoeial limits. The initially proposed acceptance criteria groups of charge variants and total aggregates have been revised in line with those proposed for the AS. Shelf-life specifications have been adapted accordingly. In addition, as a proposed biosimilar product to EU-approved Avastin, the acceptance criteria also consider the quality range of reference product where appropriate. Overall the specifications limits have been appropriately justified and are acceptable.

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 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.

The analytical methods chosen to monitor the CT-P16 FP's identity, purity, potency and quantity have been demonstrated to be suitable for their intended purpose. Both compendial and non-compendial methods have been adequately validated. Detailed information on the current and previous reference standard lots has been provided and discussed previously in the respective AS section in this report.

The batch analysis data presented derived from several lots of CT-P16 400 mg and several lots of CT-P16 100 mg manufactured throughout development. Data was obtained from testing according to the development specifications in place at the time of batch release. The changes made to analytical methods and acceptance criteria during development of CT-P16 FP were described in the dossier.

Batch analysis data also included commercial scale batches used for process validation, characterisation studies, comparability studies, stability studies, similarity studies, justification of specification. All batches met the acceptance criteria in place at the time of release. The results demonstrate consistency of the manufacturing process capabilities.

2.2.3.4. Stability of the product

Stability studies have been conducted on both presentations 400 mg and 100 mg. The studies were conducted in accordance with the guidance provided in ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products and ICH Q1A (R2) Stability Testing of New Drug Substances and Products. The proposed storage condition for Vegzelma is 5 ± 3°C.

Long-term stability data at 5 ± 3°C has been presented for batches for each presentation manufactured with either the previous or the current process for up to 48 months for the 400 mg and up to 24 months for the 100 mg presentation.

The panel of stability indicating methods applied provides assurance that potential changes in the purity, content and potency will be detected. No trends were observed and all the batches met the acceptance criteria at all timepoints at the long-term storage condition. Assignment of the shelf life is based on real time stability data (400 mg/16 mL 48 months, 100 mg/4 mL 24 months).

In addition, the same 400 mg batches were subjected to accelerated stability study (25 ± 2°C / 60 ± 5% RH), and stress stability study (40 ± 2°C / 75 ± 5% RH). Dilution for infusion stability study (5 ± 3°C and 30 ± 2°C / 75 ± 5% RH), and confirmatory photostability study (1,200,000 Lux hr Vis. and 200 Whr/m2 UV) were performed for each presentations; positioning study was conducted on 400 mg batch.

The proposed shelf-life for diluted product in 100 mL polyolefin (PP and PE) bag containing 0.9% sodium chloride is 60 days at 5 ± 3ºC and subsequently for 7 days at 30 ± 2°C / 75 ± 5% RH, which is acceptable. The finished product is light sensitive, but sufficiently protected by the outer packaging.

Finally, a forced degradation study was performed to characterise and understand the processes and pathways associated with degradation. This study was also conducted to evaluate the similarity of the degradation pathways of Vegzelma and EU-approved Avastin. Comparative stability testing was also performed with several US-licensed Avastin and several EU-approved Avastin under accelerated and stress conditions.

The post-approval stability protocol and the stability commitment has been provided and are considered acceptable.

Taken together, the presented stability data sufficiently support the proposed shelf-life of 2 years (100 mg / 4 mL) and 4 years (400 mg / 16 mL) for the unopened vial at the intended storage conditions (i.e. 2-8°C, protected from light) as per SmPC sections 6.3 and 6.4.

2.2.3.5. Biosimilarity

A comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012) has been performed. Several independent CT-P16 FP batches representative of the commercial scale and several EU-approved Avastin batches were included in the similarity study. The batches reflected a range of expiration dates and product ages. The FP material used in the analytical biosimilarity studies is considered representative of the material used in clinical trials.

The similarity ranges were established for quantitative key quality parameters using data from EU-approved Avastin batches. For key biological quality attributes, a ±3*SD quality range was set by analysis of EU-approved Avastin batches. Results of physicochemical analyses were presented without statistical analysis; instead the mean and SD as well as the spread of the underlying distribution from quantitative analyses have been compared and differences have been highlighted and discussed. Since tabular and graphical presentation allows for a clear comparison of CT-P16 to the RMP, this is considered acceptable. In addition, generally sufficient raw data has been provided to allow assessment of biosimilarity independently of statistical approach chosen. The overall approaches used for establishment of the biosimilarity assessment criteria are considered acceptable.

The comparative testing included analysis of primary structure and post-translational modifications, biological activity, glycation and glycosylation, charge heterogeneity, purity/impurity, disulfide bonds, higher order structures, content, and comparative forced degradation studies of CT-P16 and EU-approved Avastin. Appropriate analytical methods have been utilised to ensure an understanding of the EU-approved Avastin product profile and the CT-P16 product developed.

A summary of the results including a critical evaluation of biosimilarity is presented in Table 1.

Table 1. Summary of biosimilarity assessment between Vegzelma and EU-Avastin

Molecular parameter	Attribute	Methods	Key findings, conclusions
Primary structure	Intact Mass	LC-MS (reduced)	The mass of LC and HC were similar for the 2 products.
	Amino acid sequence	Peptide mapping LC-MS	Amino acid sequence coverage was confirmed to be 100 %, and the amino acid sequence of CT-P16 was confirmed to be identical to the sequence of EU-approved Avastin. Both products have the same N-terminal and C-terminal sequences.
	Post-translational modifications		

	N/C-terminal integrity	Peptide mapping MS-MS	CT-P16 and EU-approved Avastin contain the same post-translational modifications but with minor quantitative differences. The observed differences are small and adequate justification based on scientific literature was included for the lack of potential clinical relevance / impact. Overall, similarity in terms of primary structure was demonstrated.
Higher order structure	Secondary and tertiary structure	Far/Near UV CD, DSC, FTIR	Secondary and tertiary structure appear comparable. The same disulphide bond linkages in CT-P16 and EU-approved Avastin has been demonstrated. Minor differences were noted in the level of free thiol groups as compared to EU-approved Avastin.
	Disulphide bonds	Native / reduced peptide mapping LC-MS	
	Free thiols	Ellman's assay	
Content	Protein content	OD280	CT-P16 and EU-approved Avastin are similar in their protein concentration.
	Extinction coefficient	Amino acid analysis	
Charged variants	Basic species, acidic species and main variants	icIEF	The icIEF electropherograms show a similar pattern in all samples. Any detected difference are considered unlikely to be clinically significant. Minor differences between CT-P16 and EU-approved Avastin were noted in the relative proportion of the charge variants. However, based on the characterisation results presented, it can be concluded that the slight differences observed in charge variant profiles are clinically insignificant. All variants are biologically active. The applicant has appropriately discussed and justified the differences detected in CT-P16 and EU-approved Avastin to support the similarity.
		IEC-HPLC	
		Isolated fractions were further characterised via Peptide mapping (LC-MS), SEC-HPLC, CE-SDS (reduced/non-reduced), Intact mass analysis (reduced / non-reduced), VEGF-A165 Binding (ELISA), anti-proliferation assay using HUVECs, FcγRIIIa (V-type) binding affinity and FcRn binding affinity (SPR)	
Glycation and glycosylation	Glycation	LC/MS	CT-P16 was shown to have minor differences in glycation level and oligosaccharide profiles compared to EU-approved Avastin, but it has been sufficiently justified that these differences are highly unlikely to be of clinical relevance.
	N-linked glycans	Peptide mapping (LC/MS)	
	Oligosaccharide profile (afucosylation, high mannose variants, galactosylation, sialylation)	HILIC-UPLC-FLD	
		SEC-HPLC (diluted, non-diluted)	CT-P16 and EU-approved Avastin are primarily monomers and similar in their size heterogeneity.

Aggregates, fragmentation, aglycosylation	Monomers, dimers, HMW, purity/impurity	SEC-MALS	SEC-MALLS analysis indicated that the molecular weights of the monomer and HMW forms in CT-P16 and EU-approved Avastin were similar and that the HMW forms of both products consist predominantly of dimers. Non-glycosylated HC in CT-P16 and EU-approved Avastin had a similar impact on biological activity. Any observed differences are not considered clinically relevant.This conclusion is also supported by similar biological activities of the two products.
		AUC	
		CE-SDS (non-reduced/reduced)	
		Impact of non-glycosylation on Fc and Fab functionality was assessed via binding affinities to FcγRIIIa-V, FcRn, VEGF-A165 binding (ELISA) and anti-proliferation assay using HUVEC	
Biological activity	Potency	Anti-proliferation assay using HUVEC	CT-P16 and EU-approved Avastin are highly similar in their inhibition of cell proliferation and binding to VEGF-A. The descriptions and qualification data that have been provided for the analytical methods used for the analytical comparability exercise are considered sufficient. Any observed differences are unlikely to be clinically meaningful. The lack of effector functions was demonstrated in CT-P16 and EU-approved Avastin batches. In addition, CT-P16 and EU-approved Avastin were demonstrated to inhibit VEGFR2 RTK autophosphorylation and to be unable to bind a range of VEGF-A isoforms and VEGF family. Based on the biological activity similarity assessment, CT-P16 is similar to EU-approved Avastin.
	VEGF-A binding	Binding to VEGF-A165 and VEGF-A121 (ELISA)	
		Binding to VEGF-A145, VEGF-A189, VEGF-A206, VEGF-B, VEGF-C, VEGF-D, VEGF-E, PlGF-2, PlGF-2 (ELISA)	
	VEGFR2 RTK auto-phosphorylation	HUVEC (ELISA)	
	Binding to C1q	ELISA	
	Binding to FcγRIIIa (158F and V158), FcγRIIIb, FcγRIIa, FcγRIIb, FcRn, FcγRI	SPR	
	Effector functions	ADCC using SKOV-3/PBMC	
		CDC assay	
Degradation profile	Degradation due to high temperature, oxidative stress, UV-light, low and high pH stress	Protein concentration, IEC-HPLC, Peptide mapping (LC/MS), SEC-HPLC (diluted/undiluted), CE-SDS (non-reduced/reduced), Oligosaccharide profile (HILIC-UPLC_FLD), Anti-proliferation assay using HUVEC, VEGF-A165 binding (ELISA), FcRn and FcγRIIIa (V158) binding (SPR)	Similarity in degradation studies was demonstrated.

Similarity between CT-P16 and EU-approved Avastin has been demonstrated for the following physico-chemical and biological properties:

- Primary and higher order structure
- Content
- Charge heterogeneity
- Glycan profile

- Size heterogeneity and purity/impurity profile
- Antiproliferation activity, and binding to VEGF-A165 and VEGF-A121
- Binding to FcγRIIIa (F-type, V-type), FcγRIIa, FcγRIIb, FcγRI, FcRn, C1q
- ADCC and CDC activity
- Inhibition of VEGFR2 RTK autophosphorylation
- Binding to VEGF-A isoforms (VEGF-A145, VEGF-A189, VEGF-A206) and VEGF family (VEGF-B, -C, -D, and -E; PlGF-1 and -2)
- Stability under forced degradation

Minor differences in the levels of post-translational modifications, free thiol groups, relative proportion of the charge variants, individual fucosylated glycan species, levels of glycation, and levels of monomer, HMW, LMW, HC+LC and NGHC were sufficiently justified to have no clinical impact.

In conclusion, analytical similarity between Vegzelma and EU-approved Avastin has been demonstrated satisfactorily.

2.2.3.6. Post approval change management protocol(s)

N/A

2.2.3.7. Adventitious agents

The approach for adventitious agents testing was described. The MCB and WCB testing is reviewed as part of the AS control, as well as the control of raw materials. The results of viral testing performed as part of cell line qualification demonstrate that CT-P16. MCB and WCB are free of adventitious and endogenous viral agents. These results also indicate that no viral contamination occurred during cell line development and cell banking MCB and WCB testing is reviewed as part of the AS control, as well as the control of raw materials.

Viral clearance studies were performed with a suitable panel of model viruses on qualified small-scale models. Overall, the virus clearance studies are adequate. The original study reports of the virus clearance studies have been provided. The virus assays are sufficiently described in the original reports. A brief description of the qPCR assay for quantitation of MVM has been provided by the applicant. The safety margin over the estimated retroviral burden per Retrovirus-like particles in unprocessed bulk is considered satisfactory.

The TSE risk associated with the raw materials used during the development of the production cell line has been presented in the dossier. No materials of animal origin are used during manufacture of the FP. On the basis of presented information, it can be concluded that there is minimal risk of contamination by TSE in the final product.

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. No major objections have been raised concerning the AS and FP. The available quality data support biosimilarity versus EU-approved Avastin. The risk for adventitious agents is adequately controlled. 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 two minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the below aspect and are put forward and agreed as recommendations for future quality development:

-updated leachable studies data should be provided and the final study results submitted upon completion of the studies for the both the AS and the FP.

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:

Area	Number	Description	Classification*	Due date
Quality	1	to submit in H1/2026 the final report for the leachables studies for the active substance container closure.	REC	June 2026
Quality	2	to continue the leachables study to evaluate the compatibility of the CT-P16 finished product with the vial and stopper up to the end of shelf-life (i.e. 48 month time point at 5 ± 3°C). The final study report of the leachables study should be submitted by July of 2026. Furthermore, the Agency should be informed in the event that any compound of toxicological concern is identified in the study at 5 ± 3 °C prior to 48 months.	REC	July 2026

2.3. Non-clinical aspects

2.3.1. Introduction

The submitted nonclinical program is adequate for a biosimilar, and includes a battery of comparative *in vitro* primary pharmacodynamic (PD) studies (same as included under the biosimilarity studies) of CT-P16 and the Reference Medicinal Product EU-Avastin, and a repeat-dose toxicity study in cynomolgus monkeys including toxicokinetic (TK) and immunogenicity assessment.

The data from a 2-way similarity assessments from a battery of state of the art receptor-binding studies and cell-based assays, and the analytical methods employed were included. Therefore, in order to avoid redundancy, thorough discussions of functional biosimilarity and adequacy of the methods employed are included under Quality/biosimilarity section, and are only shortly summarised under nonclinical aspects.

In vitro studies were conducted using the drug product (DP) manufactured with the proposed commercial manufacturing process. The toxicology study in cynomolgus monkeys was conducted with CT-P16 DP lot 16P12B01 manufactured from Process A drug substance (DS). The comparability studies for both the DS (Process A) and the PD from commercial manufacturing process demonstrated that process changes have not had an adverse impact on the product quality.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

The *in vitro* functional assays covered all the relevant modes of action claimed in the indications for bevacizumab. Comparisons included lots used in the clinical studies. Ten lots of CT-P16 and EU-Avastin including lots used in the comparative clinical studies were analysed in main biological similarity assessments. Statistical analysis using a quality range approach set based on the variation of the RMP values, expressed as ± 3*SD, was conducted. The data was considered similar where ≥90% of data points were within the quality range of EU-Avastin.

CT-P16 and EU-Avastin had similar binding activity to the main target VEGF-A165, and to VEGF-A121, VEGF-A145, VEGF-A189 and VEGF-A206 isoforms and had similar biological activity in inhibition of proliferation of human umbilical vein endothelial cells and VEGFR2 receptor tyrosine kinase autophosphorylation. CT-P16 was similar to EU-Avastin in binding to FcRn C1q, FcγRIIIa (V and F variants), FcγRIIIb, FcγRIIa and FcγRIIb. Binding to FcγRI differed (50% of CT-P16 samples were within the quality range of EU-Avastin). Lack of triggering ADCC in PBMNCs and CDC in SKOV-3 cells was demonstrated for CT-P16 and EU-Avastin. No binding was observed to VEGF-B, VEGF-C, VEGF-D, VEGF-E, PlGF-1 and PlGF-2.

2.3.2.2. Secondary pharmacodynamic studies

No secondary pharmacology studies were performed and are not required.

2.3.2.3. Safety pharmacology programme

No separate safety pharmacology studies were performed and are not required.

2.3.2.4. Pharmacodynamic drug interactions

No pharmacology drug interaction studies were performed and are not required.

2.3.3. Pharmacokinetics

The comparative toxicokinetic analysis were performed as part of repeat-dose toxicity study for CT-P16 and EU-Avastin in cynomolgus monkeys using two doses of 10 and 50 mg/kg. Analytical methods were adequately validated for quantification of CT-P16 and EU-Avastin and anti-CT-P16 and anti-Avastin antibodies in cynomolgus monkey serum, and for formulation analysis of CT-P16 and EU-Avastin.

2.3.4. Toxicology

2.3.4.1. Single dose toxicity

No single dose toxicity studies were conducted and are not required.

2.3.4.2. Repeat dose toxicity

A GLP-compliant 4-week repeat-dose toxicity study (no 8342524) in cynomolgus monkeys with toxicokinetic assessment was conducted with CT-P16 (lot 16P12B01) and EU-Avastin. Doses of 10 mg/kg and 50 mg/kg were administered via intravenous (IV) bolus twice a week (in total of eight doses) to provide sufficient systemic exposure as determined based on exposure information in previous studies with the EU-Avastin.

The experimental setup of this study is summarised in the table below:

Table 2. Study design for 4-week Repeat-Dose Toxicity Study in Cynomolgus Monkeys

Study Design					
Group	Treatment	Number of Animals		Dose Level (mg/kg/dose)	Dose Concentration (mg/ml)
		Male	Female		
1	Vehicle Control	3	3	0	0
2	Low-CT-P16	3	3	10	5
3	Low-EU-Avastin	3	3	10	5
4	High-CT-P16	3	3	50	25
5	High-EU-Avastin	3	3	50	25 [1]

Note:[1] Nominal concentration. EU-Avastin was dosed as supplied (actual concentration was 25.1 mg/mL as listed in the Certificate of Analysis)
Abbreviations: kg, kilogram; mg, milligram; ml, milliliter

No test-article-related mortality or effects on vital signs, ophthalmic parameters, blood pressure, immunophenotyping, organ weight, growth plate evaluation and anatomic pathology were noted. CT-P16 and Avastin were well tolerated in cynomolgus monkeys up to 50 mg/kg/d when administered for 4 weeks.

Only minor test-article related effects were noted, e.g. an increased incidence of fecal abnormalities and differences in ECG values. Statistically significant, but not dose-related, higher mean PR intervals were noted in males administered CT-P16 or EU-Avastin compared with control males. These changes were considered incidental, and did not differ significantly between CT-P16 administered cynomolgus monkeys compared to EU-Avastin. Overall, no significant changes attributed to CT-P16 or EU-Avastin was observed in PR interval, QRS duration, QT interval, QTc interval, RR interval or heart rate.

Also some differences between monkeys that were administered CT-P16 and EU-Avastin were recognised: the significance of conduction delay abnormalities (incomplete right bundle branch block) exclusively noted in two monkeys of the highest CT-P16 group is unknown, but considered a background finding, and is thus not thought to raise a toxicological concern. At 50 mg/kg/bw, neutrophils and white blood cell counts were frequently increased in monkeys that were administered CT-P16, whereas this was not the case with monkeys from EU-Avastin groups. The observed increases were frequently

statistically significant. However, this was only observed after the 2nd day of dosing, later on this was not observed any more. Therefore, this observation is considered a chance finding.

2.3.4.3. Genotoxicity

No genotoxicity or mutagenicity studies were performed, and are not required.

2.3.4.4. Carcinogenicity

No carcinogenicity studies were performed, and are not required.

2.3.4.5. Reproductive and developmental toxicity

No reproductive and developmental studies were performed, and are not required.

2.3.4.6. Toxicokinetic data

Blood samples were taken pre-dose, and at approximately 0.5, 1, 2, 6, 12, 24, 48 (Day 26 only), 72, and 96 (Day 1 only) hours post-dose. For immunogenicity analysis of anti-CT-P16 and anti-EU-Avastin antibodies, blood samples were taken once during the pre-dose phase, approximately 96 hours post the Day 1 dose (prior to dosing on day 5), and approximately 72 hour post the Day 26 dose (prior to necropsy). The amount of CT-P16 or EU-Avastin and anti-drug antibodies in serum were quantified with validated analytical methods. The LLoQ for the serum concentration of CT-P16 and EU-Avastin was 10 ng/mL.

Exposure to bevacizumab increased with the increase in CT-P16 and EU-Avastin dose levels from 10 to 50 mg/kg/day. The increases in mean bevacizumab C_{max} and $AUC_{0\text{-}72h}$ values for both CT-P16 and EU-Avastin were generally dose proportional. Sex differences in concentrations were less than 2-fold.

The relative values (CT-P16/EU-Avastin) for C_{max} and $AUC_{0\text{-}72h}$ for 10 mg/kg/day dose were 104% and 106% on Day 1, respectively, and 110% and 105% on Day 26, respectively. For dose 50 mg/kg/day, the relative values were 101% and 102% on Day 1, respectively, and 98% and 110% on Day 26, respectively. Bevacizumab exposures were similar for CT-P16 and EU-Avastin.

The mean time to maximum serum concentration (T_{max}) value of CT-P16 was 0.83 hours on Day 1 and 2.67 hours on Day 26 for both 10 mg/kg/day and 50 mg/kg/day, and of EU-Avastin was 0.92 hours and 3.58 hours for 10 mg/kg/day and 50 mg/kg/day, respectively, on Day 1 and 3.42 hours and 1.17 hours for 10 mg/kg/day and 50 mg/kg/day, respectively, on Day 26.

No anti-drug antibodies were detected in blood samples collected.

2.3.4.7. Local Tolerance

Macroscopic observation and histopathological assessments of local (injection site) tolerance were performed in the repeat-dose toxicity studies. There were no toxicologically significant differences in injection site findings between control animals and the animals administered CT-P16 or EU-Avastin.

2.3.4.8. Other toxicity studies

No other toxicity studies were conducted, and are not required.

2.3.5. Ecotoxicity/environmental risk assessment

An ERA was submitted that included justification omitting the specific ERA studies (*CT-P16 belongs to proteins (is a monoclonal antibody), which do not require specific ERA studies*). The use of CT-P16 (bevacizumab) is not considered to produce risk to the environment.

2.3.6. Discussion on non-clinical aspects

The submitted nonclinical program is adequate for the development of a CT-P16 biosimilar, and includes a battery of comparative *in vitro* functional studies of CT-P16 and EU-Avastin, and a repeat-dose toxicity study in cynomolgus monkeys including toxicokinetic and immunogenicity assessment.

The *in vitro* functional studies demonstrated that CT-P16 and EU-Avastin were similar in their biological activity, *i.e.* in binding activity to the main target VEGF-A165, and to other soluble or membrane-bound VEGF-A isoforms, in inhibition of proliferation of endothelial cells and VEGFR2 autophosphorylation, and binding to Fcγ-receptors, FcRn and C1q. Of all the biological activity analyses conducted, the binding to FcγRI differed (50% of CT-P16 samples being within the quality range of EU-Avastin). Nevertheless, it was justified that although FcγRI is known to trigger weak ADCC or ADCP, the therapeutic effect of bevacizumab is not mediated by Fc-functions. Therefore, this finding is unlikely to be clinically meaningful. This justification is accepted. Moreover, the lack of triggering ADCC in PBMNCs and CDC in SKOV-3 cells was demonstrated for both, for CT-P16 and EU-Avastin. CT-P16 had similar specificity with EU-Avastin in lack of binding to other VEGF isoforms than VEGF-A or PlGF.

In conclusion, the 2-way similarity assessment data from the receptor-binding and cell-based assays demonstrate the similar functional activity of CT-P16 and EU-Avastin.

CT-P16 and EU-Avastin were well tolerated at dose levels up to maximum dose used, 50 mg/kg/day in cynomolgus monkeys. No treatment-related findings were noted with exception of minor changes (in increased incidence, fecal abnormalities and in ECG measurements, and increases of neutrophil and white blood cell counts). There were no toxicologically significant differences between CT-P16 or EU-Avastin group animals, including the injection site findings. The results of the study in cynomolgus monkeys did not reveal notable differences in effects between the CT-P16 and Avastin in their toxicological profiles.

Exposures (C_{max} and AUC_{0-72h}) to CT-P16 and EU-Avastin increased dose-proportionally, and were similar for CT-P16 and EU-Avastin. Sex differences in concentrations were less than 2-fold. The relative values (CT-P16/EU-Avastin) for C_{max} and AUC_{0-72h} for 10 mg/kg/day dose were 104% and 106% on Day 1, respectively, and 110% and 105% on Day 26, respectively. For the dose of 50 mg/kg/day, the relative values were 101% and 102% on Day 1, respectively, and 98% and 110% on Day 26, respectively.

CT-P16 or EU-Avastin did not trigger formation of anti-drug antibodies.

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, CT-P16 (bevacizumab) is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The 2-way similarity assessment data from the receptor-binding and cell-based assays support the similar functional activity of CT-P16 and EU-Avastin. Based on the functional activity analysis, CT-P16 and EU-Avastin can be expected to have the same efficacy in vitro, PK profile, and similar lack of Fc receptor mediated effector functions (ADCC, CDC).

The results from small-scale study in cynomolgus monkeys did not reveal notable differences in effects between the CT-P16 and Avastin in their toxicological or toxicokinetic profiles.

SmPC section 5.3. for CT-P16 and EU-Avastin is identical.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 3. Overview of clinical studies

Type of Study	Study ID	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Objective(s) of the Study	Study Population	Duration of Treatment	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
Pivotal PK Study	CT-P16 1.1	Phase 1, randomized, double-blind, three-arm, parallel group, single-dose study in healthy male subjects	CT-P16, US-Avastin or EU-Avastin: 5 mg/kg, a single IV infusion for 90 mins	**Primary:** To demonstrate the similarity of PK in terms of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max} of CT-P16, US-Avastin and EU- Avastin **Secondary:** - To assess the additional PK parameters - To evaluate safety and immunogenicity of CT-P16, US-Avastin and EU-Avastin	Randomized = 144 CT-P16: 47 EU-Avastin: 49 US-Avastin: 48	Up to Day 99	Healthy male subjects	Completed CSR CT-P16 1.1
Supportive Japanese PK Study	CT-16 1.2	Phase 1, randomized, double-blind, parallel group, single-dose study to compare the PK and safety in healthy Japanese male subjects	CT-P16, EU-Avastin: 5 mg/kg, a single IV infusion for 90 mins	**Primary:** To demonstrate the similarity of PK in terms of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max} of CT-P16 and EU-Avastin **Secondary:** - To assess the additional PK parameters - To evaluate safety and immunogenicity of CT-P16 and EU-Avastin	Randomized = 46 CT-P16: 22 EU-Avastin: 24	Up to Day 99	Healthy male subjects	Completed CSR CT-P16 1.2
Therapeutic Similarity Study	CT-P16 3.1	Phase 3, randomized, double-blind, active-controlled, parallel group study in patients with metastatic or recurrent nsNSCLC	**[Induction Study Period]** CT-P16 or EU-Avastin: 15 mg/kg IV on Day 1 of each cycle, to be repeated every 3 weeks up to 6 cycles co-administered with paclitaxel and carboplatin (at least for 4 cycles) **[Maintenance Study Period]** CT-P16 or EU-Avastin: monotherapy every 3 weeks until progressive disease or intolerable toxicity occurrence	**Primary:** To demonstrate CT-P16 is similar to EU-Avastin in terms of efficacy as determined by ORR during the Induction Study Period **Secondary:** - To evaluate additional efficacy parameters - To evaluate the PK profile (C_{trough}) - To evaluate the safety profile including immunogenicity - To evaluate quality of life	Randomized = 689 CT-P16: 342 EU-Avastin: 347	Approximately 3 years from the day of enrolment of the last patient	Male or female patients with metastatic or recurrent nsNSCLC	Ongoing 1st CSR CT-P16 3.1 (data cut-off date: 22 April 2021) 2nd CSR CT-P16 3.1 (data cut-off date: 21 September 2021) Estimated final CSR (up to 3 years) completion: 2Q/2024

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the concentration-time curve from time 0 to the last quantifiable concentration; C_{max}, maximum serum concentration; CSR, clinical study report; C_{trough}, trough serum concentration; EU-Avastin, European Union-approved Avastin; IV, intravenous; nsNSCLC, Non-squamous non-small cell lung cancer; ORR, objective response rate; PK, pharmacokinetics; US-Avastin, United States-licensed Avastin

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

CT-P16 (international non-proprietary name bevacizumab; the proposed name Vegzelma) is developed as a proposed biosimilar medicinal product to Avastin®.

The pharmacokinetic (PK) similarity of CT-P16 has been investigated in the following three studies:

- **Study CT-P16 1.1** (pivotal PK study): A phase 1, randomized, double-blind, 3-arm, parallel group, single-dose study to compare the PK and safety of three formulations of bevacizumab (CT-P16, EU-Avastin and US-Avastin) in healthy male subjects. This study provides pivotal PK outcomes to demonstrate bioequivalence between CT-P16, EU-Avastin, and US-Avastin.
- **Study CT-P16 1.2** (supportive Japanese PK study): A phase 1, randomized, double-blind, parallel group, single-dose study to compare the PK and safety of CT-P16 and EU-Avastin in healthy Japanese male subjects. This study was conducted to support approval of CT-P16 in Japan.

- **Study CT-P16 3.1** (comparative efficacy and safety study): A phase 3, double-blind, randomized, active-controlled, parallel group study to compare efficacy and safety of CT-P16 and EU-Avastin as first-line treatment for metastatic or recurrent nsNSCLC. This study provides comparative PK data (trough serum concentrations [C_{trough}] following repeated IV infusion) and long-term immunogenicity.

Analytical methods

Quantification of CT-P16 and bevacizumab in human serum

A MSD-ECL based method was used in the pharmacokinetics studies to quantify CT-P16 and bevacizumab (EU-Avastin and US-Avastin) concentrations in healthy human serum (clinical study CT-P16 1.2) and in human serum samples from the patients with nsNSCLC (clinical study CT-P16 3.1). An ELISA based method was used for the quantification of CT-P16 and bevacizumab (EU-Avastin and US-Avastin) concentrations in healthy human serum samples collected in the clinical study CT-P16 1.1. Both methods were, in principle, validated according to ICH M10 Bioanalytical method validation guideline.

Detection of ADA and NAb in human serum

A three-tiered approach comprising of screening, confirmation and titer was used for detection of anti-drug antibodies. Two ECL based methods (validated either by PPD laboratory or BDS) were utilised for the detection of ADAs against CT-P16 and bevacizumab (EU-Avastin and US-Avastin) and two ECL based methods (validated either by PPD laboratory or BDS) were utilised for the detection of NAbs against CT-P16 and bevacizumab (EU-Avastin and US-Avastin) in healthy and diseased human serum. In general, the method validation followed current guidance.

Clinical pivotal PK study in healthy Asian male subjects (study Ct-P16 1.1)

The study was conducted at three centres in Republic of Korea between 01st Aug 2017 and 17th Jan 2018. The bioanalytical analyses were performed at Biologics Development Services, LLC US between 9th Oct 2017 and 28th Mar 2018.

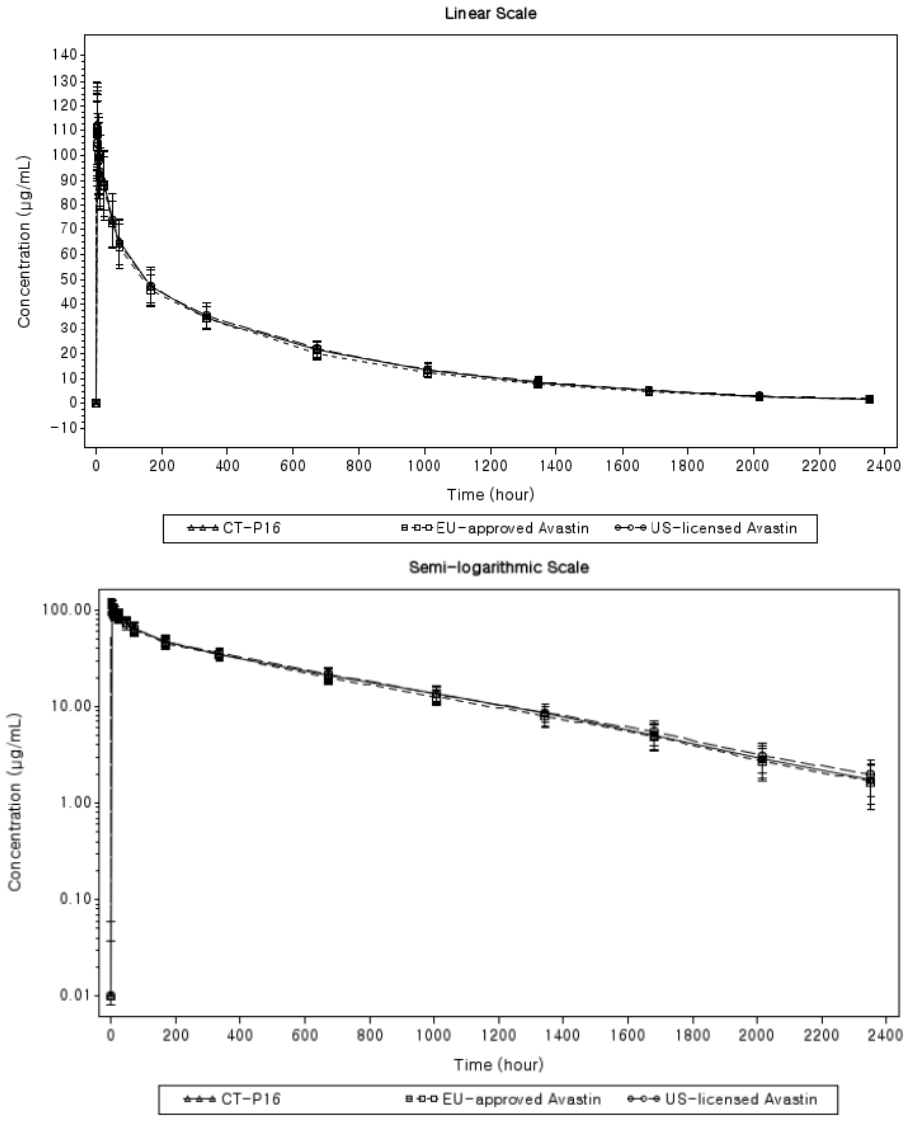
The study was a phase I, randomised (the number of subjects with body weight < 70 kg and ≥ 70 kg was balanced among the 3 treatment groups), double-blind, 3-arm, parallel group, single-dose study in adult healthy Asian male subjects. Subjects received single dose (i.e. 5 mg /kg) of either CT-P16, EU-Avastin or US-Avastin by IV infusion for 90 minutes (± 5 minutes) on Day 1. Blood samples were collected for measurement of serum concentrations of bevacizumab from all subjects at the following time points: pre-dose, immediately end-of-infusion (EOI), 1 h after EOI, 4 h after start of infusion (SOI), 8 h after SOI and 12 h after SOI, days 2, 3, 4, 8, 15, 29, 43, 57, 71, 85 and 99.

PK results:

The PK population consisted of 141 subjects (n = 46 in CT-P16 group, n =47 in the EU-Avastin group and n = 48 in the US-Avastin group).

Mean serum concentrations were similar between CT-P16, EU-Avastin and US-Avastin treatment groups (see Figure 1 below).

Figure 1. Mean (± SD) serum concentrations of CT-P16, EU-Avastin and US-Avastin versus time in study CT-P16 1.1 (PK population)



Abbreviations: EU = European Union; SD = standard deviation; US = United States.

Overall, the primary PK parameters were similar among 3 treatment groups (see Table 4).

Table 4. Summary of primary serum PK parameters for bevacizumab in study CT-P16 1.1 (PK population)

PK Parameter (unit)	Statistic	CT-P16 N = 46	EU-approved Avastin N = 47	US-licensed Avastin N = 48
$AUC_{0\text{-}inf}$ (h·µg/mL)	n	45	46	46
	Mean ± SD	42034.90 ± 6070.668	40413.44 ± 5012.778	43017.95 ± 5782.951
	CV	14.44	12.40	13.44
	GM	41608.53	40095.88	42621.36
	Median	41281.82	40294.19	42898.41
	Min, Max	30241.1, 54111.9	27362.5, 50941.1	28786.0, 54525.9
$AUC_{0\text{-}last}$ (h·µg/mL)	n	45	47	44
	Mean ± SD	41142.81 ± 5694.184	39411.98 ± 4649.319	41804.05 ± 5463.814
	CV	13.84	11.80	13.07
	GM	40757.85	39133.03	41440.57
	Median	40795.51	39445.89	41781.24
	Min, Max	30123.7, 52541.9	27156.6, 49635.7	27938.7, 53737.3
C_{max} (µg/mL)	n	46	47	48
	Mean ± SD	117.22 ± 17.756	114.06 ± 15.391	113.09 ± 17.402
	CV	15.15	13.49	15.39
	GM	115.96	113.05	111.77
	Median	116.00	111.00	112.00
	Min, Max	83.6, 173.0	83.2, 148.0	72.6, 155.0

Abbreviations: $AUC_{0\text{-}inf}$ = area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$ = area under the concentration-time curve from time zero to the last quantifiable concentration; C_{max} = maximum serum concentration; CV = coefficient of variation; EMA = European Medicines Agency; EU = European Union; GM = geometric mean; λ_z = Terminal elimination rate constant; Max = maximum; Min = minimum; PK = pharmacokinetic; SD = standard deviation; US = United States.

The 90% CIs for the geometric mean ratios of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max} were entirely contained within the predefined bioequivalence margin of 80% to 125%, indicating bioequivalence between CT-P16 and EU-Avastin, CT-P16 and US-Avastin, and EU-Avastin and US-Avastin (see Table 5).

Table 5. Statistical analysis of serum PK parameters for bevacizumab (ANCOVA) study CT-P16 1.1 (PK population)

PK Parameters (unit)	Geometric LS Means						CT-P16 /EU-approved Avastin		CT-P16 /US-licensed Avastin		EU-approved Avastin /US-licensed Avastin	
	CT-P16 N = 46		EU-approved Avastin N = 47		US-licensed Avastin N = 48							
	n	Results	n	Results	n	Results	Ratio	90% CI	Ratio	90% CI	Ratio	90% CI
$AUC_{0\text{-}inf}$ (h·µg/mL)	45	41608.92	46	40054.33	46	42593.20	103.88	[99.04,108.96]	97.69	[93.14, 102.46]	94.04	[89.68, 98.61]
$AUC_{0\text{-}last}$ (h·µg/mL)	45	40746.44	47	39058.63	44	41400.01	104.32	[99.70, 109.15]	98.42	[93.99, 103.06]	94.34	[90.14, 98.74]
C_{max} (µg/mL)	46	116.01	47	112.65	48	111.53	102.98	[98.22, 107.97]	104.02	[99.24, 109.03]	101.01	[96.39, 105.85]

Abbreviations: ANCOVA = analysis of covariance; $AUC_{0\text{-}inf}$ = area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$ = area under the concentration-time curve from time zero to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum serum concentration; EMA = European Medicines Agency; EU = European Union; λ_z = Terminal elimination rate constant; LS = least squares; PK = pharmacokinetic; US = United States.

Note: Ratio of geometric means was calculated by backed transforming difference of LS means calculated using an ANCOVA model with treatment as a fixed effect and body weight (< 70 kg versus ≥ 70 kg) assessed on Day -1 and study site as covariates.

Overall, the secondary PK endpoints (T_{max}, Vz, λz, $t_{½}$, CL and $\%AUC_{ext}$) were similar among the 3 treatment groups.

Supportive PK study in Japanese subjects (study CT-P16 1.2)

This study was conducted at one centre Anaheim Clinical Trials, LLC USA between 31st Jul and 22nd Dec 2020. Bioanalytical analyses were performed at PPD® Bioanalytical Lab USA between 29th Oct 2020 and 28th Jan 2021.

This study was a phase I, a single-centre, randomised, double-blind, parallel group, prospective single-dose study. Subjects received a single IV infusion (5 mg/kg; 90 minutes ±5 minutes) of CT-P16 or EU-Avastin according to the randomly assigned treatment groups on Day 1. Blood samples were collected for measurement of serum concentrations of bevacizumab from all subjects at the following time points: pre-dose, immediately end-of-infusion (EOI), 1 h after EOI, 4 h after start of infusion (SOI), 8 h after SOI and 12 h after SOI, days 2, 3, 4, 8, 15, 29, 43, 57, 71, 85 and 99.

PK results

The PK population consisted of 45 subjects (n = 22 subjects in the CT-P16 group and n = 23 subjects in the EU-Avastin group).

The 90% CIs of ratios of geometric LS means of C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ were entirely contained within the predefined equivalence margin of 80% to 125% which indicated that bevacizumab exposures from CT-P16 were similar to those from EU-Avastin (see Table 6).

Table 6. Statistical analysis of primary PK parameters (ANCOVA) in study CT-P16 1.2 (PK population)

Comparison	PK Parameter (unit)	Geometric LS Means[a] Test (N=22) n	Test (N=22) Result	Reference (N=23) n	Reference (N=23) Result	%Ratio (Test/Reference)[a]	90% CI[a]
CT-P16 (Test) vs EU-approved Avastin (Reference)	$AUC_{0\text{-inf}}$ (h•µg/mL)	22	37120.07	23	37810.47	98.17	(90.74, 106.22)
	$AUC_{0\text{-last}}$ (h•µg/mL)	22	36404.72	23	36820.05	98.87	(91.65, 106.67)
	C_{max} (µg/mL)	22	112.03	23	100.86	111.08	(100.37, 122.93)

Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration versus time curve from time zero extrapolated to infinity; $AUC_{0\text{-last}}$, area under the concentration-time curve from time zero to the time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum serum concentration; EU, European Union; LS, least squares; PK, pharmacokinetic.

An analysis of covariance was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and body weight (< 70 kg vs ≥70 kg) assessed on Day 1 as a covariate.

[a] The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

A statistical outlier was identified using the IQR method and robust regression method, which resulted in the detection of an unusual C_{max} value in one subject in the EU-Avastin group. Therefore, a sensitivity analysis was performed on the primary PK endpoints with data excluding the observed outlier. It should also be noted that the subject had an unusual profile shape that resembled more like subcutaneous administration and not an IV administration which aligns with the outlier analysis results.

Statistical analysis excluding the C_{max} outlier value of the subject was performed and the 90% CIs of the %ratio of geometric LS mean were within the equivalence interval (80% to 125%) supporting the same outcome as in previous Table 11; i.e., no notable differences in C_{max} between CT-P16 and EU-Avastin.

Comparative efficacy and safety study in nsNSCLC patients (study CT-P16 3.1)

The secondary objective of this study was to evaluate the PK of CT-P16 compared with EU-Avastin in terms of C_{trough}. Patients received 15 mg/kg study drug dose every 3 weeks.

PK samples were collected on Day 1 of each cycle (prior to the beginning of the study drug administration [-3 days as window were allowed]) in the induction study period, on Day 1 (-3 days as window were allowed) of cycle 1, and every 3 cycles (end of Cycle 3, Cycle 6, and Cycle 9, etc.) in the maintenance study period and EOT visit. In patients whose dose was delayed from the planned schedule, serum samples were obtained on Day 22 of the last cycle (-3 days as window were allowed).

PK and immunogenicity testing site: PPD Bioanalytical Laboratory, US

PK results

A total of 650 patients (327 patients and 323 patients in the CT-P16 and EU-Avastin treatment groups, respectively) were included in the PK population. Thirty-seven patients who did not have post-treatment PK results were excluded from PK population and 2 patients who received the incorrect treatment during the induction study period were excluded from the PK population.

The mean (standard deviation) C_{trough} at each cycle in the induction period was generally similar for the CT-P16 and EU-Avastin treatment groups in the PK population (see Table 7).

Table 7. Mean (SD) trough serum concentrations of bevacizumab (µg/L) in study CT-P16 3.1 (PK population)

Visit	CT-P16 (N=327)		EU-approved Avastin (N=323)	
Induction Cycle 1	n=318	50426.3 (39847.34)	n=316	52515.7 (32356.13)
Induction Cycle 2	n=302	73127.7 (35883.59)	n=287	81533.7 (52567.34)
Induction Cycle 3	n=283	93100.6 (50495.29)	n=269	95878.8 (53977.69)
Induction Cycle 4	n=268	96445.2 (45597.95)	n=254	101583.1 (46275.62)
Induction Cycle 5	n=252	108957.3 (55135.16)	n=238	108512.5 (49823.61)
Induction Cycle 6	n=246	116188.2 (58735.47)	n=228	114849.6 (56309.70)

Abbreviation: PK, pharmacokinetic.

2.4.2.2. Pharmacodynamics

Mechanism of action

Bevacizumab binds and neutralises the biologic activity of human Vascular Endothelial Growth Factor (VEGF). The mechanism of action (MoA) for Avastin and CT-P16 across indications is binding to soluble VEGF and preventing the interaction of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF results in the regression of tumour vascularisation, normalisation of remaining tumour vasculature, and inhibition of the formation of new tumour vasculature, thereby inhibiting tumour growth. In each approved indication, the MoA of bevacizumab is to inhibit VEGF-induced angiogenesis and vascular permeability. According to the applicant, based on an extensive analysis of the role of VEGF and VEGF inhibition in each one of the indications for which licensure is sought, there is no evidence to support claims of a unique MoA in specific indications.

Primary and Secondary pharmacology

Primary pharmacology was not separately addressed in the clinical studies. In terms of secondary pharmacology, the clinical studies conducted as part of the CT-P16 development programme included standard safety assessments such as safety laboratories and ECG recordings. These are discussed within section 2.4.8 on clinical safety.

2.4.3. Discussion on clinical pharmacology

Three clinical studies were performed in which the PK of CT-P16 was compared to that of EU-Avastin and in one study (pivotal clinical PK study CT-P16 1.1) also US-Avastin was used as a comparator product. In the clinical phase I studies (i.e. CT-P16 1.1 in healthy Asian male subjects and CT-P16 1.2 in healthy Japanese male subjects), bevacizumab was administered as a single-dose of 5 mg/kg by an IV infusion. In the clinical phase III study (i.e. CT-P16 3.1) in nsNSCLC patients, bevacizumab was administered as 15 mg/kg every 3 weeks.

Analytical methods

In general, the bioanalytical methods used in the clinical studies for CT-P16 have been appropriately described and validated according to the relevant guidelines.

Quantification of CT-P16 and bevacizumab concentration in human serum

Two analytical methods including ELISA (used in clinical study CT-P16 1.1) and MSD-ECL (used in clinical studies CT-P16 1.2 and CT-P16 3.1) were validated according to ICH M10 Bioanalytical method validation guideline. In both methods CT-P16, EU-Avastin and US-Avastin seemed to perform analytical similarity in terms of selectivity, precision and accuracy.

MSD-ECL based method was used in the analysis of healthy and nsNSCLC patient human serum samples. The usage of same analytical method for healthy and nsNSCLC samples was acceptable since the method demonstrated selectivity for both healthy and nsNSCLC serum. The analysis of clinical samples was reliable within the given accuracy and precision ranges.

Determination of ADA by MSD-ECL

Two ECL based methods were used for the detection of ADAs in the healthy and nsNSCLC serum samples by utilizing three-tiered approach. The first ADA-assay validated by PPD Laboratory was utilised in the analysis of serum samples from clinical studies CT-P16 1.2 and 3.1. Screening, confirmatory and tier cut points were determined both in healthy and NSCLC serum in acceptable manner. The intra- and inter-assay precisions for screening and confirmation met the acceptance criteria. No matrix interference in healthy nor nsNSCLC serum was observed and drug tolerance was acceptable. According to drug equivalence studies the originator drug (EU-Avastin) was comparable to CT-P16.

The second ADA-assay was used in the analysis of serum samples from clinical study CT-P16 1.1 and was validated by BDS. The method validation was acceptable and no further concerns are pursued for this method.

Determination of NAb by using MSD-ECL

Two ECL based methods were used for the detection of NAbs in the healthy and nsNSCLC serum samples. The first NAb-assay validated by PPD Laboratory was utilised in the analysis of serum samples from clinical studies CT-P16 3.1. In general, an appropriate method validation following the current guidance was provided. Screening cut points and sensitivity were evaluated both in healthy and nsNSCLC serum.

The second NAb-assay was used in the analysis of serum samples from clinical study CT-P16 1.1 and was validated by BDS. The method validation followed the current guidance and was considered acceptable.

Pivotal clinical PK study in healthy Asian male subjects (CT-P16 1.1.)

The primary endpoints $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}last}$ were based on PK samples collected up to day 99. The PK sampling period was long enough to characterise the whole PK profile of bevacizumab. All subjects' $AUC_{0\text{-}last}$ covered over 80% of $AUC_{0\text{-}inf}$.

All 90% CIs for test-to-reference/comparator of the primary PK parameters (i.e. $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max}) were within the pre-specified acceptance range of 80.00 to 125.00 (including 100.00) demonstrating that the PK of the CT-P16 is comparable with the EU-Avastin and US-Avastin. In the comparison of the AUCs between EU-Avastin and US-Avastin, the 90% CIs were between the range 80.00-125.00 but the range did not include 100.00. This is, however, not a concern. The secondary PK parameters (i.e. T_{max}, Vz, λz, $t_{½}$, CL, $\%AUC_{ext}$) were also comparable between studied treatments.

4 subjects (1 subject in the CT-P16 and EU-Avastin group and 2 subjects in the US-Avastin group) were excluded from the PK analysis of $AUC_{0\text{-}inf}$. The reason was that the interval used to determine λz was less than 1.5 -fold the estimated half-life. 5 subjects (1 subject in the CT-P16 group and 4 subjects in the US-Avastin group were excluded from the PK analysis of $AUC_{0\text{-}last}$. The reason was that the subjects withdrew before the last planned PK sampling time (i.e. day 99), after received full IMP. These exclusion criteria from the PK statistical analyses were already presented in the SAP. The applicant has conducted

sensitivity analysis of the affected AUCs including the excluded subjects. The 90% CIs of geometric LS mean ratios were entirely contained within the predefined equivalence margin of 80.00 to 125.00 (also for AUCs between EU-Avastin and US-Avastin). The bevacizumab has a linear PK, so the PK biosimilarity demonstrated in Asians can be extrapolated to the non-Asians.

There were three subjects in the CT-P16 group, one subject in the EU-Avastin group and five subjects in the US-Avastin group, who had pre-dose bevacizumab concentrations above BLQ. Although the pre-dose concentrations of bevacizumab were low, the applicant was requested to discuss reasons for the bevacizumab in pre-dose samples. In the response to D120 questions, the applicant provided a very detailed discussion on the topic. The applicant has an opinion that the probable reason for the 9 pre-dose bevacizumab concentrations could be low levels of non-specific binding in the wells of the assay plate or due to an unknown active interferent present in the serum of the subjects. The applicant also conducted a sensitivity analysis of primary PK parameters (i.e. C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$), excluding the subjects with pre-treatment measurable concentrations of bevacizumab, and the PK biosimilarity conclusions remained unchanged.

The applicant was asked to provide the certificates of analysis for the EU-Avastin batch B7234H13 and for the US-Avastin batch 3115919. In the response to D180 questions, the applicant provided the certificates of analysis for both reference products used in the study CT-P16 1.1. The protein contents were within specification limits, and highly similar between test and reference products (test CT-P16: 25.3 mg/mL, reference EU-Avastin: 25.3 mg/mL, reference US-Avastin: 25.4 mg/mL).

Supportive clinical PK study in healthy Japanese male subjects (CT-P16 1.2)

All 90% CIs for the test-to-reference ratios of the AUCs were within the pre-specified acceptance range of 80.00 to 125.00 (including 100.00) demonstrating the PK similarity between CT-P16 and EU-Avastin. In the original ANCOVA analysis, the 90% CI for the test-to reference ratio of C_{max} was within the range of 80.00 to 125.00; however, not including 100.00. A sensitivity analysis for the C_{max} parameter which excludes one subject who had C_{max} much lower and T_{max} much later than other subjects, resulted in a 90% CI included 100.00. Based on the serum bevacizumab concentration (µg/ml) vs time (h) profile of this excluded subject, it can be agreed with the applicant that the subject had received most likely subcutaneous infusion instead of IV infusion.

The mean secondary PK parameters ($t_{1/2}$, λz, CL, Vz, and $\%AUC_{ext}$) were comparable between the two treatment groups. The inter-subject variability was low in all PK parameters also in this study.

It was reported that the studied population was healthy first- or second -generation Japanese male subjects. However, in the inclusion criteria, there is no item that subjects must be Japanese. Furthermore, in the demographic data, it was reported that all subjects were Asian male and not Hispanic or Latino. There are 51 different Asian countries (in addition to Japan e.g. China, Indonesia, India, Thailand). Consequently, it is not clear if all subjects were Japanese. This study is a supportive PK study, and for EU registration purposes it is not a concern, if there have been also subjects with ethnicity other than Japanese.

The applicant was asked to provide the certificate of analysis for the EU-Avastin batch N7397H12 used in the study CT-P16 1.2. The applicant provided the requested data in the response to D180 questions. The protein content of EU-Avastin was within specification limits, and highly similar between test and reference products (test CT-P16: 25.0 mg/mL, reference EU-Avastin: 24.7 mg/mL).

Comparative efficacy and safety study in nsNSCLC patients (CT-P16 3.1)

In the phase III clinical study, the observed C_{trough} concentrations were comparable between CT-P16 group and EU-Avastin group from baseline through induction cycle 6.

Other issues

All clinical studies support the biosimilarity in clinical PK between CT-P16 and EU-Avastin.

No clinical studies in special populations and no *in vitro* or *in vivo* drug-drug interaction studies were conducted with the CT-P16 and this is acceptable.

In the proposed CT-P16 SmPC the Section "5.2 Pharmacokinetic properties" is similar as in the Avastin SmPC, which is acceptable.

2.4.4. Conclusions on clinical pharmacology

The primary PK endpoints were within predefined limits, and CT-P16 can be considered biosimilar to EU-Avastin based on the presented PK data.

CT-P16 has been developed as a biosimilar to Avastin (bevacizumab), and their similarity has been demonstrated through a series of physicochemical and biological assays. No separate clinical pharmacodynamic or PK/PD studies have been undertaken, which is considered acceptable for a biosimilar development programme.

2.4.5. Clinical efficacy

2.4.5.1. Dose response study

Not applicable for biosimilars.

2.4.5.2. Main study

Study CT-P16 3.1: A Double-Blind, Randomized, Active-Controlled, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P16 and EU-Approved Avastin as First-Line Treatment for Metastatic or Recurrent Non-Squamous Non-Small Cell Lung Cancer

Methods

Study CT-P16 3.1 is an ongoing double-blind, randomised, active-controlled, parallel-group, Phase 3 study to compare the efficacy, PK, and overall safety of CT-P16 (15 mg/kg) and EU-Avastin (15 mg/kg) when co-administered with paclitaxel and carboplatin as first-line treatment in patients with metastatic or recurrent non-squamous non-small cell lung cancer (nsNSCLC). Patients were randomly assigned in a 1:1 ratio to CT-P16 or EU-Avastin, and the patients were stratified by country, sex (female vs. male), disease status (recurrence vs. metastatic), and Eastern Cooperative Oncology Group (ECOG) performance score (0 vs. 1).

The study comprises four periods. On completion of the Screening Period, eligible patients were randomised to receive intravenous CT-P16 or EU-Avastin every 3 weeks up to 6 cycles. All patients concomitantly received intravenous paclitaxel and carboplatin every 3 weeks up to 6 cycles (at least 4 cycles). If a patient had progressive disease (PD) during or after the completion of the Induction Study Period (assessed at the end of Cycle 6) or did not enter the Maintenance Study Period due to any reason, the patient was to complete the end-of-treatment (EOT) visit, then directly enter the Follow-Up Period.

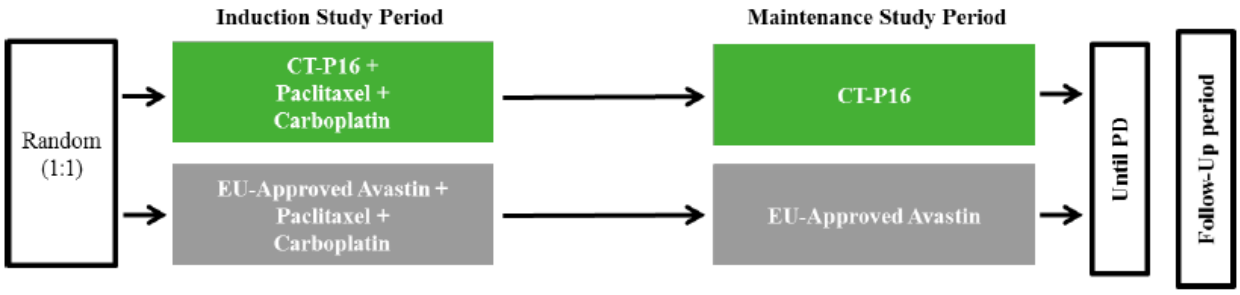
After the completion of 6 cycles during the Induction Study Period, patients with controlled disease (complete response [CR], partial response [PR], or stable disease [SD], assessed at the end of Cycle 6) entered the Maintenance Study Period, during which patients receive CT-P16 or EU-Avastin as monotherapy every 3 weeks until PD or intolerable toxicity, whichever occurs first, after which the

patients perform the EOT visit and then enter the Follow-Up Period. An EOT visit occurs 3 weeks after the last dose of the Induction Study Period or Maintenance Study Period regardless of the reason of discontinuation.

All patients who enter the Follow-Up Period due to any reason are followed every 9 weeks until death or the end of study, whichever occurs first. If PD was not confirmed during the Induction Study Period or Maintenance Study Period, tumour response evaluation is performed every 9 weeks during the Follow-Up Period. The Follow-Up Period is expected to last for up to approximately 3 years from the enrolment of the last patient.

The general design of the study is outlined in Figure 2 below.

Figure 2. Study design for Study CT-P16 3.1



- CT-P16 or EU-Approved Avastin: 15 mg/kg every 3 weeks IV
- Paclitaxel: 200 mg/m^2 every 3 weeks IV
- Carboplatin: Area under the curve 6 every 3 weeks IV
- Induction Study Period: maximum 6 cycles
- Maintenance Study Period: until disease progression, or intolerable toxicity, whichever occurs first
- Follow-Up Period: up to approximately 3 years from the last patient enrolled
- Randomization will be stratified by country, sex (female vs. male), disease status (recurrence vs. metastatic), and ECOG performance score (0 vs. 1).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD, progressive disease.

As indicated above, the study is currently ongoing. In the Response to the D120 List of Questions, the applicant provided data from a data lock corresponding to the time when the last enrolled patient had been followed up for 1 year.

- **Study Participants**

Study CT-P16 3.1 is conducted in patients with stage IV or recurrent nsNSCLC. The main eligibility criteria were as follows:

Inclusion criteria

1. Patient (male or female) was ≥ 18 years of age.
2. Patient had confirmed predominantly nsNSCLC by haematoxylin and eosin staining or immunohistochemistry.
3. Patient had recurrent disease or Stage IV diagnosis according to the American Joint Committee on Cancer 8th edition on Lung Cancer Staging. Stage IV was defined as follows:
   a. Separate tumour nodule(s) in a contralateral lobe, or

b. Tumour with pleural or pericardial nodules, or

c. Malignant pleural or pericardial effusion related to tumour, or

d. Single or multiple extrathoracic metastases in a single organ or in multiple organs.

4. Patient had at least 1 measurable lesion by RECIST version 1.1. Target lesions situated in a previously irradiated area were considered measurable if recurrence had been demonstrated in such lesions.

   a. Tumour lesions: ≥ 10 mm in long axis by CT scan, or

   b. Malignant lymph nodes: ≥ 15 mm in short axis by CT scan

5. Patient had an ECOG performance status of 0 or 1.

6. Patient had a life expectancy > 6 months based on clinical judgement.

7. Patient had negative result in both epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement confirmed by biopsy or cytology specimens.

8. Patient had adequate organ function as determined from relevant haematology and clinical chemistry laboratory assessments.

9. Patient and/or their legally authorised representative had been informed and was given ample time and opportunity to read and/or understand the nature and purpose of this study and had signed the ICF before any study-specific procedures.

Exclusion criteria

1. Patient had predominantly squamous cell histology NSCLC. If small cell elements were present, the patient was ineligible.

2. Patient had clinically significant third-space fluid; for example, ascites or pleural effusions that could not be controlled by drainage or other procedures prior to Day 1 of Cycle 1.

3. Patient had untreated CNS metastases or CNS metastasis with bleeding risk at investigator's discretion and/or leptomeningeal disease. However, treated and clinically stable (asymptomatic; off steroids) brain metastases were allowed.

4. Patient had invasion of major blood vessels. Patient with a tumour cavitation, in the opinion of the investigator, who was likely to bleed was excluded as well.

5. Patient had received previous anticancer systemic therapy including one or more of the following:

   a. Cytotoxic chemotherapy for metastatic nsNSCLC

   b. Cytotoxic chemotherapy for non-metastatic nsNSCLC within 12 months prior to Day 1 of Cycle 1

   c. Antineoplastic biological therapy, immunotherapy, or targeted therapy

   d. Bevacizumab (or a bevacizumab-proposed biosimilar product).

6. Patient had received previous surgical procedure including one or more of the following:

   a. Surgery for metastatic nsNSCLC

   b. Surgery for non-metastatic nsNSCLC within 6 months prior to Day 1 of Cycle 1

c. Open biopsy or open pleurodesis within 28 days prior to Day 1 of Cycle 1

d. Core biopsy or other minor surgical procedure (eg, placement of vascular access device, closed pleurodesis, thoracentesis, and mediastinoscopy) within 14 days prior to Day 1 of Cycle 1.

7. Patient had received previous anticancer radiotherapy including one or more of the following:

   a. Radiotherapy for metastatic nsNSCLC (but radiotherapy as part of the palliative therapy and/or treatment for CNS metastases completed at least 14 days prior to Day 1 of Cycle 1 was allowed)

   b. Radiotherapy for non-metastatic nsNSCLC within 6 months prior to Day 1 of Cycle 1

   c. Any toxicity related with radiotherapy prior to Day 1 of Cycle 1.

8. Patient had a medical history of other significant concurrent disease, with a comprehensive list of representative examples provided in the protocol.

Study CT-P16 3.1 is a global multi-centre trial conducted in a total of 164 study centres in 21 countries (Belarus, Brazil, Bulgaria, Chile, Croatia, Georgia, Hungary, India, Japan, Malaysia, Mexico, Peru, Poland, Portugal, Republic of Korea, Romania, Russian Federation, Serbia, Thailand, Ukraine, Vietnam).

- **Treatments**

During the Induction Study Period, patients received 15 mg/kg IV of either CT-P16 or EU-Avastin every 3 weeks up to 6 cycles. Patients received paclitaxel 200 mg/m^2 IV and carboplatin AUC 6.0 IV every 3 weeks up to 6 cycles (at least 4 cycles). After the Induction Study Period, either CT-P16 or EU-Avastin as a monotherapy (15 mg/kg IV) was maintained every 3 weeks until either PD or intolerable toxicity occurrence, whichever occurred first.

Study treatments (CT-P16 or EU-Avastin, carboplatin, and paclitaxel) were administered on the same day. If one of them had to be delayed, study treatment had to be delayed. If one of them had to be permanently discontinued, study treatment had to be discontinued. Uncoupling of study treatment was not allowed until at least 4 cycles of the Induction Study Period had been completed; thus, paclitaxel and/or carboplatin could be discontinued at Cycle 5 or 6 of the Induction Study Period.

Treatment during the Induction Study Period and Maintenance Study Period could be delayed for up to 3 weeks from the planned schedule if warranted by adverse events or laboratory findings (haematological or non-haematological toxicity); specific instructions were provided in the study protocol. If treatment was delayed more than 3 weeks, the patient had to be discontinued. Dose modifications were not permitted for bevacizumab but were allowed for paclitaxel and carboplatin.

During the Induction Study Period, study treatment was administered in the following order:

- Hydration (according to local practice)
- Dexamethasone 20 mg

  Oral, approximately 12 and 6 hours prior to administration of paclitaxel *or*
  IV infusion, 30 to 60 minutes prior to administration of paclitaxel
- Diphenhydramine (or its equivalent) 50 mg

  IV infusion 30 to 60 minutes prior to administration of paclitaxel
- Cimetidine 300 mg or ranitidine 50 mg

IV infusion 30 to 60 minutes prior to administration of paclitaxel

- Paclitaxel 200 mg/m^2

  IV infusion over approximately 3 hours

- Carboplatin AUC 6.0

  IV infusion over approximately 30 minutes after administration of paclitaxel

- CT-P16 or EU-Avastin 15 mg/kg

  IV infusion over 30 to 90 minutes after administration of carboplatin

An antiemetic could be used based on local practice, and the dose of dexamethasone, diphenhydramine, and cimetidine could be adjusted at the investigator's discretion.

CT-P16 or EU-Avastin was diluted in a total volume of 100 mL of 0.9% sodium chloride and administered by IV infusion with an infusion pump. The dose was delivered over 90 minutes (±15 minutes) at the Cycle 1 of the Induction Study Period. If the infusion was well tolerated, the infusion of Cycle 2 of the Induction Study Period could be administered over 60 minutes (±10 minutes). If the 60-minute infusion was well tolerated, all subsequent infusions could be administered over 30 minutes (±10 minutes). The study drug was required to be handled by delegated unblinded staff.

- **Objectives**

The primary objective of study CT-P16 3.1 was to demonstrate that CT-P16 was similar to EU-Avastin in terms of efficacy as determined by objective response rate (ORR) during the Induction Study Period.

The secondary objectives of the study are:

- To evaluate additional efficacy profiles including ORR during the Whole Study Period, response duration, time to progression (TTP), progression-free survival (PFS), and overall survival (OS)
- To evaluate the PK of trough serum concentration (C_{trough})
- To evaluate safety profile including immunogenicity
- To evaluate quality of life (QoL)

- **Outcomes/endpoints**

The primary efficacy endpoint was the ORR based on the best overall response (BOR) during the Induction Study Period by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Categorisation of overall response at each visit was based on the following response categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and inevaluable (NE). ORR was defined as the proportion of patients with a confirmed BOR of CR or PR (the 'responder'). All other patients in the ITT or PP population except responders were considered non-responders, including patients without post-baseline tumour assessment. For CR or PR, BOR was confirmed by the subsequent assessment based on RECIST v.1.1. For a BOR of SD, measurements had to meet its criteria at least once after start of study treatment for a minimum interval of 6 weeks (42 days) considering +/- 6 days, which is equivalent to a minimum time of 36 days.

The secondary efficacy endpoints were:

- ORR based on BOR during the Whole Study Period by RECIST version 1.1

- Response duration: the time between initial response (complete response [CR] or partial response [PR]) and PD/recurrence or death from any cause, whichever occurred first
- TTP: the time from randomisation to determined PD/recurrence
- PFS: the time from randomisation to determined PD/recurrence or death from any cause, whichever occurred first
- OS: the time from randomisation to death from any cause

An independent tumour review committee (ITRC) was used to review the images for tumour responses. In addition to the ITRC, images were separately reviewed by local investigators. Local results were used for eligibility and treatment practice purposes. Central and local image review results were analysed and listed separately.

Quality of life was assessed with the Questionnaire Core 30 (QLQ-C30) and Quality of Life Questionnaire Lung Cancer-specific module (QLQ-LC13), using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ).

- **Sample size**

A sample size of 305 patients per group was planned to provide 80% power to show similarity in efficacy between CT-P16 and EU-Avastin based on the expected ORR of 38% with an equivalence margin of -12.5 to 12.5 using a 95% CI (two one-sided alpha 0.025) of the difference in ORR. Approximately 678 patients (339 in each group) were planned to be enrolled for the anticipated drop-out rate of 10%.

- **Randomisation and Blinding (masking)**

An interactive web response system (IWRS) was used for the randomisation. An unblinded statistician generated a computer-generated randomisation schedule for IWRS, which linked sequential patient randomisation numbers to treatment codes.

Patients who qualified for randomisation were randomly assigned on Day 1 of Cycle 1 of the Induction Study Period in a 1:1 ratio to receive CT-P16 or EU-Avastin. The randomisation was balanced by using permuted blocks and was stratified by country, sex (female vs. male), disease status (recurrence vs. metastatic), and ECOG performance score (0 vs. 1).

The study was double-blinded during the study period.

The blind should be broken for the individual patients only if specific emergency treatment would be dictated by knowing the study drug status of the patient. The investigator could, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS.

The randomisation codes of 10 patients were unblinded to patients, investigators, and study site personnel before data cut-off date as per the investigator's request for the administration of second line treatment at the investigator's discretion; there was no specific emergency related to patient safety. The identification of the study drugs for the patients was revealed by the investigator's decision using the applicable procedure in the IWRS and the date, time, and reason for the unblinding were documented in the appropriate field of the eCRF and source documents.

As planned in the protocol, the overall randomisation code was broken on 16 July 2021 for reporting purpose after database lock (15 July 2021) to generate the first CSR, dated 13 September 2021. The unblinded analyses were performed as per statistical analysis plan (SAP) version 1.0 (finalised on 14 July 2021). The unblinded personnel was pre-defined before breaking the study blind. The database was

locked on 03 December 2021 to generate the second CSR and the unblinded analyses were performed as per SAP version 2.0 (finalised on 02 December 2021). The study has been blinded and will be blinded to the investigators, patients, and pre-defined CELLTRION, Inc. and PPD blinded personnel until the completion of the study and the database sets finalised for study termination.

The randomisation codes for all the other patients, investigators, or study site personnel will not be revealed until all final clinical data are entered into the database and the database is locked and released for analysis.

- **Statistical methods**

Analysis Populations

The MAA submission contained the CSR that was the first of three planned reports for this study, and included efficacy data obtained up to end of Maintenance Cycle 3 date prior to cut-off date (22 April 2021) for the confirmation of BOR during the Induction Period. Also, PK and QoL data up to end of Induction Cycle 6 were included. In the Response to the D120 List of Questions, the applicant provided the second CSR; the cut-off date of 21 September 2021 for this CSR corresponds to the time when the last enrolled patient had completed 1 year of follow-up. The second CSR also contained analyses for time-dependent secondary endpoints.

All analyses were conducted using SAS® software Version 9.4 or higher.

The primary population for the efficacy analysis was ITT population consisting of patients who were successfully screened and randomly assigned to study drug (regardless of whether any study treatment dosing was completed).

A supportive efficacy analysis was performed using the PP population consisting of randomly assigned patients who had at least 1 response evaluation after receiving at least 1 full dose of study drug (CT-P16 or EU-Avastin) in the Induction Study Period and who did not have any major protocol deviations that could have affected the interpretation of the primary endpoint including being treated with opposite treatment to which the patients was assigned, non-compliance of inclusion or exclusion criteria, significant GCP non-compliance, prohibited therapies or missing primary efficacy assessment.

Additionally, the primary analysis was performed excluding patients with major protocol deviation related to COVID-19 in ITT population as supportive analysis and the patients were flagged in listings.

Final determinations of the PP population were made at the data review meeting before unblinding. In both analysis populations patients were analysed as per the randomised treatment.

The primary endpoint was objective response rate (ORR) based on the best overall response (BOR) during the Induction Study Period. For CR or PR, BOR had to be confirmed by the subsequent assessment. BOR was categorised as CR, PR, SD, PD, or NE. The ORR was defined as the proportion of patients with a confirmed BOR of CR or PR (the 'responder'). All other patients in the ITT or PP population except responders were considered as non-responders, including patients without post-baseline tumour assessment. Central assessment of tumour response was considered primary, while local assessment was used as a sensitivity analysis.

The similarity criterion had been set such that the confidence limits of the 95% confidence interval (CI) of the difference of ORR from each treatment group was entirely within the interval (-12.5, 12.5).

The primary analysis (ORR based on central review) was performed with a logistic regression model considering region (Europe, Middle East, and Africa [EMEA] vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrence vs. metastatic), and ECOG performance status at baseline (0 vs.

1) as covariates with treatment groups (CT-P16 and EU-Avastin) as a fixed effect. In calculation for the ORR in each treatment group, the applicant assigned weights for the fixed model effects (corresponding to the levels of stratification factors) proportionally based on the distribution of stratification factor levels in the population studied.

Tipping point analysis was conducted using central review data based on exact binomial approach in the ITT population to evaluate the sensitivity of conclusion to the missing data (no response evaluation or evaluated as 'NE') assumptions. Tipping point analyses were conducted under Missing Not at Random (MNAR) scenarios. Imputation was done by gradually shifting the number of responders by treatment group to make MNAR scenarios. In response D120 LoQ, also an analysis of ORR corresponding to MAR assumption was provided to give a base case to the aforementioned tipping point analysis. In this analysis, missing responses that were considered uninformative were multiple imputed based on patients' stratification factors.

Results

- **Participant flow**

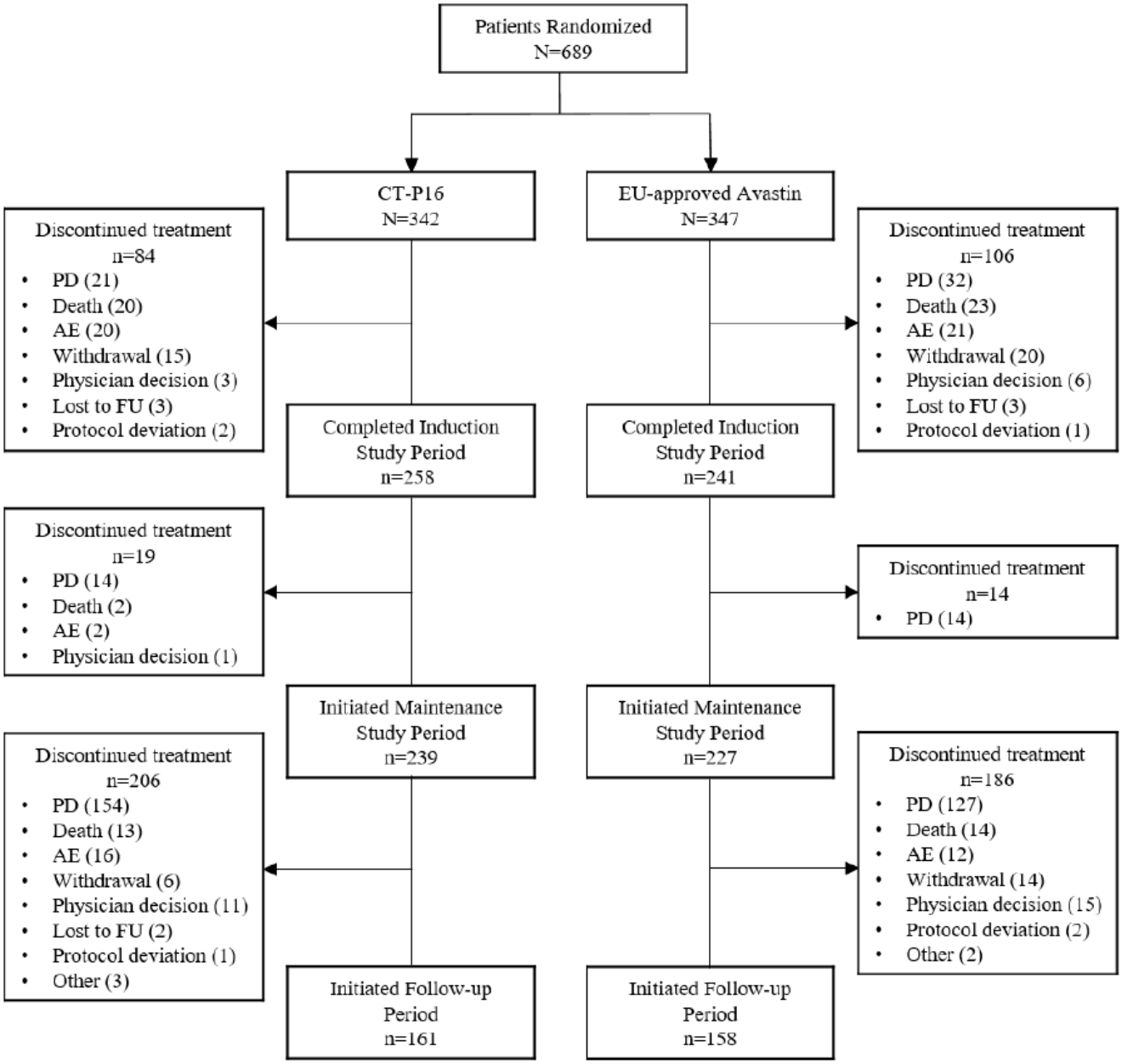
A total of 1.530 patients were screened for the study. Of these, 841 patients were screen failed; the most frequently reported primary reason for screening failure was inclusion/exclusion criteria not met (773 patients).

A total of 689 patients were randomly assigned to study drug and initiated the Induction Study Period (342 patients in the CT-P16 treatment group and 347 patients in the EU-Avastin treatment group). Of these, 499 (72.4%) patients completed the Induction Study Period (258 [75.4%] in the CT-P16 treatment group and 241 [69.5%] in the EU-Avastin treatment group). The most frequently reported reason for study treatment discontinuation in the Induction Study Period was PD (21 [6.1%] patients and 32 [9.2%] patients in the CT-P16 and EU-Avastin treatment groups, respectively). Among the patients who had completed the Induction Study Period, a total of 33 (4.8%) patients did not enter to Maintenance Study Period (19 [5.6%] patients in the CT-P16 treatment group and 14 [4.0%] patients in the EU-Avastin treatment group, respectively) and the most frequently reported reason for the study treatment discontinuation was PD (14 [4.1%] patients and 14 [4.0%] patients in the CT-P16 and EU-Avastin treatment groups, respectively).

A total of 466 (67.6%) patients initiated the Maintenance Study Period (239 [69.9%] patients in the CT-P16 treatment group and 227 [65.4%] patients in the EU-Avastin treatment group). Based on updated data received with the D120 responses, 392 (56.9%) patients discontinued the Maintenance Study Period (206 [60.2%] patients in CT-P16 treatment group and 186 [53.6%] patients in EU-Avastin treatment group). The most frequently reported reason for study treatment discontinuation in the Maintenance Study Period was PD (154 [45.0%] patients and 127 [36.6%] patients in the CT-P16 and EU-Avastin treatment groups, respectively).

Overall patient disposition is summarised in Figure 3 below and Table 8.

Figure 3. Patient disposition in study CT-P16 3.1 (data lock 21 Sep 2021)



Abbreviations: AE, adverse event; FU, follow-up; PD, progressive disease; SAP, statistical analysis plan.

Table 8. Patient disposition in study CT-P16 3.1 (data lock 21 Sep 2021)

	CT-P16 (N=342)	EU-approved Avastin (N=347)	Total (N=689)
	Number (%) of patients		
Total number of patients			
Screened			1,530
Screening failure			841
Primary reason for screening failure			
Inclusion/exclusion criteria not met			773
Patient withdrew consent			53
Other			15
Randomized	342	347	689
Initiated Induction Study Period	342 (100.0)	347 (100.0)	689 (100.0)
Completed Induction Study Period	258 (75.4)	241 (69.5)	499 (72.4)
Discontinued Induction Study Period	84 (24.6)	106 (30.5)	190 (27.6)
Reason for study treatment discontinuation in Induction Study Period			
Adverse event	20 (5.8)	21 (6.1)	41 (6.0)
Death	20 (5.8)	23 (6.6)	43 (6.2)
Lost to Follow-up	3 (0.9)	3 (0.9)	6 (0.9)
Physician decision	3 (0.9)	6 (1.7)	9 (1.3)
Progressive disease	21 (6.1)	32 (9.2)	53 (7.7)
Protocol violation	2 (0.6)	1 (0.3)	3 (0.4)
Withdrawal by patient	15 (4.4)	20 (5.8)	35 (5.1)
Initiated Maintenance Study Period	239 (69.9)	227 (65.4)	466 (67.6)
Discontinued Maintenance Study Period	206 (60.2)	186 (53.6)	392 (56.9)
Reason for study treatment discontinuation in Maintenance Study Period			
Adverse event	16 (4.7)	12 (3.5)	28 (4.1)
Death	13 (3.8)	14 (4.0)	27 (3.9)
Lost to Follow-up	2 (0.6)	0	2 (0.3)
Physician decision	11 (3.2)	15 (4.3)	26 (3.8)
Progressive disease	154 (45.0)	127 (36.6)	281 (40.8)
Protocol violation	1 (0.3)	2 (0.6)	3 (0.4)

	CT-P16 (N=342)	EU-approved Avastin (N=347)	Total (N=689)
	Number (%) of patients		
Withdrawal by patient	6 (1.8)	14 (4.0)	20 (2.9)
Others	3 (0.9)	2 (0.6)	5 (0.7)
Initiated Follow-Up Period	161 (47.1)	158 (45.5)	319 (46.3)
Reason for ending participation in the study			
Death	164 (48.0)	168 (48.4)	332 (48.2)
Lost to Follow-up	19 (5.6)	11 (3.2)	30 (4.4)
Withdrawal by patient	44 (12.9)	45 (13.0)	89 (12.9)
Other	2 (0.6)	2 (0.6)	4 (0.6)

As seen in Table 8, the reason for ending participation in the study was death in a total of 332 patients. Among these patients, the reported reason for death was disease progression in 220 patients (110 patients in the CT-P16 group and 110 patients in the EU-Avastin group), adverse event in 37 patients (17 patients in the CT-P16 group and 20 patients in the EU-Avastin group), concurrent illness in 7 patients (3 patients in the CT-P16 group and 4 patients in the EU-Avastin group), unknown in 28 patients (13 patients in the CT-P16 group and 15 patients in the EU-Avastin group), and other in 40 patients (21 patients in the CT-P16 group and 19 patients in the EU-Avastin group).

A total of 68 (9.9%) patients had at least 1 major protocol deviation. Patients with major protocol deviation were excluded from the PP population. The most frequently reported major protocol deviation was missing primary efficacy assessment (21 [6.1%] patients and 39 [11.2%] patients in the CT-P16 and EU-Avastin treatment groups, respectively). These patients did not have any tumour assessment result at post-baseline in central and/or local review. Only one patient had a major protocol deviation due to COVID-19. Major protocol deviations are summarised in 9.

Table 9. Major Protocol Deviations in Study CT-P16 3.1 (ITT Population)

	CT-P16 (N=342)	EU-approved Avastin (N=347)	Total (N=689)
	Number (%) of patients		
Patients with at least 1 major protocol deviation	24 (7.0)	44 (12.7)	68 (9.9)
Mis-randomizations	2 (0.6)	2 (0.6)	4 (0.6)
Non-compliance of Inclusion or Exclusion criteria	0	3 (0.9)	3 (0.4)
Significant GCP Non-compliance	0	0	0
Receiving Any Prohibited Therapies	0	0	0
Missing Primary Efficacy Assessment	21 (6.1)	39 (11.2)	60 (8.7)
Other Deviation Affecting Primary Endpoint	1 (0.3)	0	1 (0.1)

Abbreviations: GCP, Good Clinical Practice; ITT, Intent-to-Treat.

The applicant was requested to clarify the notable imbalance between treatment groups with respect to the proportion of subjects excluded from the PP population, in particular due to missing primary efficacy assessment, and the reasons for the missing primary efficacy assessment. In the D120 responses, the

applicant clarified that an imbalance between the treatment groups was particularly observed in missing primary efficacy assessment being due to 'patient withdrawal' (1 [0.3%] patient and 14 [4.0%] patients in the CT-P16 and EU-Avastin treatment groups, respectively).

- **Recruitment**

The first patient was randomised into the study on 01 February 2019, and the study remains ongoing.

- **Conduct of the study**

The original protocol (Version 1.0) was dated 12 June 2018. The protocol was amended 12 times during the course of the study. One of the amendments was global, resulting in Protocol Version 2.0; other amendments were country-specific. The amendments primarily concerned additional specifications and minor adjustments in eligibility criteria.

According to the applicant, the study was conducted according to the ICH E6 (R2) risk and quality processes described in the applicable procedural documents. The quality management approach implemented in this study was documented and complied with the current ICH GCP guidelines on quality and risk management. Monitoring activities comprised a combination of centralised and risk-based monitoring activities as well as periodic on-site monitoring visits. According to audit certificates provided by the applicant, 8 study sites were subject to routine clinical site audits. Based on major protocol deviations reported by the applicant, no instances of significant GCP non-compliance were identified (Table 14).

The study was not subject to GCP inspections by regulatory authorities.

- **Baseline data**

The study enrolled a predominantly Caucasian population. Median age was 62 years, 35% were female and 65% male, and 69% were either former or current smokers. Disease status at baseline was metastatic in 92% of patients. The demographic characteristics and stratification factors are summarised in 10, and baseline disease characteristics are summarised in Table 11.

Table 10. Demographic Characteristics and Stratification Factors at Screening in CT-P16 3.1 (ITT Population)

	CT-P16 (N=342)	EU-Avastin (N=347)	Total (N=689)
Demographic Characteristics			
Age (years)			
Mean ± SD	61.3 ± 9.01	61.5 ± 9.42	61.4 ± 9.21
Median	62.0	62.0	62.0
Minimum, maximum	32, 82	26, 82	26, 82
Female fertility status[1], n (%)			
Surgically sterilized	13 (10.9%)	7 (5.6%)	20 (8.2%)
Post-menopausal	95 (79.8%)	104 (83.2%)	199 (81.6%)
Potentially able to bear children	11 (9.2%)	14 (11.2%)	25 (10.2%)
Race, n (%)			
American Indian or Alaska Native	9 (2.6%)	9 (2.6%)	18 (2.6%)
Asian	59 (17.3%)	55 (15.9%)	114 (16.5%)
Black or African American	2 (0.6%)	1 (0.3%)	3 (0.4%)
Native Hawaiian or Other Pacific Islander	0	0	0
White or Caucasian	264 (77.2%)	264 (76.1%)	528 (76.6%)
Not allowed by Investigator Country Regulations[2]	0	0	0
Other	8 (2.3%)	18 (5.2%)	26 (3.8%)
Ethnicity, n (%)			
Hispanic or Latino	57 (16.7%)	66 (19.0%)	123 (17.9%)
Non-Hispanic or non-Latino	282 (82.5%)	275 (79.3%)	557 (80.8%)
Not Allowed by Investigator Country Regulations[3]	0	2 (0.6%)	2 (0.3%)
Unknown[4]	3 (0.9%)	4 (1.2%)	7 (1.0%)
Smoking history, n (%)			

	CT-P16 (N=342)	EU-Avastin (N=347)	Total (N=689)
Current smoker	75 (21.9%)	88 (25.4%)	163 (23.7%)
Former smoker	163 (47.7%)	148 (42.7%)	311 (45.1%)
Never smoker	104 (30.4%)	111 (32.0%)	215 (31.2%)
Height (cm)			
n	342	346	688
Mean ± SD	166.85 ± 9.866	166.53 ± 10.034	166.69 ± 9.945
Median	167.00	168.00	167.00
Minimum, maximum	133.0, 194.0	138.0, 194.0	133.0, 194.0
Weight (kg) at baseline			
n	342	346	688
Mean ± SD	68.76 ± 15.767	69.78 ± 15.283	69.27 ± 15.523
Median	67.00	69.00	68.00
Minimum, maximum	36.0, 131.0	35.0, 126.0	35.0, 131.0
Stratification factors			
Disease status, n (%)			
Recurrence	25 (7.3%)	33 (9.5%)	58 (8.4%)
Metastatic	317 (92.7%)	314 (90.5%)	631 (91.6%)
ECOG performance status, n (%)			
Grade 0	105 (30.7%)	110 (31.7%)	215 (31.2%)
Grade 1	237 (69.3%)	237 (68.3%)	474 (68.8%)
Sex, n (%)			
Male	223 (65.2%)	222 (64.0%)	445 (64.6%)
Female	119 (34.8%)	125 (36.0%)	244 (35.4%)
Region[5], n (%)			
EMEA	226 (66.1%)	230 (66.3%)	456 (66.2%)
America	59 (17.3%)	62 (17.9%)	121 (17.6%)
Asia	57 (16.7%)	55 (15.9%)	112 (16.3%)

Note: Height and weight results summarized were the screening assessment values. ECOG performance status result summarized was the assessment value prior to study treatment administration at Induction Cycle 1.

[1] Fertility status was collected for female patient only. Percentages were calculated by using the number of female patients as the denominator

[2] When the race information of patients was not allowed to be disclosed due to country regulation

[3] When the ethnicity information of patients was not allowed to disclose due to country regulation

[4] When patients did not know their ethnicity

[5] The randomization was stratified by country, sex, ECOG, and disease status at screening. However, the primary analysis for the primary endpoint was performed considering region, sex, ECOG, and disease status as covariates. Use of region instead of country in statistical models was discussed at the DRM

Abbreviation: SD, standard deviation

Table 11. Baseline Disease Characteristics in Study CT-P16 3.1 (ITT Population)

	CT-P16 (N=342)	EU-Avastin (N=347)	Total (N=689)
Disease Status, n (%)			
Recurrence	25 (7.3%)	33 (9.5%)	58 (8.4%)
Metastatic	317 (92.7%)	314 (90.5%)	631 (91.6%)
Final pathological diagnosis, n (%)			
Adenocarcinoma	336 (98.2%)	340 (98.0%)	676 (98.1%)
Large cell carcinoma	3 (0.9%)	2 (0.6%)	5 (0.7%)
Non-Small Cell Carcinoma, NOS	1 (0.3%)	1 (0.3%)	2 (0.3%)
Squamous cell carcinoma	0	0	0
Small cell carcinoma	0	0	0
Adenosquamous carcinoma	2 (0.6%)	2 (0.6%)	4 (0.6%)
Other	0	2 (0.6%)	2 (0.3%)
Current histologic grade, n (%)			
GX: Grade of differentiation cannot be assessed	131 (38.3%)	118 (34.0%)	249 (36.1%)
G1: Well differentiated	32 (9.4%)	33 (9.5%)	65 (9.4%)
G2: Moderately differentiated	85 (24.9%)	91 (26.2%)	176 (25.5%)
G3: Poorly differentiated	83 (24.3%)	88 (25.4%)	171 (24.8%)
G4: Undifferentiated	9 (2.6%)	15 (4.3%)	24 (3.5%)
Current clinical stage, n (%)			
Stage IA	0	0	0
Stage IB	0	0	0
Stage IIA	0	0	0
Stage IIB	0	0	0
Stage IIIA	0	0	0
Stage IIIB	0	1 (0.3%)	1 (0.1%)
Stage IIIC	0	0	0
Stage IVA	147 (43.0%)	164 (47.3%)	311 (45.1%)

	CT-P16 (N=342)	EU-Avastin (N=347)	Total (N=689)
Stage IVB	170 (49.7%)	149 (42.9%)	319 (46.3%)
Recurrent	25 (7.3%)	33 (9.5%)	58 (8.4%)
Current N Stage			
N0	60 (17.5%)	66 (19.0%)	126 (18.3%)
N1	25 (7.3%)	40 (11.5%)	65 (9.4%)
N2	138 (40.4%)	133 (38.3%)	271 (39.3%)
N3	116 (33.9%)	104 (30.0%)	220 (31.9%)
NX	3 (0.9%)	4 (1.2%)	7 (1.0%)
EGFR (epidermal growth factor receptor)			
Negative	342 (100.0%)	345 (99.4%)	687 (99.7%)
Positive	0	2 (0.6%)	2 (0.3%)
Not Done	0	0	0
ALK (anaplastic lymphoma kinase)			
Negative	342 (100.0%)	347 (100.0%)	689 (100.0%)
Positive	0	0	0
Not Done	0	0	0

Abbreviation: NOS, not otherwise specified

- **Numbers analysed**

The number of patients in the statistical analysis sets is displayed in Table 12 . Out of 689 patients in the ITT Population, 621 (90.1%) patients were included in the PP Population. The primary reason for excluding a patient from the PP Population was a major protocol deviation of a missing primary efficacy assessment (21 patients in the CT-P16 group and 39 patients in the EU-Avastin group).

Table 12. Number of Patients in Statistical Analysis Sets in Study CT-P16 3.1 (ITT Population)

Number of Patients (%)	CT-P16 (N=342)	EU-Avastin (N=347)	Total (N=689)
	n (%)		
Intent-to-Treat Population	342 (100.0%)	347 (100.0%)	689 (100.0%)
Per-Protocol Population	318 (93.0%)	303 (87.3%)	621 (90.1%)

- **Outcomes and estimation**

Analyses of primary endpoint: ORR

The ORR based on BOR during the Induction Study Period from central review for the ITT and PP populations is summarised in Table 13.

Table 13. Objective Response Rates and Best Overall Response during the Induction Study Period in Study CT-P16 3.1 (Central) (ITT and PP Populations)

	ITT (Primary)		PP (Supportive)	
	CT-P16 (N=342)	EU-Avastin (N=347)	CT-P16 (N=318)	EU-Avastin (N=303)
Number of Responders (%)	145 (42.4%)	146 (42.1%)	144 (45.3%)	143 (47.2%)
Number of Non-Responders (%)	197 (57.6%)	201 (57.9%)	174 (54.7%)	160 (52.8%)
Objective Response Rate (%) (95% CI)	42.40 (37.16 - 47.64)	42.07 (36.88 - 47.27)	45.28 (39.81 - 50.75)	47.19 (41.57 – 52.82)
Risk Difference Estimate[1] (95% CI)	**0.40 (-7.02, 7.83)**		-1.90 (-9.80, 6.00)	
Best overall response, n (%)				
Complete response	2 (0.6%)	3 (0.9%)	2 (0.6%)	3 (1.0%)
Partial response	143 (41.8%)	143 (41.2%)	142 (44.7%)	140 (46.2%)
Stable disease	156 (45.6%)	140 (40.3%)	154 (48.4%)	138 (45.5%)
Progressive disease	17 (5.0%)	19 (5.5%)	17 (5.3%)	19 (6.3%)
Inevaluable	3 (0.9%)	3 (0.9%)	3 (0.9%)	3 (1.0%)
Missing	21 (6.1%)	39 (11.2%)	0	0

Note: Objective response rate was defined as the proportion of patients whose best overall response was CR or PR (considered as the 'Responder'). All other patients except responders were considered as non-responder including patients without postbaseline disease assessment.
[1] Logistic regression model included treatment groups (CT-P16 and EU-Avastin) as a fixed effect and region (EMEA vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrence vs. metastatic), and ECOG performance score at baseline (0 vs. 1) as covariates.
Abbreviations: CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PP, per-protocol; PR, partial response

In the ITT population, the 95% CI for difference (CT-P16 and EU-Avastin) in ORR during the Induction Study Period was within the equivalence margin of -12.5 to 12.5 (-7.02 to 7.83). The ORRs were similar in the CT-P16 and EU-Avastin treatment groups (42.40% [95% CI: 37.16 – 47.64] and 42.07% [95% CI: 36.88 – 47.27], respectively) and the risk difference (CT-P16 - EU-Avastin) estimate was 0.4%. For BORs, a similar proportion of patients in the CT-P16 and EU-Avastin treatment groups had CR (2 [0.6%] patients and 3 [0.9%] patients in the CT-P16 and EU-Avastin treatment groups, respectively) and PR (143 [41.8%] patients and 143 [41.2%] patients in the CT-P16 and EU-Avastin treatment groups, respectively) in the ITT population.

In the PP population, the ORRs and the BORs were similar to those in the ITT population. The 95% CI for difference was also within the equivalence margin of -12.5 to 12.5 (-9.80 to 6.00), which supports the result of the primary analysis. The ORRs were similar in the CT-P16 and EU-Avastin treatment groups (45.28% [95% CI: 39.81 – 50.75] and 47.19% [95% CI: 41.57 – 52.82], respectively) and the risk difference (CT-P16 - EU-Avastin) estimate was -1.9%. A similar proportion of patients in the CT-P16 and EU-Avastin treatment groups had CR (2 [0.6%] patients and 3 [1.0%] patients in the CT-P16 and

EU-Avastin treatment groups, respectively) and PR (142 [44.7%] patients and 140 [46.2%] patients in the CT-P16 and EU-Avastin treatment groups, respectively).

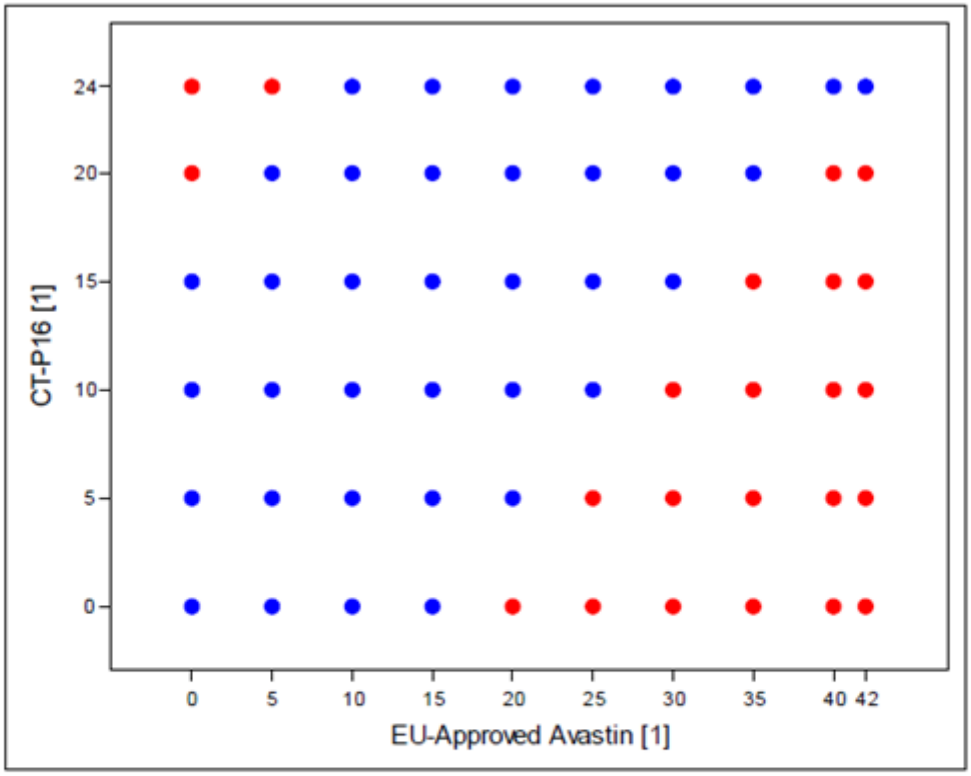
In order to evaluate the impact of missing data on the efficacy primary endpoint results, tipping point analyses were conducted for the primary efficacy endpoint (central review data) for ITT Population. Overall 66 patients were considered as missing cases in the tipping point analysis: 60 patients (21 [6.1%] patients and 39 [11.2%] patients in the CT-P16 and EU-Avastin treatment groups, respectively) with missing primary efficacy assessment and 6 patients (3 patients each in the CT-P16 and EU-Avastin, respectively) with best overall response of NE.

In the tipping point analysis, the two-sided 95% CIs for the difference in proportion between CT-P16 and EU-Avastin treatment groups were contained within the equivalence margin of (-12.5, 12.5) when differences in the imputed number of responders between the two treatment groups were 15 or below. The differences in the imputed number of responders of up to 15 did not alter the conclusion of therapeutic equivalence between the two treatment groups. The tipping point analyses are summarised in Table 14.

In response to D120 LoQ, to address the possible impact of missing data and their reasons on the ORR results, an additional analysis was provided based on the applicant's interpretation of missing at random assumption. Among those with missing efficacy evaluation, the reported reasons were: 15 patient withdrawal (1 and 14 in CT-P16 and EU-Avastin, respectively), 5 lost to follow-up, 1 investigator's decision and 1 protocol violation. These were considered uninformative cases as were the additional 6 patients with BOR of unevaluable. The patients who discontinued treatment due to AE (6 in CT-P16 and 5 in EU-Avastin) or death (10 in CT-P16 and 15 in EU-Avastin) before tumour assessment were analysed in two ways: In scenario 1, the subset of 10 cases of death due to clinical progression by investigator's opinion (5 in CT-P16, 5 in EU-Avastin) were considered as non-responders while the rest were considered uninformative. In scenario 2, all of the discontinuations due to AE or death before scheduled tumour assessment were considered as uninformative cases.

The two scenarios analysed resulted in very similar estimates of risk difference of ORR for CT-P16 vs. and EU-Avastin: -2.34% [95% CI: -10.21 – 5.54] according to scenario 1 (all patients with missing tumour assessment considered uninformative except for deaths potentially due to PD that were analysed as non-response) and -2.36 [95% CI: -10.27 – 5.55] according to scenario 2 (with all patients with missing tumour assessment considered uninformative).

Figure 4. Tipping Point Results for Objective Response Rate during Induction Study Period (Central) (ITT Population)



Note: The 95% confidence intervals of the difference between two proportions (CT-P16 and EU-Avastin group) were estimated by exact binomial approach.
Blue dots indicate that the two-sided 95% CI for the difference in proportion between CT-P16 and EU-Avastin is included in the equivalence margin of (-12.5, 12.5).
Red dots indicate that the two-sided 95% CI for the difference in proportion between CT-P16 and EU-Avastin is not included in the equivalence margin of (-12.5, 12.5).
[1] Shift for the number of responders in CT-P16 and EU-Avastin. Assumed number of responder for patients with no response evaluation result or 'Inevaluable (NE)'.

Table 14. Tipping Point Results for Objective Response Rate during Induction Study Period (Central) (ITT Population)

	Shift for the Number of Responders in EU-Avastin[1]									
Shift for the Number of Responders in CT-P16[1]	0	5	10	15	20	25	30	35	40	42
0	(-7.13, 7.78)	(-8.59, 6.33)	(-10.05, 4.88)	(-11.50, 3.46)	(-12.97, 2.04)†	(-14.38, 0.61)†	(-15.80, -0.46)†	(-17.23, -1.75)†	(-18.65, -2.88)†	(-19.22, -3.78)†
5	(-5.70, 9.22)	(-7.16, 7.78)	(-8.61, 6.36)	(-10.09, 4.94)	(-11.50, 3.51)	(-12.93, 2.08)†	(-14.36, 0.66)†	(-15.78, -0.46)†	(-17.20, -1.56)†	(-17.77, -2.00)†
10	(-4.26, 10.67)	(-5.72, 9.25)	(-7.20, 7.83)	(-8.61, 6.41)	(-10.05, 4.98)	(-11.48, 3.55)	(-12.91, 2.12)†	(-14.33, 0.69)†	(-15.75, -0.46)†	(-16.32, -0.90)†
15	(-2.82, 12.13)	(-4.31, 10.72)	(-5.72, 9.30)	(-7.16, 7.88)	(-8.59, 6.45)	(-10.02, 5.02)	(-11.45, 3.59)	(-12.88, 2.16)†	(-14.30, 0.73)†	(-14.87, 0.15)†
20	(-1.40, 13.60)†	(-2.83, 12.18)	(-4.26, 10.76)	(-5.70, 9.34)	(-7.14, 7.92)	(-8.57, 6.49)	(-10.00, 5.06)	(-11.42, 3.63)	(-12.85, 2.19)†	(-13.42, 1.62)†
24	(-0.22, 14.77)†	(-1.65, 13.35)†	(-3.09, 11.93)	(-4.53, 10.51)	(-5.97, 9.09)	(-7.40, 7.66)	(-8.83, 6.23)	(-10.26, 4.80)	(-11.68, 3.36)	(-12.25, 2.79)

Note: Objective response rate is defined as the proportion of patients whose confirmed best overall response is CR or PR (the 'Responder'). Tipping point analyses is conducted under MNAR (Missing Not at Random) scenarios. The 95% confidence intervals of the difference between two proportions (CT-P16 and EU-Avastin group) were estimated by exact binomial approach.
† Two-sided 95% CI for the difference in proportion between CT-P16 and EU-Avastin is not included in the equivalence margin of (-12.5, 12.5).
[1] Assumed number of responder for patients with no response evaluation result or 'Inevaluable (NE)'.

ORR's based on local investigator reviews were presented as a sensitivity analysis; the results are displayed in Table 15 for the ITT population, and Table 16 for the PP population. For both analyses, the 95% CI for difference between CT-P16 and EU-Avastin in ORR during the Induction Study Period was within the equivalence margin of -12.5 to 12.5 (ITT: 4.87% [95 %CI: -2.53 to 12.26]; PP: 2.90% [95 % CI: -4.99 to 10.79]). Whereas the 95% CI's for both the ITT and PP populations were contained within the pre-specified equivalence margin, it is noted that the point estimates for the treatment difference were larger than in results based on central review.

Table 15. Objective Response Rate During the Induction Study Period: Local Review (ITT Population)

	CT-P16 (N=342)	EU-Approved Avastin (N=347)
Best overall response, n (%)		
Complete response	0	2 (0.6)
Partial response	150 (43.9)	134 (38.6)
Stable disease	158 (46.2)	147 (42.4)
Progressive disease	10 (2.9)	23 (6.6)
Inevaluable	3 (0.9)	4 (1.2)
Missing	21 (6.1)	37 (10.7)
Objective response rate (%) (95% CI)	43.86 (38.60 - 49.12)	39.19 (34.06 - 44.33)
Risk difference (CT-P16 - EU-approved Avastin) estimate[1]	4.87	
95% CI for difference (CT-P16 - EU-approved Avastin) estimate[1]	(-2.53, 12.26)	

Abbreviations: CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EMEA, Europe, the Middle East, and Africa; ITT, Intent-to-Treat; PR, partial response.

1. Logistic regression model including treatment groups (CT-P16 and EU-Approved Avastin) as a fixed effect and region (EMEA vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrence vs. metastatic), and ECOG performance score at baseline (0 vs. 1) as covariates was used.

Note: Objective response rate was defined as the proportion of patients whose best overall response was CR or PR (considered as the 'Responder'). All other patients except responders were considered as non-responder including patients without post-baseline disease assessment.

Table 16. Objective Response Rate During the Induction Study Period: Local Review (PP Population)

	CT-P16 (N=318)	EU-Approved Avastin (N=303)
Best overall response, n (%)		
Complete response	0	2 (0.7)
Partial response	148 (46.5)	131 (43.2)
Stable disease	157 (49.4)	143 (47.2)
Progressive disease	10 (3.1)	23 (7.6)
Inevaluable	3 (0.9)	4 (1.3)
Missing	0	0
Objective response rate (%) (95% CI)	46.54 (41.06 - 52.02)	43.89 (38.31 - 49.48)
Risk difference (CT-P16 - EU-approved Avastin) estimate[1]	2.90	
95% CI for difference (CT-P16 - EU-approved Avastin) estimate[1]	(-4.99, 10.79)	

Abbreviations: CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EMEA, Europe, the Middle East, and Africa; PP, Per-Protocol; PR, partial response.

1. Logistic regression model including treatment groups (CT-P16 and EU-Approved Avastin) as a fixed effect and region (EMEA vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrence vs. metastatic), and ECOG performance score at baseline (0 vs. 1) as covariates was used.

Note: Objective response rate was defined as the proportion of patients whose best overall response was CR or PR (considered as the 'Responder'). All other patients except responders were considered as non-responder including patients without post-baseline disease assessment.

A post-hoc analysis was also carried out to assess the concordance between the ITRC and the local investigator assessments of tumour response.

Table 17. Concordance between Local and Central Results for Responder and Non-Responder (ITT population)

Treatment	Local Assessment	Central Assessment	
		Responder	Non-responder
CT-P16 (N=342)	Responder	**113 (33.04%)**	37 (10.82%)
	Non-responder	32 (9.36%)	**160 (46.78%)**
	Concordance Rate	**79.82%**	
EU-Avastin (N=347)	Responder	**104 (29.97%)**	32 (9.22%)
	Non-responder	42 (12.10%)	**169 (48.70%)**
	Concordance Rate	**78.67%**	

Note: Patients with best overall response of Complete Response (CR) or Partial Response (PR) are considered as 'Responder'. All other patients except responders are considered as 'Non-Responder' including patients without post-baseline disease assessment.

In addition, a post-hoc analysis of ITRC ORR based on response result at each cycle was conducted. Results are displayed in Table 18 and Table 19.

Table 18. ORR, Point Estimates with 95% CI at Induction Cycle 6 (Central)

Visit Category	ITT Population		PP Population	
	CT-P16 (N=342)	EU-Avastin (N=347)	CT-P16 (N=318)	EU-Avastin (N=303)
Induction Cycle 6				
Responder	146 (42.7%)	151 (43.5%)	143 (45.0%)	148 (48.8%)
Non-Responder	196 (57.3%)	196 (56.5%)	175 (55.0%)	155 (51.2%)
ORR (%) (95% CI)	42.69 (37.45 - 47.93)	43.52 (38.30 - 48.73)	44.97 (39.50 - 50.44)	48.84 (43.22 - 54.47)
Risk Difference (%) (95% CI)	-0.77 (-8.21, 6.68)		-3.79 (-11.69, 4.11)	

Note: Objective response rate is defined as the proportion of patients whose overall response is CR or PR (the 'Responder'). All other patients except responders is considered as non-responder including patients without post-baseline disease assessment.
Abbreviations: CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response

Table 19. ORR Result of Each Cycle based on Overall Response (Central)

Visit Category	ITT Population		PP Population	
	CT-P16 (N=342)	EU-Avastin (N=347)	CT-P16 (N=318)	EU-Avastin (N=303)
Induction Cycle 2				
ORR (%) (95% CI)	29.53 (24.70 - 34.37)	25.94 (21.33 - 30.55)	31.45 (26.34 - 36.55)	29.70 (24.56 - 34.85)
Induction Cycle 4				
ORR (%) (95% CI)	39.77 (34.58 - 44.95)	36.60 (31.53 - 41.67)	42.45 (37.02 - 47.89)	41.58 (36.03 - 47.13)
Induction Cycle 6				
ORR (%) (95% CI)	42.69 (37.45 - 47.93)	43.52 (38.30 - 48.73)	44.97 (39.50 - 50.44)	48.84 (43.22 - 54.47)
Induction Study Period				
ORR (%) (95% CI)	42.40 (37.16 - 47.64)	42.07 (36.88 - 47.27)	45.28 (39.81 - 50.75)	47.19 (41.57 – 52.82)
Risk Difference Estimate (95% CI)[1]	0.40 (-7.02, 7.83)		-1.90 (-9.80, 6.00)	
Minatenance Cycle 3				
ORR (%) (95% CI)	24.85 (20.27 - 29.43)	25.07 (20.51 - 29.63)	26.73 (21.87 - 31.59)	27.72 (22.68 - 32.76)

Note: Objective response rate is defined as the proportion of patients whose overall response is CR or PR (the'Responder'). All other patients except responders is considered as non-responder including patients without post-baseline disease assessment.

[1] Logistic regression model included treatment groups (CT-P16 and EU-Avastin) as a fixed effect and region (EMEA vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrence vs. metastatic), and ECOG performance score at baseline (0 vs. 1) as covariates.

Abbreviations: CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response.

Evaluation of efficacy is primarily based on longitudinal assessment of changes in target tumour sizes but neither statistical summaries nor visualisation of these raw data were included in original submission. In D120 LoQ, the applicant was requested to provide a descriptive analysis for evolution of sum of diameter of target lesion by treatment group and further by whether or not response was achieved.

Figure 5. Spaghetti Plot for Change from Baseline (%) of Sum of Diameter for Target Lesion - CT-P16 (ITT Population)

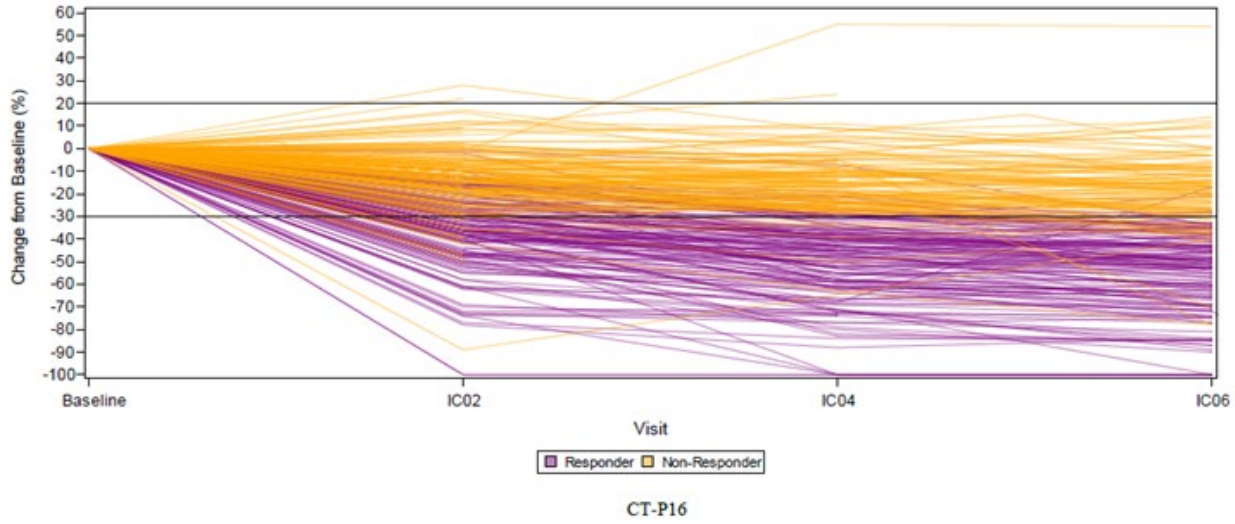
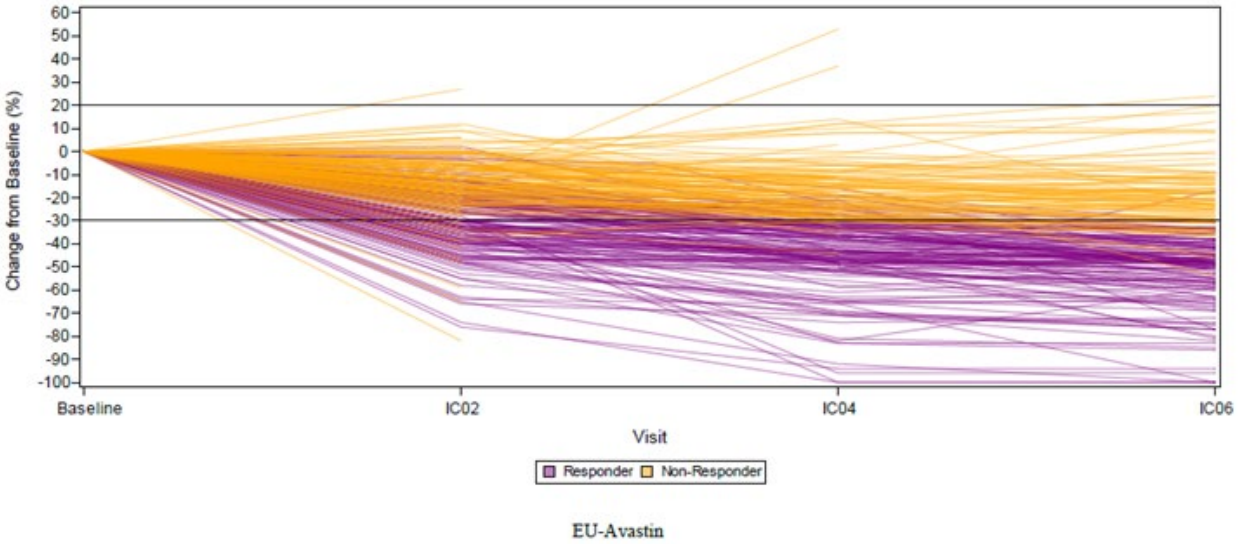


Figure 6. Spaghetti Plot for Change from Baseline (%) of Sum of Diameter for Target Lesion - EU-Avastin (ITT Population)



The changes in individual patients' target tumour sizes are visualised in CT-P16 and EU-Avastin groups in Figure 5 and 6, respectively. In addition, summary of statistics of target tumour % changes of diameter were provided by the applicant at start of induction cycle 2, 4 and 6. By induction cycle 2, those that achieved RECIST v1.1 response (BOR of CR or PR) in CT-P16 and EU-Avastin had, on average, mean reduction of 37.1% and 31.5% in tumour size, respectively. Among the RECIST v1.1 non-responders, the respective mean reductions were 12.8% and 14.0%.

Analyses of secondary endpoints: PFS and OS

PFS was defined as time from randomisation to determined progression disease (PD)/recurrence or death from any cause, whichever occurs first. PD/recurrence or death that occurred on or before beginning another new anticancer therapy was regarded as an event. Censoring was defined as following:

Table 20. Reasons for censoring and censoring dates

Reason for Censoring	Censoring Date
No tumor assessment after randomization	The date of randomization
No event and no anticancer therapy	Last tumor assessment date
Initiation of new anticancer therapy[1]	Last tumor assessment date before anticancer therapy
Event after missing two or more tumor assessment[2]	Last tumor assessment date before event

Note: The last tumor assessment date on which tumor assessment was neither 'missing' nor 'inevaluable' were used for censoring date.
[1] A patient was considered as taking a new anticancer therapy if there was any record of salvage treatment, which included chemotherapy/immunotherapy/targeted therapy, radiotherapy and surgery.
[2] If there was only one missing tumor assessment before an event, then it was considered as an event case. Otherwise, it was considered as a censoring case.

In the ITT population, 72.5% (248/342) patients and 70.9% (246/347) patients had died or had PD/recurrence in the CT-P16 and EU-Avastin treatment groups, respectively. The median PFS were 7.9 [95% CI: 6.9 – 8.3] months and 7.2 [95% CI: 6.5 – 8.3] months for the CT-P16 and EU-Avastin treatment groups, respectively. The hazard ratio of PFS was 0.92 (95% CI: 0.77 – 1.10).

In the PP population, 72.3% (230/318) patients and 73.3% (222/303) patients had died or had PD/recurrence in the CT-P16 and EU-Avastin treatment groups, respectively. The median PFS was 8.3 [95% CI: 7.2 – 8.5] months and 8.1 [95% CI: 6.8 – 8.6] months for the CT-P16 and EU-Avastin treatment groups, respectively. The hazard ratio of PFS was 0.93 (95% CI: 0.76 – 1.12).

The summary of PFS (Central) for the Study CT-P16 3.1 is presented below in Table 21. A Kaplan-Meier plot of PFS from central review is presented for the ITT population in Figure 7 and for the PP population in Figure 8.

Table 21. Summary of Progression Free Survival (Central)

	ITT Population		PP Population	
	CT-P16 (N=342)	EU-Avastin (N=347)	CT-P16 (N=318)	EU-Avastin (N=303)
Number of Patients with Events	**248 (72.5%)**	**246 (70.9%)**	**230 (72.3%)**	**222 (73.3%)**
PD/Recurrence	186 (54.4%)	188 (54.2%)	183 (57.5%)	185 (61.1%)
Death	62 (18.1%)	58 (16.7%)	47 (14.8%)	37 (12.2%)
Number of Patients with Censoring	**94 (27.5%)**	**101 (29.1%)**	**88 (27.7%)**	**81 (26.7%)**
No Tumor Assessment	6 (1.8%)	18 (5.2%)	0	0
No Event and No Anticancer Therapy	46 (13.5%)	46 (13.3%)	46 (14.5%)	45 (14.9%)
Initiation of New Anticancer Therapy	42 (12.3%)	37 (10.7%)	42 (13.2%)	36 (11.9%)
Event after Missing Two or More Tumor Assessment	0	0	0	0
Survival Time (Months)[1]				
25th Percentile (95% CI)	5.5 [4.1, 6.2)	4.8 [3.7, 6.1)	6.2 [4.6, 6.3)	6.0 [4.7, 6.3)
Median (95% CI)	7.9 [6.9, 8.3)	7.2 [6.5, 8.3)	8.3 [7.2, 8.5)	8.1 [6.8, 8.6)
75th Percentile (95% CI)	11.5 [10.6, 12.6)	12.5 [10.7, 13.6)	11.8 [10.8, 12.8)	12.8 [11.0, 14.5)
Hazard Ratio (95% CI)[2]	**0.92 (0.77, 1.10)**		**0.93 (0.76, 1.12)**	
Estimates of Survival Rates (95% CI)[1]				
6 months	0.73 (0.68, 0.78)	0.71 (0.65, 0.75)	0.76 (0.71, 0.80)	0.75 (0.70, 0.80)
12 months	0.23 (0.18, 0.28)	0.27 (0.22, 0.32)	0.24 (0.19, 0.29)	0.29 (0.23, 0.34)
24 months	0.09 (0.05, 0.15)	0.06 (0.02, 0.12)	0.10 (0.06, 0.15)	0.06 (0.02, 0.12)
36 months	N.E (N.E, N.E)	N.E (N.E, N.E)	N.E (N.E, N.E)	N.E (N.E, N.E)

[1] Estimates and corresponding 95% CIs are based on Kaplan-Meier method.
[2] Adjusted stratified Cox regression model is used to estimate the hazard ratio and its 95% CI for receiving CT-P16 compared with receiving EU-Avastin using region (EMEA vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrence vs. metastatic), and ECOG performance score at baseline (0 vs. 1) as stratification factors.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; N.E., not estimable; PD, progressive disease; PP, per-protocol

Figure 7. Kaplan-Meier Plot of Progression-Free Survival in Study CT-P16 3.1 (Central) (ITT Population)

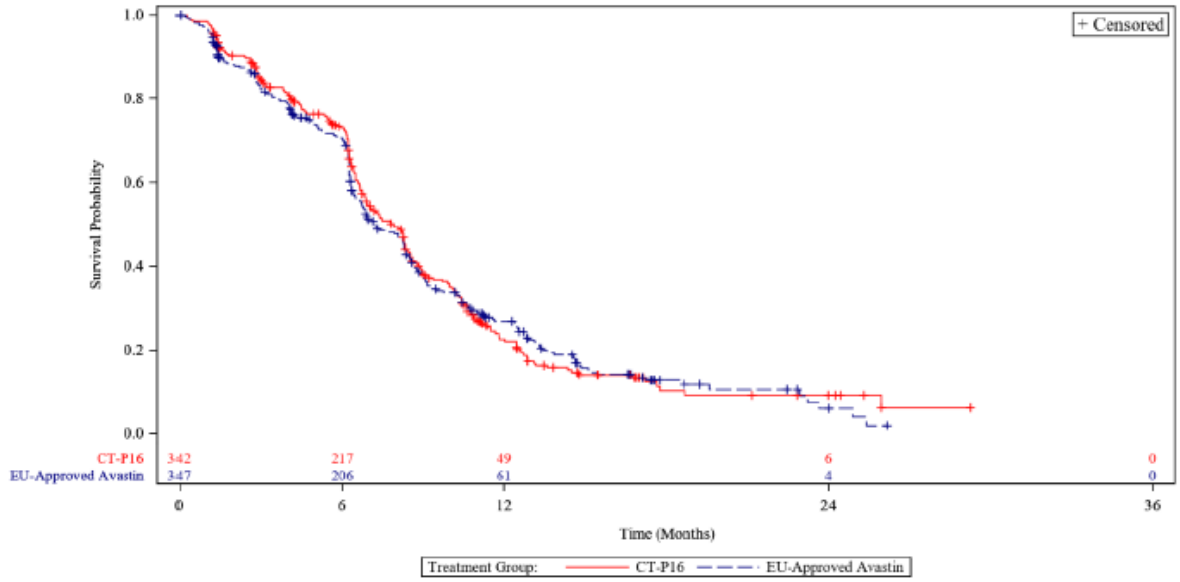
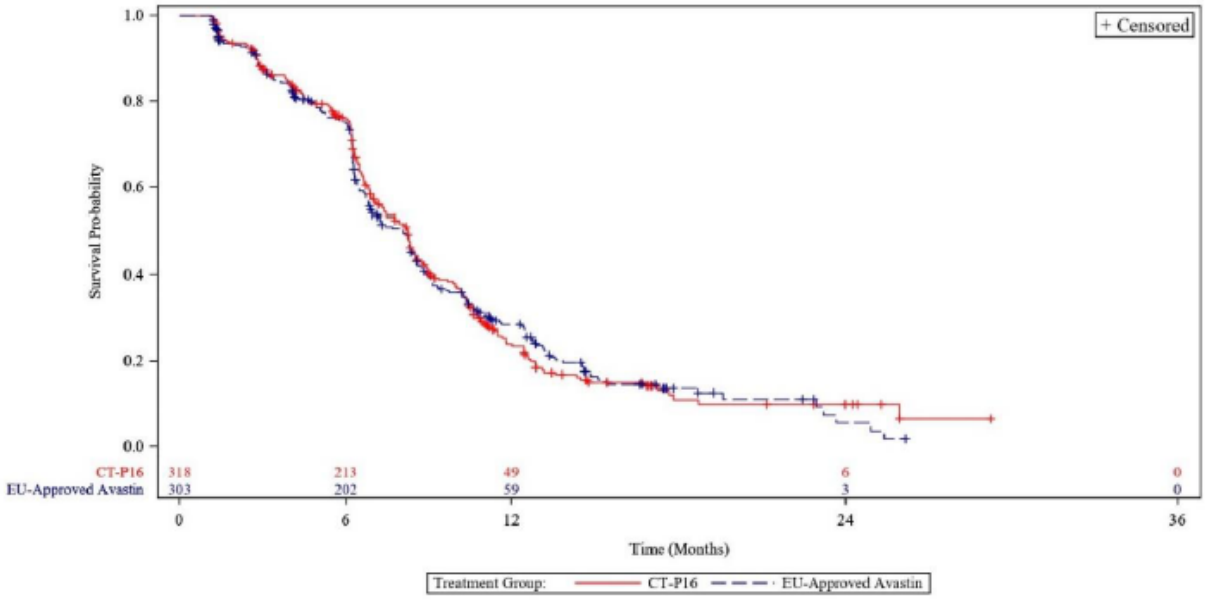


Figure 8. Kaplan-Meier Plot of Progression-Free Survival in Study CT-P16 3.1 (Central) (PP Population)



In response to the D180 LoQ, the applicant performed PFS analysis where death cases that occurred during the Follow-Up Period were regarded as an event and patients who withdrew from the study without any event or anticancer therapy were censored at the last date of tumour assessment as they were in the original analysis. The applicant also performed PFS analysis in which study treatment withdrawal and anticancer therapy with no PD/recurrence or death were newly considered as an event in addition to censoring logic implemented in the previous sensitivity analysis. With respect to the comparison between CT-P16 and EU-Avastin, the results of these additional analyses were similar to the original PFS analysis.

OS was defined as time from randomisation to death from any cause. Death was regarded as an event and non-death was censored at the last known alive date.

In the ITT population, 48.0% (164/342) patients and 48.4% (168/347) patients had died in the CT-P16 and EU-Avastin treatment groups, respectively. The median OS was 17.1 [95% CI: 14.6 – 18.7] months and 15.6 [95% CI: 13.4 – 18.0] months for the CT-P16 and EU-Avastin treatment groups, respectively. The hazard ratio of OS was 0.95 (95% CI: 0.77 – 1.19).

In the PP population, 147 (46.2%) patients and 145 (47.9%) patients had died in the CT-P16 and EU-Avastin treatment groups, respectively. The median OS was 17.5 [95% CI: 15.5 – 19.2] months and 17.0 [95% CI: 14.6 – 20.5] months for the CT-P16 and EU-Avastin treatment groups, respectively. The hazard ratio of OS was 0.96 (95% CI: 0.76 – 1.22).

The summary of OS for Study CT-P16 3.1 is presented below in Table 22. Kaplan-Meier plots of OS are presented for the ITT population in Figure 9 and for the PP population in Figure 10.

Table 22. Summary of Overall Survival

	ITT Population		PP Population	
	CT-P16 (N=342)	EU-Avastin (N=347)	CT-P16 (N=318)	EU-Avastin (N=303)
Number of Patients with Events	**164 (48.0%)**	**168 (48.4%)**	**147 (46.2%)**	**145 (47.9%)**
Death	164 (48.0%)	168 (48.4%)	147 (46.2%)	145 (47.9%)
Number of Patients with Censoring	**178 (52.0%)**	**179 (51.6%)**	**171 (53.8%)**	**158 (52.1%)**
Non-Death	178 (52.0%)	179 (51.6%)	171 (53.8%)	158 (52.1%)
Survival Time (Months)[1]				
25th Percentile (95% CI)	9.1 [8.0, 10.9)	8.4 [7.1, 9.7)	10.6 [8.7, 11.3)	9.3 [8.2, 10.8)
Median (95% CI)	17.1 [14.6, 18.7)	15.6 [13.4, 18.0)	17.5 [15.5, 19.2)	17.0 [14.6, 20.5)
75th Percentile (95% CI)	N.E [25.0, N.E)	26.3 [25.3, N.E)	N.E [25.0, N.E)	26.9 [25.3, N.E)
Hazard Ratio (95% CI)[2]	**0.95 (0.77, 1.19)**		**0.96 (0.76, 1.22)**	
Estimates of Survival Rates (95% CI)[1]				
12 months	0.66 (0.60, 0.71)	0.62 (0.56, 0.67)	0.69 (0.63, 0.74)	0.65 (0.59, 0.70)
24 months	0.36 (0.29, 0.43)	0.36 (0.29, 0.43)	0.38 (0.31, 0.46)	0.37 (0.30, 0.45)
36 months	N.E (N.E, N.E)	N.E (N.E, N.E)	N.E (N.E, N.E)	N.E (N.E, N.E)

[1] Estimates and corresponding 95% CIs are based on Kaplan-Meier method.
[2] Adjusted stratified Cox regression model is used to estimate the hazard ratio and its 95% CI for receiving CT-P16 compared with receiving EU-Avastin using region (EMEA vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrence vs. metastatic), and ECOG performance score at baseline (0 vs. 1) as stratification factors.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; N.E., not estimable; PP, per-protocol

Figure 9. Kaplan-Meier Plot of Overall Survival in Study CT-P16 3.1 (ITT Population)

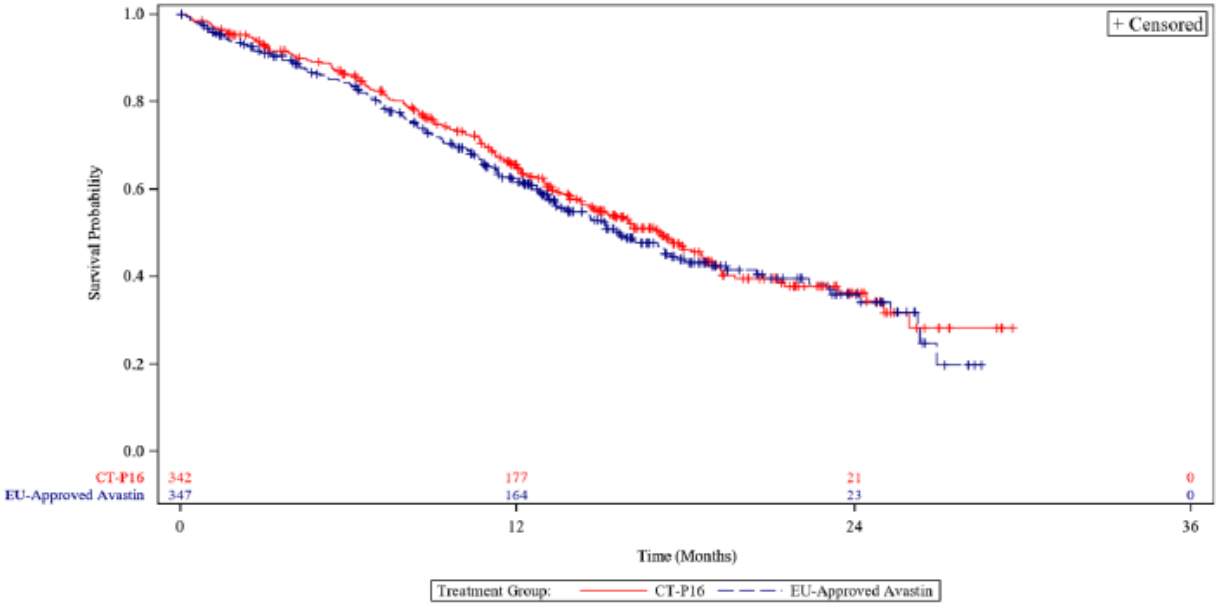
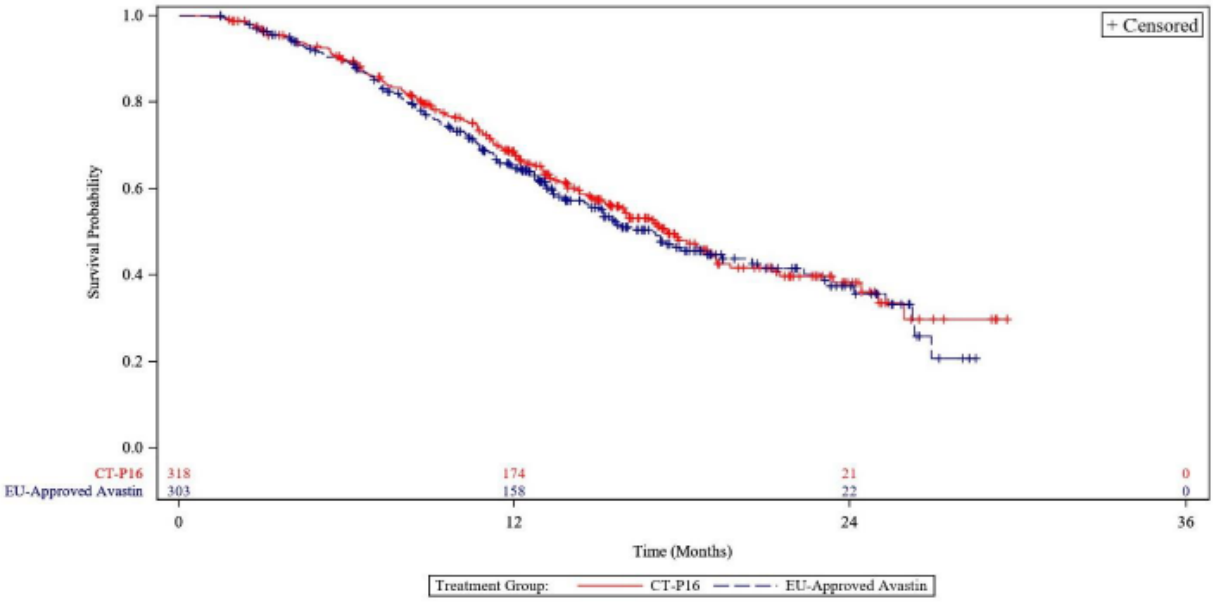


Figure 10. Kaplan-Meier Plot of Overall Survival in Study CT-P16 3.1 (PP Population)

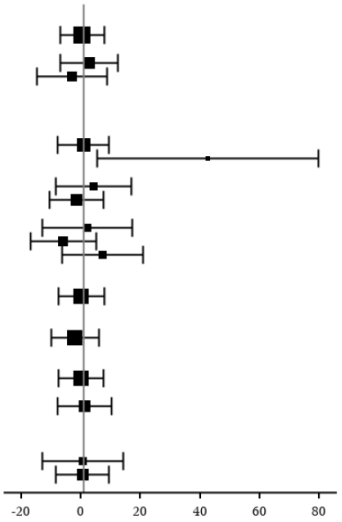


- **Ancillary analyses**

Forest plots for risk difference based on ITRC ORR by stratification factors as well as other subgroups deemed relevant by the applicant are displayed in Figure 11 for the ITT population and in Figure 12 for the PP population.

Figure 11. Forest Plot of Risk Difference of ORR (Central) by Subgroup (ITT Population)

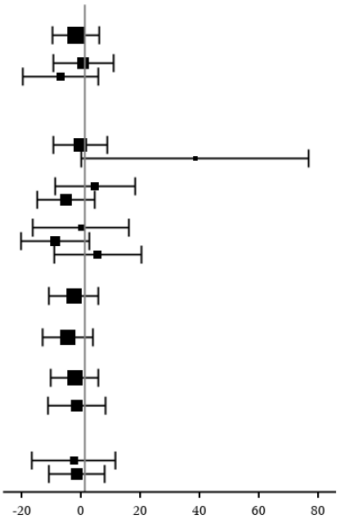
Subgroup	CT-P16 Events/N (%)		EU-Approved Avastin Events/N (%)		Risk Difference (95% CI)
All subjects	145/342	(42.4%)	146/347	(42.1%)	0.40 (-7.02, 7.83)
Age					
< 65	91/203	(44.8%)	90/213	(42.3%)	2.62 (-7.04, 12.27)
>= 65	54/139	(38.8%)	56/134	(41.8%)	-3.19 (-14.96, 8.58)
Race					
American Indian Or Alaska Native	4/9	(44.4%)	3/9	(33.3%)	NE (NE, NE)
Asian	21/59	(35.6%)	25/55	(45.5%)	NE (NE, NE)
Black Or African American	0/2	(0.0%)	0/1	(0.0%)	NE (NE, NE)
White	114/264	(43.2%)	112/264	(42.4%)	0.75 (-7.77, 9.28)
Other	6/8	(75.0%)	6/18	(33.3%)	42.47 (5.24, 79.69)
Sex					
F	57/119	(47.9%)	55/125	(44.0%)	4.20 (-8.61, 17.01)
M	88/223	(39.5%)	91/222	(41.0%)	-1.52 (-10.65, 7.60)
Smoking History					
Current Smoker	29/75	(38.7%)	32/88	(36.4%)	1.99 (-13.07, 17.04)
Former Smoker	61/163	(37.4%)	65/148	(43.9%)	-6.07 (-17.09, 4.96)
Never Smoker	55/104	(52.9%)	49/111	(44.1%)	7.21 (-6.51, 20.93)
Disease Status					
Recurrence	10/25	(40.0%)	12/33	(36.4%)	NE (NE, NE)
Metastatic	135/317	(42.6%)	134/314	(42.7%)	0.04 (-7.73, 7.81)
Prior Radiation Therapy					
Yes	16/41	(39.0%)	9/42	(21.4%)	NE (NE, NE)
No	129/301	(42.9%)	137/305	(44.9%)	-2.11 (-10.08, 5.85)
Prior Anti-Cancer Systemic Therapy					
Yes	2/6	(33.3%)	2/10	(20.0%)	NE (NE, NE)
No	143/336	(42.6%)	144/337	(42.7%)	-0.02 (-7.55, 7.50)
Region					
EMEA	97/226	(42.9%)	96/230	(41.7%)	1.10 (-8.03, 10.22)
America	29/59	(49.2%)	25/62	(40.3%)	NE (NE, NE)
Asia	19/57	(33.3%)	25/55	(45.5%)	NE (NE, NE)
ECOG Status					
Grade 0	52/105	(49.5%)	54/110	(49.1%)	0.48 (-13.14, 14.09)
Grade 1	93/237	(39.2%)	92/237	(38.8%)	0.41 (-8.38, 9.19)



Note: ORR=Objective Response Rate, CI=Confidence Interval, NE=Not Estimable, N=Number of patients in subgroup.
In order to estimate Risk Difference and its 95% CI, Logistic Regression model including treatment groups (CT-P16 and EU-Approved Avastin) as a fixed effect and region (EMEA vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrence vs. metastatic), and ECOG performance score at baseline (0 vs. 1) as covariates was used. When covariate is considered as subgroup, the 3 remaining factors were adjusted for the model. When there is only one response level (responder or non-responder) within each level of covariates or there is a convergence failure in the Logistic Regression model, Risk Difference and its 95% CI were presented as 'NE (NE, NE)'.

Figure 12. Forest Plot of Risk Difference of ORR (Central) by Subgroup (PP Population)

Subgroup	CT-P16 Events/N (%)		EU-Approved Avastin Events/N (%)		Risk Difference (95% CI)
All subjects	144/318	(45.3%)	143/303	(47.2%)	-1.90 (-9.80, 6.00)
Age					
< 65	90/192	(46.9%)	88/191	(46.1%)	0.57 (-9.58, 10.72)
>= 65	54/126	(42.9%)	55/112	(49.1%)	-7.03 (-19.89, 5.82)
Race					
American Indian Or Alaska Native	4/8	(50.0%)	3/6	(50.0%)	NE (NE, NE)
Asian	20/54	(37.0%)	25/46	(54.3%)	NE (NE, NE)
Black Or African American	0/2	(0.0%)	0/1	(0.0%)	NE (NE, NE)
White	114/246	(46.3%)	109/234	(46.6%)	-0.32 (-9.34, 8.70)
Other	6/8	(75.0%)	6/16	(37.5%)	38.33 (-0.03, 76.70)
Sex					
F	57/108	(52.8%)	54/112	(48.2%)	4.59 (-8.87, 18.05)
M	87/210	(41.4%)	89/191	(46.6%)	-5.23 (-14.96, 4.51)
Smoking History					
Current Smoker	29/70	(41.4%)	31/75	(41.3%)	-0.12 (-16.36, 16.12)
Former Smoker	60/154	(39.0%)	64/133	(48.1%)	-8.83 (-20.41, 2.75)
Never Smoker	55/94	(58.5%)	48/95	(50.5%)	5.48 (-9.16, 20.12)
Disease Status					
Recurrence	10/23	(43.5%)	11/29	(37.9%)	NE (NE, NE)
Metastatic	134/295	(45.4%)	132/274	(48.2%)	-2.60 (-10.87, 5.66)
Prior Radiation Therapy					
Yes	16/36	(44.4%)	9/34	(26.5%)	NE (NE, NE)
No	128/282	(45.4%)	134/269	(49.8%)	-4.60 (-13.01, 3.81)
Prior Anti-Cancer Systemic Therapy					
Yes	2/6	(33.3%)	2/9	(22.2%)	NE (NE, NE)
No	142/312	(45.5%)	141/294	(48.0%)	-2.32 (-10.32, 5.69)
Region					
EMEA	97/213	(45.5%)	95/203	(46.8%)	-1.51 (-11.16, 8.13)
America	29/53	(54.7%)	23/54	(42.6%)	NE (NE, NE)
Asia	18/52	(34.6%)	25/46	(54.3%)	NE (NE, NE)
ECOG Status					
Grade 0	52/101	(51.5%)	52/96	(54.2%)	-2.56 (-16.71, 11.60)
Grade 1	92/217	(42.4%)	91/207	(44.0%)	-1.58 (-11.02, 7.86)



Note: ORR=Objective Response Rate, CI=Confidence Interval, NE=Not Estimable, N=Number of patients in subgroup.
In order to estimate Risk Difference and its 95% CI, Logistic Regression model including treatment groups (CT-P16 and EU-Approved Avastin) as a fixed effect and region (EMEA vs. America vs. Asia), sex (female vs. male), disease status at baseline (recurrence vs. metastatic), and ECOG performance score at baseline (0 vs. 1) as covariates was used. When covariate is considered as subgroup, the 3 remaining factors were adjusted for the model. When there is only one response level (responder or non-responder) within each level of covariates or there is a convergence failure in the Logistic Regression model, Risk Difference and its 95% CI were presented as 'NE (NE, NE)'.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as

well as the biosimilarity assessment (see later sections).

Table 23. Summary of efficacy for trial CT-P16 3.1

Title: Double-Blind, Randomized, Active-Controlled, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P16 and EU-Approved Avastin as First-Line Treatment for Metastatic or Recurrent Non-Squamous Non-Small Cell Lung Cancer		
Study identifier	Project code: CT-P16 3.1 EudraCT number: 2018-002147-28	
Design	Randomised, parallel-group, double-blind, multicentre study	
	Duration of main phase: Duration of Run-in phase:	Repeat dose until progression disease or intolerable toxicity (approximately 3 years from the enrolment of the last patient) Screening Period: within 28 days prior to randomisation (extended to 8 weeks of Screening Period for patients with CNS metastases to provide sufficient time for CNS treatment) Induction Study Period: every 3 weeks up to 6 cycles Maintenance Study Period: every 3 weeks until PD or intolerable toxicity Follow-Up Period: every 9 weeks until death or the end of study
Hypothesis	To demonstrate that CT-P16 is equivalent to EU-Avastin	
Treatment groups	CT-P16	Induction Study Period: 15 mg/kg IV of CT-P16 will be administered on Day 1 of each cycle and will be repeated every 3 weeks until 6 cycles. Paclitaxel 200 mg/m^2 IV and carboplatin area under the curve (AUC) 6 IV also will be administered on Day 1 of each cycle and will be repeated every 3 weeks up to 6 cycles (at least 4 cycles) Maintenance Period: CT-P16 as a monotherapy maintained every 3 weeks until progressive disease (PD) or intolerable toxicity occurrence Number randomised=342
	EU-Avastin	Induction Study Period: 15 mg/kg IV of EU-Avastin will be administered on Day 1 of each cycle and will be repeated every 3 weeks until 6 cycles. Paclitaxel 200 mg/m^2 IV and carboplatin area under the curve (AUC) 6 IV also will be administered on Day 1 of each cycle and will be repeated every 3 weeks up to 6 cycles (at least 4 cycles) Maintenance Period: EU-Avastin as a monotherapy maintained every 3 weeks until progressive disease (PD) or intolerable toxicity occurrence Number randomised=347

<table>
<tr><td rowspan="7">Endpoints and definitions</td><td>Primary efficacy endpoint</td><td>ORR during the Induction Study Period</td><td>defined as an objective response rate based on BOR by RECIST v1.1</td></tr>
<tr><td rowspan="6">Secondary efficacy endpoint</td><td>ORR during the Whole Study Period</td><td>defined as an objective response rate based on BOR by RECIST v1.1</td></tr>
<tr><td>Response duration</td><td>defined as the time between initial response (CR or PR) and PD/recurrence or death due to any cause, whichever occurs first</td></tr>
<tr><td>TTP</td><td>defined as the time from randomisation until PD/recurrence</td></tr>
<tr><td>PFS</td><td>defined as the time from randomisation until PD/recurrence or death due to any cause, whichever occurs first</td></tr>
<tr><td>OS</td><td>defined as the time from randomisation until death due to any cause</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Database lock</td><td colspan="3">15 July 2021</td></tr>
<tr><td colspan="4"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">• Efficacy population
- Intent-to-treat (ITT) Population: The ITT population is defined as all patients randomly assigned to study drug, regardless of whether or not any study treatment dosing is completed and successfully screened. Patients were assigned to treatment groups based on randomisation. The primary population for the primary efficacy analysis was the ITT population.
- Per-Protocol Population: The PP population is defined as all randomly assigned patients who have at least one response evaluation after receiving at least one full dose of study drug (CT P16 or EU Approved Avastin) in the Induction Study Period and who do not have any major protocol deviation. A major protocol deviation was one that may affect the interpretation of primary endpoint and it was defined in the SAP. Final determinations of the PP population were made at the blinded data review meeting before unblinding. Patients were assigned to treatment groups based on randomisation. A supportive efficacy analysis was repeated using the PP population.
• Tumour evaluation was assessed at Screening and every 2 cycles during the Induction Study Period and every 3 cycles during the Maintenance Study Period, and at the EOT visit. During the Follow-Up Period, it will be performed every 9 weeks until PD, death, withdrawal or start of new anti-cancer therapy if PD is not confirmed during the Induction or Maintenance Study Periods.</td></tr>
<tr><td rowspan="4">Descriptive statistics and estimate variability</td><td colspan="3">Primary analysis (ITT population; Central ITRC review)</td></tr>
<tr><td colspan="3">Number (%) of patients</td></tr>
<tr><td>Treatment group
(ITT Population)</td><td>CT-P16
(N=342)</td><td>EU-Avastin
(N=347)</td></tr>
<tr><td>Number of Responders (%)</td><td>145 (42.4%)</td><td>146 (42.1%)</td></tr>
</table>

	Number of Non-Responders (%)	197 (57.6%)	201 (57.9%)
	Objective Response Rate (%) (95% CI)	42.40 (37.16 - 47.64)	42.07 (36.88 - 47.27)
	Risk Difference Estimate (95% CI)	0.40 (-7.02, 7.83)	
	Best overall response, n (%)		
	Complete response	2 (0.6%)	3 (0.9%)
	Partial response	143 (41.8%)	143 (41.2%)
	Stable disease	156 (45.6%)	140 (40.3%)
	Progressive disease	17 (5.0%)	19 (5.5%)
	Inevaluable	3 (0.9%)	3 (0.9%)
	Missing	21 (6.1%)	39 (11.2%)
Descriptive statistics and estimate variability	**Supportive analysis (PP population; Central review)**		
	Number (%) of patients		
	Treatment group (PP Population)	CT-P16 (N=318)	EU-Avastin (N=303)
	Number of Responders (%)	144 (45.3%)	143 (47.2%)
	Number of Non-Responders (%)	174 (54.7%)	160 (52.8%)
	Objective Response Rate (%) (95% CI)	45.28 (39.81 – 50.75)	47.19 (41.57 – 52.82)
	Risk Difference Estimate (95% CI)	-1.90 (-9.80, 6.00)	
	Best overall response, n (%)		
	Complete response	2 (0.6%)	3 (1.0%)
	Partial response	142 (44.7%)	140 (46.2%)
	Stable disease	154 (48.4%)	138 (45.5%)
	Progressive disease	17 (5.3%)	19 (6.3%)
	Inevaluable	3 (0.9%)	3 (1.0%)
	Missing	0	0

2.4.5.3. Clinical studies in special populations

Not applicable for biosimilars.

2.4.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.4.5.6. Supportive studies

Not applicable.

2.4.6. Discussion on clinical efficacy

As outlined above, data used to support biosimilarity of CT-P16 with EU-Avastin from a clinical efficacy perspective stems from one clinical study (Study CT-P16 3.1), conducted in patients with metastatic or recurrent non-squamous non-small cell lung cancer.

Design and conduct of clinical studies

Study CT-P16 3.1 is an ongoing double-blind, randomised, active-controlled, parallel-group study comparing CT-P16 (15 mg/kg) and EU-Avastin (15 mg/kg) when co-administered with paclitaxel and carboplatin as first-line treatment in patients with metastatic or recurrent nsNSCLC. Eligible patients were randomised in a 1:1 ratio to receive intravenous CT-P16 or EU-Avastin every 3 weeks. All patients concomitantly received intravenous paclitaxel and carboplatin every 3 weeks up to 6 cycles (at least 4 cycles). After the completion of 6 cycles during the Induction Study Period, patients with controlled disease (complete response [CR], partial response [PR], or stable disease [SD], assessed at the end of Cycle 6) entered the Maintenance Study Period, during which patients receive CT-P16 or EU-Avastin as monotherapy every 3 weeks until PD or intolerable toxicity.

The basic design of the study is acceptable and consistent with expectations for a clinical biosimilarity study. The eligibility criteria adequately define an appropriate target population for the clinical study, and similar eligibility criteria have been applied in multiple prior studies for bevacizumab biosimilars. Dose selection for study drugs was in accordance with the authorised posology for Avastin.

The primary objective of study CT-P16 3.1 was to demonstrate that CT-P16 was similar to EU-Avastin in terms of efficacy as determined by objective response rate (ORR) during the Induction Study Period. Secondary objectives include ORR during the Whole Study Period, response duration, time to progression (TTP), progression-free survival (PFS), and overall survival (OS). The primary and secondary objectives are consistent with expectations for a clinical biosimilarity trial; demonstration of similarity based on ORR is consistent with regulatory precedent and is endorsed as an appropriate primary objective. In addition to a BOR approach, ORR has been reported by treatment cycle; this additional analysis is endorsed as providing relevant additional information for assessment of biosimilarity. Data for the secondary endpoints were not included in the initial submission but were received within the applicant's responses to the D120 List of Questions.

A key requirement for an equivalence study is assay sensitivity, i.e. ability to detect a true difference between the outcomes between the comparative treatments. Despite the 'standard' response definitions as per RECIST 1.1 the actual performance of the measure may differ between studies and may depend on design and quality considerations. An Independent Tumour Review Committee (ITRC) was used for the primary analysis. Images for tumour assessment were reviewed separately centrally and locally, and both image review results were analysed and listed separately. Based on the imaging charter, the

operations were deemed to be consistent with conventional expectations for an ITRC. The reported rates of inter-rater concordance are considered acceptable and indicate adequate sensitivity to detect differences in radiographic outcomes between patients and thus between treatment groups.

The equivalence margin of -12.5% to 12.5% is similar to the margin previously applied in MAAs for other bevacizumab biosimilars for demonstrating similar efficacy in first-line NSCLC indication. According to the meta-analysis across 4 trials, randomised bevacizumab, added to chemotherapy, increases the probability of objective response by at least 12.89 percentage points (based on lower limit of 95% confidence intervals). Thereby, the proposed margin is believed to preserve at least some positive fraction of the originator's efficacy. No clinical justification for the equivalence margin is given by the applicant. According to the Clinical Overview, the equivalence margin was agreed with EMA via CHMP Scientific Advice (EMEA/H/SA/3334/1/2016/III), however, there is no discussion about the equivalence margin for a nsNSCLC population and thereby the accuracy of the applicant's statement could not be ascertained. Given the several recent precedents for the acceptability of an equivalence margin similar to that proposed by the applicant, the issue was not pursued.

The sample size rationale, parameters and results appear consistent. The sample size is adequate for the purpose.

The measures for the blinding of the study seem adequate and for the safety precaution the IWRS system seems relevant as well as the policy for the unblinding. The number of cases when treatment was unblinded at individual patient level is low and, as such, unlikely to risk to credibility of the results.

The number of stratification factors exceeds the recommended number of ICH guideline E9 Statistical Principles for Clinical Trials. The number of randomisation strata is 168 and the number of patients randomised must have been very small in a considerable proportion of strata. As such it is questionable whether the randomisation procedure was optimal in ensuring balanced treatment groups with respect to the key factors. However, as the randomisation actually resulted in reasonable balance with respect each of the stratification factors, this potential methodological caveat can be ignored.

Randomisation was stratified by country and, as per ICH E9 Statistical Principles for Clinical Trials, factors on which randomisation has been stratified should be accounted for later in the analysis. In this study, the countries were pooled into three geographic regions for the statistical analysis. In the D120 responses, the applicant provided an adequate rationale for pooling the countries into the regions for the purpose of the statistical analysis and summarised the numbers of study subjects from each region.

Due to the excessive number of strata and low assumed number of patients in many of them, a fully stratified statistical analysis of outcome would not be feasible. Instead a parsimonious model, e.g. logistic regression, must be used to account for stratification factors in the statistical comparison between treatment groups. The logistic regression model assumes that the odds (hence probability) of response may differ depending - in addition to treatment assignment - on the covariates: geographic region where the patient participates in the study, sex, baseline disease status and baseline ECOG performance status. When a single response rate for a treatment group or difference between treatment groups is estimated from a logistic regression model the result is specific to the chosen levels of the covariates or the weights used for averaging. In calculation for the ORR in each treatment group, the applicant assigned weights for the fixed model effects (corresponding to the levels of stratification factors) proportionally based on the distribution of stratification factor levels in the population studied. This is considered appropriate.

Evaluation of efficacy is primarily based on longitudinal assessment of changes in target tumour sizes but neither statistical summaries nor visualisation of these raw data were included in original submission. In D120 LoQ, the applicant was requested to provide a descriptive analysis for evolution of sum of diameter of target lesion by treatment group and further by whether or not response was achieved.

A total of 1.530 patients were screened for the study. Of these, 841 patients were screen failed, most commonly for not meeting inclusion/exclusion criteria. A total of 689 patients were randomly assigned to study drug and initiated the Induction Study Period (342 patients in the CT-P16 treatment group and 347 patients in the EU-Avastin treatment group). Of these, 499 (72.4%) patients completed the Induction Study Period (258 [75.4%] in the CT-P16 treatment group and 241 [69.5%] in the EU-Avastin treatment group). A total of 466 (67.6%) patients initiated the Maintenance Study Period (239 [69.9%] patients in the CT-P16 treatment group and 227 [65.4%] patients in the EU-Avastin treatment group). Of these, 392 (56.9%) patients discontinued the Maintenance Study Period (206 [60.2%] patients in CT-P16 treatment group and 186 [53.6%] patients in EU-Avastin treatment group). Overall, the most common reason for discontinuation during both the induction and maintenance periods was PD. The number of patients discontinuing due to PD during the Induction Period was slightly higher in the EU-Avastin group than the CT-P16 group; however, during the Maintenance Period, the number of patients discontinuing due to PD was conversely higher in the CT-P16 group. Overall, the reasons for discontinuation were balanced between treatment groups.

The reason for ending participation in the study was death in a total of 332 patients. Among these patients, the reported reason for death was disease progression in 220 patients (110 patients in the CT-P16 group and 110 patients in the EU-Avastin group), adverse event in 37 patients (17 patients in the CT-P16 group and 20 patients in the EU-Avastin group), concurrent illness in 7 patients (3 patients in the CT-P16 group and 4 patients in the EU-Avastin group), unknown in 28 patients (13 patients in the CT-P16 group and 15 patients in the EU-Avastin group), and other in 40 patients (21 patients in the CT-P16 group and 19 patients in the EU-Avastin group).

A total of 68 (9.9%) patients had at least 1 major protocol deviation and are consequently not included in the PP population. The most frequently reported major protocol deviation was missing primary efficacy assessment (21 [6.1%] patients and 39 [11.2%] patients in the CT-P16 and EU-Avastin treatment groups, respectively). This imbalance has been taken into consideration through tipping point analyses. The applicant was also requested to clarify reasons behind the notable imbalance between treatment groups. In the D120 responses, the applicant clarified that an imbalance between the treatment groups was particularly observed in missing primary efficacy assessment due to 'patient withdrawal' (1 [0.3%] patient and 14 [4.0%] patients in the CT-P16 and EU-Avastin treatment groups, respectively). Although the difference between groups was in itself not completely insubstantial, it was agreed that the distribution of these withdrawals across sites, with mostly single withdrawals for any given centre, is consistent with the imbalance occurring by chance.

There were 12 amendments to the original study protocol. In addition to one global protocol amendment, a number of country-specific amendments were introduced into the study protocol. Of the 11 country-specific amendments, 6 are dated prior to enrolment of first patient into the study. Overall, these are not considered to have any significant effect on the reliability or integrity of the study.

Based on major protocol deviations reported by the applicant, no instances of significant GCP non-compliance were identified. The study was not subject to GCP inspections by regulatory authorities.

The study enrolled a predominantly Caucasian population. Median age was 62 years, 35% were female and 65% male, and 69% were either former or current smokers. Disease status at baseline was metastatic in 92% of patients. Two thirds of the participants were enrolled in EMEA regions. Despite the criticism of possible over-stratification, the treatment groups were in good balance with respect to the stratification factors, and overall, no significant imbalances were noted between the treatment groups with respect to demographic and baseline characteristics.

The numbers of subjects in the ITT population correspond to the pre-defined sample size (339 in each group). The overall proportion (90.1 %) of subjects considered to comprise the PP population is reasonable given the importance of protocol-compliance in an equivalence setting. There is, however, a

notable imbalance between treatment groups with respect to the proportion of subjects excluded from the PP population, in particular due to missing primary efficacy assessment. As indicated above, the applicant provided adequate clarification regarding the imbalance.

Efficacy data and additional analyses

Study CT-P16 3.1 met its primary endpoint. In the ITT population, the risk difference in ORR during the Induction Period was 0.40%, and the 95% confidence interval [-7.02 – 7.83] was contained within the pre-specified equivalence margin of -12.5 – 12.5. The reported ORR's (42.40% [95% CI: 37.16 – 47.64] for CT-P16 and 42.07% [95% CI: 36.88 – 47.27] for EU-Avastin) are in line with those reported in other recent trials for bevacizumab biosimilars.

The number of patients with missing primary efficacy assessment and hence excluded from Per Protocol population was considerably lower for CT-P16 than EU-Avastin (21 [6.1%] vs. 39 [11.2%]). In the ITT analyses these missing assessments are defaulted to non-response which contributes to the comparison between the treatment groups.

In addition to central review (central independent reviewer) of ORR during the Induction Study Period, as a sensitivity analysis the ORR during Induction Study Period was also reviewed on local level by investigators. In these analyses, the point estimates for the treatment difference were larger than in the central review, although the 95% CI's were still contained within the pre-specified equivalence margin. The applicant was requested to explain the difference, and in its response to the D120 LoQ, the applicant elaborated on local and central tumour assessment and explained differences thereof as requested. Additionally, according to a post-hoc analysis conducted by the applicant, local and central assessment showed similar extent of concordance between the two treatment groups (79.82% and 78.67% for CT-P16 and EU-Avastin, respectively). Therefore, it is considered implausible that the observed differences impair conclusion on biosimilarity, and no further concern is raised in this regard.

Tipping point analysis was conducted (using central review data) in the ITT population to evaluate the sensitivity of conclusion to the missing data (no response evaluation or evaluated as 'NE') assumptions. According to the applicant, the differences in the imputed number of responders of up to 15 did not alter the conclusion from the primary analysis that appears hence to be robust and not significantly impacted by missing data. The applicant states that these analyses were conducted under Missing Not at Random (MNAR) scenarios: imputation was done by gradually shifting the number of responders by treatment group to make MNAR scenarios.

In response to D120 LoQ, the applicant provided a summary of reported reasons for missing efficacy assessment and analyses that correspond to missing at random assumption and discussed whether or not the reasons for the assessment being missing is predictive of the outcome. Lack of post-baseline tumour assessment due to death as the reported reason was somewhat more common in EU-Avastin group as compared with CT-P16. Even larger was the difference between number of patients without post-baseline tumour assessment due to patient withdrawal. Although speculative, these differences may be due to a chance imbalance between the treatment groups in the underlying life expectancy. While it is questionable whether early deaths, treatment withdrawals and losses to follow-up can be considered as uninformative about the likelihood of response as per RECIST v1.1, the applicant's missing-at-random analysis provides a helpful benchmark: Whereas the primary analysis may have underestimated the ORR of EU-Avastin as compared with CT-P16 by considering all of the early deaths and withdrawals as evidence of non-response, the missing at random analysis corresponds to a somewhat opposite scenario that likely is overly optimistic about EU-Avastin's ORR relative to CT-P16. Both analyses lead to the same conclusion concerning similar efficacy.

Based on the analysis provided in response to D120 LoQ, the distribution and patterns of individual target tumour size % changes during the induction period, based on centralised assessment of radiographs, were visually similar between CT-P16 and EU-Avastin. Not only were the proportions of responders as RECIST v1.1 similar in the two treatment groups but also the degree of shrinkage (or growth) among responders and non-responders appeared similar in both treatment groups.

The concordance of local and central assessment of tumour response can be considered acceptable and in line with the level concordance typically reported in NSCLC clinical trials applying RECIST 1.1.

The post-hoc analysis of ORR by treatment cycle showed similar response rates between the treatment groups in the ITT population. A difference of about 4% was noted in the PP population for Induction Cycle 6, but the 95% CI's for the Induction Cycle 6 risk differences were contained with the pre-specified equivalence margin for both populations.

Analyses for time-dependent endpoints (PFS, OS) were provided within the applicant's response to the D120 LoQ and additional PFS analyses were provided in response to the D180 LoQ. In general, the analyses, following a data lock when the last enrolled patient had completed 1 year of follow-up, demonstrate very similar results in both treatment groups and can in principle be considered to provide additional support for the claim of biosimilarity between CT-P16 and EU-Avastin.

Changes on quality of life -related endpoints were generally small, with high interindividual variability. No robust conclusion can be made, but no concerning differences between treatment groups can be identified. The worsening alopecia and peripheral neuropathy can reasonably be ascribed to the concomitant chemotherapy.

Based on a forest plot for risk difference based on ITRC ORR by stratification factors as well as other relevant subgroups, the results with respect to absolute response rates or treatment differences appear consistent across the subgroups explored.

2.4.7. Conclusions on the clinical efficacy

Clinical efficacy data to support biosimilarity of CT-P16 with EU-Avastin stems from the ongoing study CT-P16 3.1, conducted in patients with metastatic or recurrent nsNSCLC. The design and other general characteristics of the study are considered fit for the purpose of demonstrating biosimilarity. The primary endpoint was ORR (based on BOR) during the Induction Study Period. For the ITT and the PP populations, the reported CT-P16 – EU-Avastin risk differences of 0.40 (95% CI -7.02, 7.83) and -1.90 (95% CI -9.80, 6.00), respectively, were entirely contained within the pre-specified equivalence margin of -12.5 to 12.5. As such, the primary analysis can be considered to support biosimilarity, and available sensitivity analyses support this view. The analyses for time-dependent endpoints (PFS, OS) can also be considered supportive of biosimilarity.

In conclusion, CT-P16 can be considered biosimilar to EU-Avastin from a clinical efficacy perspective.

2.4.8. Clinical safety

The safety information is based primarily on data from Study CT-P16 3.1 in nsNSCLC patients, from Study CT-P16 1.1 in healthy subjects (pivotal PK study) and supportive information from CT-P16 1.2 in healthy Japanese subjects. Study CT-P16 3.1 in nsNSCLC patients is ongoing and has been completed up to 1 year from the last enrolled patient. Clinical data up to the cut-off date (21 September 2021) has been provided by the applicant that includes complete data for all patients through Induction Study Period and data for a total of 148 (21.5%) patients who have completed 1 year of treatment (≥ Maintenance Cycle 12).

2.4.8.1. Patient exposure

Overall extent of exposure

The clinical Safety Population includes data from 876 subjects; 689 nsNSCLC patients in Study CT-P16 3.1, 141 healthy male subjects in Study CT-P16 1.1 and 46 healthy male subjects in Study CT-P16 1.2. Patients with nsNSCLC received either CT-P16 or EU-Avastin (15 mg/kg) every 3 weeks up to 18 weeks (6 cycles) in combination therapy with paclitaxel and carboplatin (6 cycles [at least 4 cycles]) during the Induction Study Period. Following the combination therapy, patients continued with CT-P16 or EU-Avastin (15 mg/kg) every 3 weeks as monotherapy in the Maintenance Study Period until disease progression or intolerable toxicity, whichever occurred first. In addition, 187 healthy subjects received a single dose (5 mg/kg) of CT-P16, EU-Avastin or US-Avastin in studies CT-P16 1.1 and 1.2.

Exposure in Study CT-P16 3.1

The number of patients who received the study drug during the Induction Study Period and up to the maintenance cycle 12 is summarised in Table 24 and the number of patients that received chemotherapy during the Induction Study Period in Table 25.

Table 24. Overall Exposure to CT-P16 or EU-Avastin in Study CT-P16 3.1 up to the Maintenance Cycle 12 (Safety Population)

	CT-P16 (N=345)	EU-Avastin (N=344)	Total (N=689)
Induction Study Period			
Induction Cycle 1	345 (100.0)	344 (100.0)	689 (100.0)
Induction Cycle 2	330 (95.7)	317 (92.2)	647 (93.9)
Induction Cycle 3	309 (89.6)	277 (80.5)	586 (85.1)
Induction Cycle 4	292 (84.6)	269 (78.2)	561 (81.4)
Induction Cycle 5	272 (78.8)	248 (72.1)	520 (75.5)
Induction Cycle 6	263 (76.2)	240 (69.8)	503 (73.0)
Maintenance Study Period			
Maintenance Cycle 1	242 (70.1)	224 (65.1)	466 (67.6)
Maintenance Cycle 2	234 (67.8)	217 (63.1)	451 (65.5)
Maintenance Cycle 3	223 (64.6)	204 (59.3)	427 (62.0)
Maintenance Cycle 4	184 (53.3)	153 (44.5)	337 (48.9)
Maintenance Cycle 5	175 (50.7)	150 (43.6)	325 (47.2)
Maintenance Cycle 6	167 (48.4)	140 (40.7)	307 (44.6)
Maintenance Cycle 7	133 (38.6)	108 (31.4)	241 (35.0)
Maintenance Cycle 8	126 (36.5)	107 (31.1)	233 (33.8)
Maintenance Cycle 9	118 (34.2)	105 (30.5)	223 (32.4)
Maintenance Cycle 10	84 (24.3)	88 (25.6)	172 (25.0)
Maintenance Cycle 11	78 (22.6)	84 (24.4)	162 (23.5)
Maintenance Cycle 12	70 (20.3)	78 (22.7)	148 (21.5)

Note: Patients who received at least 1 dose of CT-P16 at any time during the treatment period up to cut-off date (21 September 2021) were analysed under the CT-P16 treatment group.

Table 25. Overall Exposure to Chemotherapy in Study CT-P16 3.1 during the Induction Study Period (Safety Population)

	CT-P16 (N=345)	EU-Avastin (N=344)	Total (N=689)
Paclitaxel			
Induction Cycle 1	345 (100.0)	344 (100.0)	689 (100.0)
Induction Cycle 2	330 (95.7)	318 (92.4)	648 (94.0)
Induction Cycle 3	309 (89.6)	278 (80.8)	587 (85.2)
Induction Cycle 4	293 (84.9)	269 (78.2)	562 (81.6)
Induction Cycle 5	253 (73.3)	238 (69.2)	491 (71.3)
Induction Cycle 6	242 (70.1)	224 (65.1)	466 (67.6)
Carboplatin			
Induction Cycle 1	345 (100.0)	344 (100.0)	689 (100.0)
Induction Cycle 2	330 (95.7)	318 (92.4)	648 (94.0)
Induction Cycle 3	309 (89.6)	277 (80.5)	586 (85.1)
Induction Cycle 4	293 (84.9)	269 (78.2)	562 (81.6)
Induction Cycle 5	256 (74.2)	241 (70.1)	497 (72.1)
Induction Cycle 6	249 (72.2)	226 (65.7)	475 (68.9)

Note: Patients who received at least 1 dose of CT-P16 at any time during the treatment period up to cut-off date (21 September 2021) were analysed under the CT-P16 treatment group.

Administered dose intensities during the induction and maintenance study periods in the Study CT-P16 3.1 is summarised in Table 26 and Table 27.

Table 26. Dose Intensity During the Induction Study Period (Safety Population)

	CT-P16 (N=345)	EU-approved Avastin (N=344)	Total (N=689)
Administered dose intensity during the Induction Study Period (mg/kg/week)			
n	345	344	689
Mean (standard deviation)	4.69 (0.410)	4.73 (0.366)	4.71 (0.389)
Median (minimum, maximum)	4.87 (2.6, 5.4)	4.88 (3.3, 5.3)	4.88 (2.6, 5.4)
Relative dose intensity during the Induction Study Period (%)			
n	345	344	689
Mean (standard deviation)	93.83 (8.208)	94.56 (7.322)	94.20 (7.781)
Median (minimum, maximum)	97.37 (51.9, 107.7)	97.67 (66.2, 105.0)	97.67 (51.9, 107.7)

Abbreviation: PP, Per-Protocol.

Table 27. Dose Intensity During the Maintenance Study Period (Safety Population)

	CT-P16 (N=345)	EU-approved Avastin (N=344)	Total (N=689)
Administered dose intensity (mg/kg/week) during maintenance cycles			
n	242	224	466
Mean (standard deviation)	4.84 (0.299)	4.84 (0.310)	4.84 (0.304)
Median (minimum, maximum)	4.97 (3.2, 5.2)	4.99 (3.3, 5.3)	4.98 (3.2, 5.3)
Relative dose intensity (%) during maintenance cycles			
n	242	224	466
Mean (standard deviation)	96.78 (5.981)	96.82 (6.194)	96.80 (6.077)
Median (minimum, maximum)	99.36 (64.9, 103.5)	99.82 (66.7, 105.0)	99.63 (64.9, 105.0)

The mean (SD) administered dose intensity of paclitaxel in the Study CT-P16 3.1 was 61.95 (6.493) mg/m^2/week and 62.35 (6.087) mg/m^2/week, and the mean (SD) relative dose intensity was 94.59% (7.702) and 95.24% (7.194) in the CT-P16 and EU-Avastin treatment groups, respectively.

The mean (SD) administered dose intensity of carboplatin in the Study CT-P16 3.1 was 1.85 (0.200) AUC/week and 1.86 (0.181) AUC/week, and the mean (SD) relative dose intensity was 93.60% (8.464) and 94.14% (7.575) in the CT-P16 and EU-Avastin treatment groups, respectively.

Baseline Demographics in Study CT-P16 3.1

For the demographics and baseline characteristics of Study CT-P16 3.1, please see section 2.4.5.

The most frequently reported medical history SOCs were vascular disorder (157 [45.9%] and 157 [45.2%] patients), gastrointestinal disorders (100 [29.2%] and 104 [30.0%] patients), and surgical and medical procedures (107 [31.3%] patients and 86 [24.8%] patients) in CT-P16 and EU-Avastin treatment groups, respectively. The most frequently reported medical history PTs were hypertension (119 [34.8%] and 125 [36.0%] patients), renal cyst (38 [11.1%] and 39 [11.2%] patients, and chronic obstructive pulmonary disease (34 [9.9%] and 41 [11.8%] patients) in the CT-P16 and EU-Avastin treatment groups, respectively.

Overall, 64 (9.3%) patients (27 [7.9%] patients and 37 [10.7%] patients in the CT-P16 and EU-Avastin treatment groups, respectively) had at least 1 previous surgical procedure. The most frequently reported previous surgical procedure was lung lobectomy (20 [5.8%] patients and 32 [9.2%] patients in the CT-P16 and EU-Avastin treatment groups, respectively).

Overall, 83 (12.0%) patients (41 [12.0%] patients and 42 [12.1%] patients in the CT-P16 and EU-Avastin treatment groups, respectively) had at least 1 previous radiotherapy. Most of previous radiotherapy was indicated for metastatic nsNSCLC. The most frequently reported lesion location of previous radiotherapy was brain (30 [8.8%] patients and 28 [8.1%] patients in the CT-P16 and EU-Avastin treatment groups, respectively).

Overall, 16 (2.3%) patients (6 [1.8%] patients and 10 [2.9%] patients in the CT-P16 and EU-Avastin treatment groups, respectively) had at least 1 previous anti-cancer systemic therapy. Cytotoxic chemotherapy was the only type of previous anti-cancer systemic therapy (6 [1.8%] patients and 10 [2.9%] patients in the CT-P16 and EU-Avastin treatment groups, respectively). The most frequently reported previous anti-cancer systemic therapy was cisplatin (4 [1.2%] patients and 6 [1.7%] patients in the CT-P16 and EU-Avastin treatment groups, respectively).

2.4.8.2. Adverse events

An overview of the adverse events in Study CT-P16 3.1 is shown in Table 28.

Table 28. Overview of Adverse Events in the Study CT-P16 3.1 (Safety Population)

	2nd CSR (Cut-off Date: 21 September 2021)					
	Induction Study Period		Maintenance Study Period		Whole Study Period[1]	
	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)
Total number of TEAEs	2284	2032	665	535	2957	2576
Number (%) of subjects with ≥ 1 TEAE	328 (95.1)	315 (91.6)	175 (50.7)	155 (45.1)	332 (96.2)	320 (93.0)
Related	144 (41.7)	147 (42.7)	82 (23.8)	76 (22.1)	178 (51.6)	174 (50.6)
Unrelated	313 (90.7)	300 (87.2)	147 (42.6)	126 (36.6)	318 (92.2)	307 (89.2)
Number (%) of subjects with ≥ 1 grade 3 or higher TEAE	121 (35.1)	119 (34.6)	49 (14.2)	34 (9.9)	151 (43.8)	144 (41.9)
Related	37 (10.7)	42 (12.2)	16 (4.6)	10 (2.9)	52 (15.1)	49 (14.2)
Unrelated	100 (29.0)	94 (27.3)	36 (10.4)	24 (7.0)	126 (36.5)	115 (33.4)
Number (%) of subjects with ≥ 1 TESAE	48 (13.9)	55 (16.0)	20 (5.8)	22 (6.4)	69 (20.0)	73 (21.2)
Related	14 (4.1)	19 (5.5)	4 (1.2)	4 (1.2)	18 (5.2)	23 (6.7)
Unrelated	38 (11.0)	38 (11.0)	16 (4.6)	18 (5.2)	55 (15.9)	54 (15.7)
Number (%) of subjects with ≥ 1 TEAE leading to study drug discontinuation	34 (9.9)	35 (10.2)	21 (6.1)	19 (5.5)	55 (15.9)	55 (16.0)
Related	12 (3.5)	15 (4.4)	10 (2.9)	6 (1.7)	22 (6.4)	21 (6.1)
Unrelated	22 (6.4)	20 (5.8)	11 (3.2)	13 (3.8)	33 (9.6)	34 (9.9)
Number (%) of subjects with ≥ 1 TEAE leading to death	16 (4.6)	16 (4.7)	6 (1.7)	8 (2.3)	23 (6.7)	24 (7.0)
Related	3 (0.9)	6 (1.7)	0	1 (0.3)	3 (0.9)	7 (2.0)
Unrelated	13 (3.8)	10 (2.9)	6 (1.7)	7 (2.0)	20 (5.8)	17 (4.9)

Note: At each level of summarization, subjects were counted once if they reported 1 or more events.
Numbers that changed from the 1st CSR to the 2nd CSR are highlighted in yellow.
[1] Whole Study Period includes data from Follow-up Period in addition to Induction Study Period and Maintenance Study Period

Study CT-P16 3.1

The most common adverse events in Study CT-P16 3.1 are shown in Table 29.

At least 1 TEAE was reported for 96.2% and 93.0% of patients in the CT-P16 and EU-Avastin groups, respectively. The most frequently reported TEAE was alopecia (220 [63.8%] patients and 218 [63.4%] patients in the CT-P16 and EU-Avastin treatment groups, respectively).

Overall, the frequency of TEAEs was somewhat higher in the CT-P16 group compared to EU-Avastin group both during the induction (95.1% vs 91.6%) and maintenance study periods (50.7% vs 45.1%). At least 5% difference was reported for CT-P16 vs. EU-Avastin in SOCs blood and lymphatic system disorders (50.4% vs. 42.2%), general disorders and administration site conditions (41.2% vs. 34.9%) and nervous system disorders (52.5% vs. 47.4%). Most notably, in SOC blood and lymphatic system disorders, anaemia was reported for 31.6% vs 27.0%, leukopenia for 8.4% vs 6.7%, neutropenia for 21.7% vs 16.0% and thrombocytopenia for 18.3% vs 13.7% of patients in the CT-P16 and EU-Avastin groups, respectively.

Table 29. Summary of TEAEs Reported for at Least 5% of Patients by PT in Either Treatment Group by SOC and PT in Study CT-P16 3.1 (Safety Population)

Period	Induction Study Period		Maintenance Study Period		Whole Study Period[1]	
SOC PT	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)
Total number of TEAEs	**2284**	**2032**	**665**	**535**	**2957**	**2576**
Number (%) of patients with at least 1 TEAE	**328 (95.1)**	**315 (91.6)**	**175 (50.7)**	**155 (45.1)**	**332 (96.2)**	**320 (93.0)**
Blood And Lymphatic System Disorders	**166 (48.1)**	**143 (41.6)**	**30 (8.7)**	**19 (5.5)**	**174 (50.4)**	**145 (42.2)**
Anaemia	102 (29.6)	91 (26.5)	16 (4.6)	12 (3.5)	109 (31.6)	93 (27.0)
Leukopenia	26 (7.5)	23 (6.7)	4 (1.2)	3 (0.9)	29 (8.4)	23 (6.7)
Neutropenia	71 (20.6)	54 (15.7)	7 (2.0)	5 (1.5)	75 (21.7)	55 (16.0)
Thrombocytopenia	56 (16.2)	45 (13.1)	11 (3.2)	5 (1.5)	63 (18.3)	47 (13.7)
Gastrointestinal Disorders	**133 (38.6)**	**133 (38.7)**	**45 (13.0)**	**28 (8.1)**	**155 (44.9)**	**140 (40.7)**
Constipation	24 (7.0)	27 (7.8)	15 (4.3)	8 (2.3)	38 (11.0)	33 (9.6)
Diarrhoea	39 (11.3)	41 (11.9)	8 (2.3)	8 (2.3)	43 (12.5)	47 (13.7)
Nausea	69 (20.0)	65 (18.9)	7 (2.0)	2 (0.6)	74 (21.4)	65 (18.9)
Vomiting	25 (7.2)	25 (7.3)	6 (1.7)	6 (1.7)	29 (8.4)	30 (8.7)
General disorders and administration site conditions	**115 (33.3)**	**99 (28.8)**	**55 (15.9)**	**33 (9.6)**	**142 (41.2)**	**120 (34.9)**

Period	Induction Study Period		Maintenance Study Period		Whole Study Period[1]	
SOC PT	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)
Asthenia	53 (15.4)	46 (13.4)	15 (4.3)	9 (2.6)	63 (18.3)	54 (15.7)
Fatigue	37 (10.7)	33 (9.6)	15 (4.3)	10 (2.9)	45 (13.0)	39 (11.3)
Pyrexia	14 (4.1)	14 (4.1)	12 (3.5)	5 (1.5)	22 (6.4)	17 (4.9)
Infections and infestations	**63 (18.3)**	**57 (16.6)**	**31 (9.0)**	**39 (11.3)**	**85 (24.6)**	**88 (25.6)**
Pneumonia	13 (3.8)	11 (3.2)	2 (0.6)	8 (2.3)	15 (4.3)	18 (5.2)
Urinary tract infection	13 (3.8)	6 (1.7)	10 (2.9)	4 (1.2)	20 (5.8)	9 (2.6)
Investigations	**105 (30.4)**	**94 (27.3)**	**51 (14.8)**	**42 (12.2)**	**130 (37.7)**	**115 (33.4)**
Alanine aminotransferase increased	14 (4.1)	14 (4.1)	11 (3.2)	9 (2.6)	23 (6.7)	19 (5.5)
Aspartate aminotransferase increased	12 (3.5)	14 (4.1)	12 (3.5)	4 (1.2)	22 (6.4)	17 (4.9)
Gamma-glutamyltransferase increased	12 (3.5)	10 (2.9)	11 (3.2)	9 (2.6)	22 (6.4)	19 (5.5)
Neutrophil count decreased	16 (4.6)	19 (5.5)	0	1 (0.3)	16 (4.6)	19 (5.5)
Platelet count decreased	27 (7.8)	23 (6.7)	5 (1.4)	3 (0.9)	29 (8.4)	23 (6.7)
Weight decreased	21 (6.1)	21 (6.1)	15 (4.3)	10 (2.9)	34 (9.9)	28 (8.1)
Metabolism and nutrition disorders	**84 (24.3)**	**73 (21.2)**	**41 (11.9)**	**28 (8.1)**	**104 (30.1)**	**88 (25.6)**
Decreased Appetite	30 (8.7)	34 (9.9)	12 (3.5)	11 (3.2)	42 (12.2)	41 (11.9)
Musculoskeletal and connective tissue disorders	**74 (21.4)**	**61 (17.7)**	**25 (7.2)**	**25 (7.3)**	**90 (26.1)**	**78 (22.7)**
Arthralgia	28 (8.1)	20 (5.8)	7 (2.0)	8 (2.3)	34 (9.9)	28 (8.1)
Myalgia	11 (3.2)	15 (4.4)	4 (1.2)	5 (1.5)	15 (4.3)	18 (5.2)
Pain in extremity	16 (4.6)	15 (4.4)	2 (0.6)	4 (1.2)	18 (5.2)	19 (5.5)
Nervous system disorders	**173 (50.1)**	**152 (44.2)**	**19 (5.5)**	**24 (7.0)**	**181 (52.5)**	**163 (47.4)**
Headache	15 (4.3)	10 (2.9)	6 (1.7)	11 (3.2)	21 (6.1)	20 (5.8)
Neuropathy peripheral	52 (15.1)	47 (13.7)	3 (0.9)	6 (1.7)	53 (15.4)	50 (14.5)
Paraesthesia	34 (9.9)	28 (8.1)	1 (0.3)	1 (0.3)	35 (10.1)	29 (8.4)
Peripheral sensory neuropathy	33 (9.6)	34 (9.9)	3 (0.9)	3 (0.9)	35 (10.1)	35 (10.2)
Renal and urinary disorders	**33 (9.6)**	**36 (10.5)**	**30 (8.7)**	**29 (8.4)**	**59 (17.1)**	**56 (16.3)**
Proteinuria	19 (5.5)	20 (5.8)	26 (7.5)	23 (6.7)	41 (11.9)	37 (10.8)
Respiratory, thoracic and mediastinal disorders	**61 (17.7)**	**59 (17.2)**	**31 (9.0)**	**33 (9.6)**	**82 (23.8)**	**80 (23.3)**
Cough	12 (3.5)	9 (2.6)	7 (2.0)	16 (4.7)	17 (4.9)	24 (7.0)
Dyspnoea	7 (2.0)	12 (3.5)	16 (4.6)	10 (2.9)	22 (6.4)	21 (6.1)

Period	Induction Study Period		Maintenance Study Period		Whole Study Period[1]	
SOC PT	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)
Epistaxis	14 (4.1)	18 (5.2)	0	2 (0.6)	14 (4.1)	19 (5.5)
Skin and subcutaneous tissue disorders	**229 (66.4)**	**223 (64.8)**	**11 (3.2)**	**9 (2.6)**	**231 (67.0)**	**225 (65.4)**
Alopecia	220 (63.8)	218 (63.4)	1 (0.3)	1 (0.3)	220 (63.8)	218 (63.4)
Vascular disorders	**35 (10.1)**	**36 (10.5)**	**17 (4.9)**	**11 (3.2)**	**47 (13.6)**	**39 (11.3)**
Hypertension	26 (7.5)	29 (8.4)	13 (3.8)	11 (3.2)	34 (9.9)	33 (9.6)

Note: TEAEs with PT reported at least 5% of incident rate in either treatment group are summarized. At each level of summarization, patients are counted once if they reported one or more events.
[1] Whole Study Period includes data from Follow-up Period in addition to Induction Study Period and Maintenance Study Period
Abbreviations: PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

At least 1 related TEAE was reported for 178 (51.6%) and 174 (50.6%) patients in the CT-P16 and the EU-Avastin treatment groups, respectively. The most commonly reported related TEAE by SOC was blood and lymphatic system disorders (52 [15.1%] and 45 [13.1%] patients, respectively). The most commonly reported related TEAE by PT was proteinuria (36 [10.4%] and 32 [9.3%] patients, respectively) (Table 30).

Table 30. Summary of Study Drug-Related TEAEs (Reported for at Least 5% of Patients by PT in Either Treatment Group) by SOC and PT in Study CT-P16 3.1 (Safety Population)

Period	Induction Study Period		Maintenance Study Period		Whole Study Period[1]	
SOC PT	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)
Number (%) of patients with at least 1 TEAE	**328 (95.1)**	**315 (91.6)**	**175 (50.7)**	**155 (45.1)**	**332 (96.2)**	**320 (93.0)**
Related	144 (41.7)	147 (42.7)	82 (23.8)	76 (22.1)	178 (51.6)	174 (50.6)
Unrelated	313 (90.7)	300 (87.2)	147 (42.6)	126 (36.6)	318 (92.2)	307 (89.2)
Blood and lymphatic system disorders	**42 (12.2)**	**38 (11.0)**	**11 (3.2)**	**13 (3.8)**	**52 (15.1)**	**45 (13.1)**
Anaemia	22 (6.4)	24 (7.0)	4 (1.2)	7 (2.0)	25 (7.2)	29 (8.4)
Neutropenia	11 (3.2)	16 (4.7)	2 (0.6)	5 (1.5)	13 (3.8)	18 (5.2)
Thrombocytopenia	15 (4.3)	7 (2.0)	7 (2.0)	3 (0.9)	22 (6.4)	9 (2.6)
Renal and urinary disorders	**18 (5.2)**	**20 (5.8)**	**25 (7.2)**	**22 (6.4)**	**40 (11.6)**	**36 (10.5)**
Proteinuria	16 (4.6)	16 (4.7)	23 (6.7)	21 (6.1)	36 (10.4)	32 (9.3)
Skin and subcutaneous tissue disorders	**31 (9.0)**	**30 (8.7)**	**8 (2.3)**	**4 (1.2)**	**37 (10.7)**	**34 (9.9)**
Alopecia	23 (6.7)	21 (6.1)	0	0	23 (6.7)	21 (6.1)
Vascular disorders	**21 (6.1)**	**21 (6.1)**	**12 (3.5)**	**10 (2.9)**	**31 (9.0)**	**27 (7.8)**
Hypertension	18 (5.2)	19 (5.5)	9 (2.6)	10 (2.9)	25 (7.2)	25 (7.3)

Note: TEAEs with PT reported at least 5% of incident rate in either treatment group are summarized. At each level of summarization, patients are counted once if they reported one or more events.
[1] Whole Study Period includes data from Follow-up Period in addition to Induction Study Period and Maintenance Study Period
Abbreviations: PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

Grade ≥ 3 TEAEs was reported for 151 (43.8%) and 144 (41.9%) patients in the CT-P16 and the EU-Avastin treatment groups, respectively (Table 36). The most common ≥ Grade 3 TEAE was neutropenia, reported for 36 (10.4%) and 25 (7.3%) patients in the CT-P16 and EU-Avastin groups, respectively. Notably, dyspnoea was reported for 7 vs 0 patients (6 vs 0 during maintenance study period) and pulmonary embolism for 6 vs 3 of patients (2 vs 0 during maintenance study period) in the CT-P16 and EU-Avastin groups, respectively (Table 31).

Table 31. Summary of TEAEs by Severity of Grade 3 or Higher in Study CT-P16 3.1 (Safety Population)

Period	Induction Study Period		Maintenance Study Period		Whole Study Period[1]	
SOC PT	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)
Number (%) of patients with ≥ 1 TEAE of grade 3 or higher	**121 (35.1)**	**119 (34.6)**	**49 (14.2)**	**34 (9.9)**	**151 (43.8)**	**144 (41.9)**
Grade 3	86 (24.9)	82 (23.8)	37 (10.7)	22 (6.4)	103 (29.9)	94 (27.3)
Grade 4	19 (5.5)	21 (6.1)	6 (1.7)	4 (1.2)	25 (7.2)	26 (7.6)
Grade 5	16 (4.6)	16 (4.7)	6 (1.7)	8 (2.3)	23 (6.7)	24 (7.0)
Grade 3 or higher TEAEs by SOC/PT (reported for ≥ 1% of patients by PT in either treatment group)						
Blood and lymphatic system disorders	**54 (15.7)**	**50 (14.5)**	**4 (1.2)**	**1 (0.3)**	**58 (16.8)**	**51 (14.8)**
Anaemia	11 (3.2)	16 (4.7)	2 (0.6)	0	13 (3.8)	16 (4.7)
Febrile neutropenia	7 (2.0)	3 (0.9)	0	0	7 (2.0)	3 (0.9)
Leukopenia	3 (0.9)	2 (0.6)	1 (0.3)	0	4 (1.2)	2 (0.6)
Neutropenia	34 (9.9)	25 (7.3)	2 (0.6)	0	36 (10.4)	25 (7.3)

Period	Induction Study Period		Maintenance Study Period		Whole Study Period[1]	
SOC PT	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)
Thrombocytopenia	12 (3.5)	11 (3.2)	0	1 (0.3)	12 (3.5)	12 (3.5)
General disorders and administration site conditions	**16 (4.6)**	**14 (4.1)**	**8 (2.3)**	**3 (0.9)**	**23 (6.7)**	**18 (5.2)**
Asthenia	4 (1.2)	4 (1.2)	0	1 (0.3)	4 (1.2)	5 (1.5)
Fatigue	6 (1.7)	5 (1.5)	4 (1.2)	0	9 (2.6)	6 (1.7)
Infections and infestations	**15 (4.3)**	**16 (4.7)**	**7 (2.0)**	**10 (2.9)**	**22 (6.4)**	**25 (7.3)**
COVID-19 pneumonia	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.9)	2 (0.6)	4 (1.2)
Pneumonia	5 (1.4)	10 (2.9)	2 (0.6)	3 (0.9)	7 (2.0)	12 (3.5)
Investigations	**20 (5.8)**	**23 (6.7)**	**6 (1.7)**	**1 (0.3)**	**26 (7.5)**	**24 (7.0)**
Neutrophil count decreased	5 (1.4)	11 (3.2)	0	0	5 (1.4)	11 (3.2)
Platelet count decreased	5 (1.4)	3 (0.9)	1 (0.3)	0	6 (1.7)	3 (0.9)
Weight decreased	4 (1.2)	1 (0.3)	1 (0.3)	0	5 (1.4)	1 (0.3)
Metabolism and nutrition disorders	**12 (3.5)**	**16 (4.7)**	**3 (0.9)**	**3 (0.9)**	**15 (4.3)**	**19 (5.5)**
Decreased appetite	1 (0.3)	3 (0.9)	0	1 (0.3)	1 (0.3)	4 (1.2)
Hypertriglyceridaemia	3 (0.9)	1 (0.3)	1 (0.3)	0	4 (1.2)	1 (0.3)
Nervous system disorders	**13 (3.8)**	**10 (2.9)**	**2 (0.6)**	**4 (1.2)**	**15 (4.3)**	**14 (4.1)**
Peripheral sensory neuropathy	4 (1.2)	2 (0.6)	0	0	4 (1.2)	2 (0.6)
Renal and urinary disorders	**4 (1.2)**	**2 (0.6)**	**2 (0.6)**	**2 (0.6)**	**6 (1.7)**	**4 (1.2)**
Proteinuria	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)	4 (1.2)	2 (0.6)
Respiratory, thoracic and mediastinal disorders	**13 (3.8)**	**8 (2.3)**	**9 (2.6)**	**0**	**24 (7.0)**	**8 (2.3)**
Dyspnoea	1 (0.3)	0	6 (1.7)	0	7 (2.0)	0
Pulmonary embolism	4 (1.2)	3 (0.9)	2 (0.6)	0	6 (1.7)	3 (0.9)
Vascular disorders	**13 (3.8)**	**13 (3.8)**	**8 (2.3)**	**6 (1.7)**	**19 (5.5)**	**17 (4.9)**
Hypertension	12 (3.5)	11 (3.2)	5 (1.4)	6 (1.7)	15 (4.3)	15 (4.4)

Note: At each level of summarization, patients are counted once if they reported one or more events and the most severe event is counted.
[1] Whole Study Period includes data from Follow-up Period in addition to Induction Study Period and Maintenance Study Period
Abbreviations: PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

Study CT-P16 1.1

Altogether 23 (50.0%), 34 (72.3%), and 26 (54.2%) subjects experienced at least 1 TEAE in the CT-P16, EU-Avastin and US-Avastin treatment groups, respectively.

The most frequently reported TEAE by SOC was investigations for 10 (21.7%), 15 (31.9%) and 13 (27.1%) subjects in the CT-P16, EU-Avastin and US-Avastin treatment groups, respectively.

The most frequently reported TEAE by PT was diarrhoea for 3 (6.5%), 6 (12.8%) and 4 (8.3%) subjects, blood CPK increased for 3 (6.5%), 5 (10.6%) and 4 (8.3%) subjects, CRP increased for 2 (4.3%), 5 (10.6%) and 4 (8.3%) subjects and nasopharyngitis for 4 (8.7%), 1 (2.1%) and 6 (12.5%) subjects in the CT-P16, EU-Avastin and US-Avastin treatment groups, respectively.

TEAEs considered by the investigator to be related to the study drug were reported for 9 (19.6%), 20 (42.6%) and 16 (33.3%) subjects in the CT-P16, EU-Avastin and US-Avastin treatment groups, respectively. The most frequently reported related TEAEs were diarrhoea for 3 (6.5%), 6 (12.8%) and 2 (4.2%), and CRP increased for 1 (2.2%), 4 (8.5%) and 4 (8.3%) subjects in the CT-P16, EU-Avastin and US-Avastin treatment groups, respectively.

Most of the TEAEs were of grade 1 or grade 2 in severity while total of 6 TEAEs observed in 4 subjects (2.8%; 2 subjects [4.3%] in each of the CT-P16 and the EU-Avastin treatment groups) were of grade 3 or 4 severity. Among the TEAEs of grade 3 or 4 in severity, 2 TEAEs of grade 4 (blood CPK increased and hyperuricaemia) observed in the EU-Avastin treatment group were considered possibly related to the study drug. All other TEAEs of grade 3 or 4 severity were considered unrelated to the study drug.

Study CT-P16 1.2

Overall, 2 (9.1%) subjects in the CT-P16 and 3 (12.5%) subjects in the EU-Avastin treatment group experienced at least 1 TEAE. Treatment emergent adverse events considered related to the study drug were reported for 1 (4.5%) subject in the CT-P16 treatment group [drug eruption] and 1 (4.2%) subject in the EU-Avastin treatment group [nausea and dizziness]). All TEAEs were recovered before or at the end-of-study (EOS) visit.

All TEAEs, regardless of relationship to study drugs, were reported once each. Food allergy and drug eruption were each reported by 1 (4.5%) subject in the CT-P16 treatment group. Nausea and dizziness, AST increased and CPK increased, and periodontitis were reported by 1 (4.2%) subject each in the EU-Avastin treatment group.

One TEAE was grade 4 in severity (blood CPK increased), 1 TEAE was grade 3 in severity (AST increased), and 1 TEAE was grade 2 in severity (periodontitis). The TEAEs with grades 2, 3, and 4 were reported in the EU-Avastin treatment group and were considered unrelated to the study drug. All other reported TEAEs were grade 1 in severity. The TEAEs with grade 1 were considered related to the study drug regardless of the treatment group except for 1 TEAE of food allergy reported in the CT-P16 treatment group, which was considered unrelated to the study drug.

2.4.8.3. Serious adverse event/deaths/other significant events

Deaths and other serious adverse events

Study CT-P16 3.1

In Study CT-P16 3.1, 23 (6.7%) patients in CT-P16 and 24 (7.0%) patients in EU-Avastin treatment group died due to TEAE. Of these, 3 (0.9%) deaths in the CT-P16 and 7 (2.0%) in the EU-Avastin group were considered to be study drug-related (Table 32).

Table 32. Summary of Death Cases Due to Related TEAEs Reported during Study Periods of Study CT-P16 3.1

Patient No.	Study Period	Date of TEAE onset (Duration from Last dose)	Date of Death	TEAE PT	Relation to Study Drug
Treatment Group: CT-P16					
Patient 1	Induction Study Period	2020-08-20 (IC5D21)	2020-08-29	Sepsis	Definite
Patient 2	Induction Study Period	2020-05-21 (IC4D22)	2020-05-22	Subarachnoid Haemorrhage	Probable
Patient 3	Induction Study Period	2020-01-10 (IC2D15)	2020-01-10	Pulmonary Haemorrhage	Definite
Treatment Group: EU-approved Avastin					
Patient 4	Induction Study Period	2019-04-11 (IC1D1)	2019-05-01	Cerebral Infarction	Possible
Patient 5	Maintenance Study Period	2019-09-16 (MC2D11)	2019-09-16	Sudden Death	Possible
Patient 6	Induction Study Period	2020-05-14 (IC2D8)	2020-05-14	Pulmonary Haemorrhage	Possible
Patient 7	Induction Study Period	2020-05-18 (IC1D11)	2020-05-18	Pulmonary Haemorrhage	Definite
Patient 8	Induction Study Period	2020-03-19 (IC2D10)	2020-03-25	Lung Abscess	Definite
Patient 9	Induction Study Period	2020-07-20 (IC2D7)	2020-07-20	Cardiac Arrest	Probable
Patient 10	Induction Study Period	2019-11-19 (IC1D5)	2019-11-20	Septic Shock	Definite

Abbreviations: D, day; IC, Induction Cycle; MC, Maintenance Cycle; PT, preferred term; TEAE, treatment-emergent adverse event.

TESAEs were reported for 69 (20.0%) and 73 (21.2%) patients in the CT-P16 and the EU-Avastin treatment groups, respectively. The most common TESAE by SOC in all Study Periods was infections and infestations, reported for 22 (6.4%) and 24 (7.0%) patients. Of the patients who reported at least 1 TESAE, 18 (5.2%) and 23 (6.7%) patients experienced events considered to be related to the study drug. The most frequently reported TESAE in both treatment groups was pneumonia reported for 8 (2.3%) and 10 (2.9%) patients in the CT-P16 and EU-Avastin treatment groups, respectively (Table 33).

Table 33. Summary of TESAEs (Reported for at Least 1% of Patients by PT in Either Treatment Group) by SOC and PT in Study CT-P16 3.1 (Safety Population)

Period	Induction Study Period		Maintenance Study Period		Whole Study Period[1]	
SOC PT	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)
Total number of TESAEs	**75**	**70**	**22**	**25**	**99**	**95**
Number (%) of patients with ≥ 1 TESAE	**48 (13.9)**	**55 (16.0)**	**20 (5.8)**	**22 (6.4)**	**69 (20.0)**	**73 (21.2)**
Related	14 (4.1)	19 (5.5)	4 (1.2)	4 (1.2)	18 (5.2)	23 (6.7)
Unrelated	38 (11.0)	38 (11.0)	16 (4.6)	18 (5.2)	55 (15.9)	54 (15.7)
Blood and lymphatic System disorders	**11 (3.2)**	**8 (2.3)**	**1 (0.3)**	**0**	**12 (3.5)**	**8 (2.3)**
Febrile neutropenia	6 (1.7)	2 (0.6)	0	0	6 (1.7)	2 (0.6)
Neutropenia	5 (1.4)	1 (0.3)	0	0	5 (1.4)	1 (0.3)
Infections and infestations	**16 (4.6)**	**15 (4.4)**	**6 (1.7)**	**10 (2.9)**	**22 (6.4)**	**24 (7.0)**
COVID-19 pneumonia	2 (0.6)	1 (0.3)	3 (0.9)	3 (0.9)	5 (1.4)	4 (1.2)
Pneumonia	6 (1.7)	9 (2.6)	2 (0.6)	2 (0.6)	8 (2.3)	10 (2.9)
Respiratory, thoracic and mediastinal disorders	**10 (2.9)**	**7 (2.0)**	**4 (1.2)**	**0**	**16 (4.6)**	**7 (2.0)**
Pulmonary embolism	4 (1.2)	1 (0.3)	1 (0.3)	0	5 (1.4)	1 (0.3)

Note: At each level of summarization, patients are counted once if they reported one or more events.
[1] Whole Study Period includes data from Follow-up Period in addition to Induction Study Period and Maintenance Study Period
Abbreviations: PT, preferred term; SOC, system organ class; TESAE, treatment-emergent serious adverse event

Study CT-P16 1.1 and 1.2

No deaths or TESAEs were reported during the studies in healthy subjects.

Adverse events of special interest

Study CT-P16 3.1

Hypersensitivity/infusion-related reactions (IRR), gastrointestinal perforations and fistulae, wound healing complications, hypertension, posterior reversible encephalopathy syndrome (PRES), proteinuria, arterial thromboembolism (ATE), venous thromboembolism (VTE), hemorrhages, congestive heart failure (CHF), and ovarian failure/fertility were considered AESIs in study CT-P16 3.1.

Hypersensitivity/Infusion-related reactions

Altogether 11 (3.2%) patients in the CT-P16 treatment group and 16 (4.7%) patients in the EU-Avastin treatment group were reported with at least 1 TEAESI due to hypersensitivity/IRRs.

Other TEAESIs

- 3 (0.9%) patients in the CT-P16 treatment group and 5 (1.5%) patients in the EU-Avastin treatment group) were reported for gastrointestinal perforations and fistulae.
- 1 patient (0.3%) was reported for wound healing complications in the CT-P16 treatment group.

- 44 (12.8%) patients in the CT-P16 treatment group and 39 (11.3%) patients in the EU-Avastin treatment group were reported with at least 1 TEAESI due to hypertension. PT hypertension was most frequently reported, in 34 (9.9%) patients in the CT-P16 treatment group and 33 (9.6%) patients in the EU-Avastin treatment group), followed by blood pressure increased in 7 (2.0%) patients in each study groups.
- 1 (0.3%) patient was reported for PRES in the CT-P16 treatment group.
- 42 (12.2%) patients in the CT-P16 treatment group and 38 (11.0%) patients in the EU-Avastin treatment group were reported with at least 1 TEAESI due to proteinuria. PT proteinuria was most frequently reported, in 41 (11.9%) patients in the CT-P16 treatment group and 37 (10.8%) patients in the EU-Avastin treatment group.
- 2 (0.6%) patients in the CT-P16 treatment group and 4 (1.2%) patients in the EU-Avastin treatment group were reported with at least 1 TEAESI due to ATE.
- 10 (2.9%) patients in the CT-P16 treatment group and 5 (1.5%) patients in the EU-Avastin treatment group were reported with at least 1 TEAESI due to VTE. Pulmonary embolism was the most frequently reported, in 8 (2.3%) patients in the CT-P16 treatment group and 3 (0.9%) patients in the EU-Avastin treatment group), followed by deep vein thrombosis in 2 (0.6%) patients in each study group.
- 40 (11.6%) patients in the CT-P16 treatment group and 37 (10.8%) patients in the EU-Avastin treatment group were reported with at least 1 TEAESI due to haemorrhages. Epistaxis was most frequently reported, in 14 (4.1%) patients in the CT-P16 treatment group and 19 (5.5%) patients in the EU-Avastin treatment group, followed by haematuria in 9 (2.6%) patients in the CT-P16 treatment group and 10 (2.9%) patients in the EU-Avastin treatment group.
- 3 (0.9%) patients in the CT-P16 treatment group and 2 (0.6%) patients in the EU-Avastin treatment group were reported with at least 1 TEAESI due to CHF.
- No cases of TEAESI due to ovarian failure/fertility were reported.

Study CT-P16 1.1 and 1.2

In Studies CT-P16 1.1 and CT-P16 1.2 conducted in healthy subjects, an AESI was pre-defined as an event of hypersensitivity/IRR.

Study CT-P16 1.1: In the CT-P16 and the EU-Avastin treatment groups, 2 (4.3%) subjects reported an IRR in each group and there were 4 (8.3%) subjects reported in the US-Avastin treatment group. All observed IRRs were related to the study drug and were grade 1 in severity. All subjects recovered from IRR without any medication and no subject discontinued due to the event.

Study CT-P16 1.2: No cases of hypersensitivity/IRR were reported.

2.4.8.4. Laboratory findings

Clinical Laboratory Evaluations

An abnormality of the test result for clinical laboratory parameters, e.g. clinical chemistry, haematology, urinalysis and coagulation, was reported as a TEAE if it was determined to be clinically significant by the investigator or if the investigator reported the result as a TEAE.

The majority of laboratory parameters in the clinical studies had no CTCAE grade, i.e. the post-baseline laboratory result did not satisfy any CTCAE grade criteria, or were CTCAE grade 1 (mild) or grade 2 (moderate).

Study CT-P16 3.1

The most frequently reported grade 3 or higher clinical chemistry parameter was hypertriglyceridemia; grade 3 was reported for 17 (4.9%) patients and 20 (5.8%) patients, and grade 4 for 6 (1.7%) and 8 (2.3%) patients in the CT-P16 and the EU-Avastin treatment groups, respectively.

The most frequently reported grade 3 or higher haematology parameter was neutrophil count decreased; grade 3 was reported for 27 (7.8%) and 26 (7.6%) patients, and grade 4 for 12 (3.5%) and 9 (2.6%) patients in the CT-P16 and the EU-Avastin treatment groups, respectively. Most of grade 3 or higher haematology parameters in both treatment groups were reported during the Induction Study Period.

Study CT-P16 1.1 and 1.2

The laboratory parameters with CTCAE grade 3 or 4 are shown in Table 34 and Table 35.

Table 34. Summary of Subjects with CTCAE Grade ⩾ 3 in Study CT-P16 1.1. (Safety Population)

Laboratory Category CTCAE Term CTCAE Grade, n (%)	CT-P16 N = 46	EU-approved Avastin N = 47	US-licensed Avastin N = 48	Total N = 141
Hematology				
Lymphocyte count decreased				
Grade 3 (Severe)	0	0	1 (2.1)	1 (0.7)
Clinical Chemistry				
Aspartate aminotransferase increased				
Grade 3 (Severe)	0	2 (4.3)	0	2 (1.4)
CPK increased				
Grade 3 (Severe)	1 (2.2)	2 (4.3)	1 (2.1)	4 (2.8)
Grade 4 (Life-threatening)	2 (4.3)	2 (4.3)	0	4 (2.8)
Hyperuricemia				
Grade 4 (Life-threatening)	0	1 (2.1)	0	1 (0.7)

Abbreviations: CPK = creatine phosphokinase; CTCAE = Common Terminology Criteria for Adverse Events; EU = European Union; US = United States.
Note: The overall summary included only the worst case during unscheduled and scheduled visits.

Table 35. Summary of Subjects with CTCAE Grade 3 or Higher in Study CT-P16 1.2 (Safety Population)

CTCAE[(a)] Term Grade, n (%)	CT-P16 (N=22)	EU-approved Avastin (N=24)	Overall (N=46)
		Number (%) of Subjects	
Chemistry			
AST increased			
Grade 3 (Severe)	0	1 (4.2)	1 (2.2)
CPK increased			
Grade 3 (Severe)	1 (4.5)	1 (4.2)	2 (4.3)
Grade 4 (Life-threatening)	0	2 (8.3)	2 (4.3)
Hypertriglyceridemia			
Grade 3 (Severe)	4 (18.2)	1 (4.2)	5 (10.9)

Abbreviations: AST, aspartate aminotransferase; CPK, creatinine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events.

The summary includes only the worst case during post-baseline unscheduled and scheduled visits.

(a) CTCAE v5.0.

Vital signs, Physical Examination, ECG and Other Observations Related to Safety

Study CT-P16 3.1

Mean changes from baseline in vital sign (systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature) and body weight measurements were small, and there were no notable differences between the CT-P16 and EU-Avastin treatment groups.

The majority of patients had normal baseline physical examination results that remained normal throughout the study periods. The most commonly reported abnormalities at baseline were in the respiratory system (148 [42.9%] patients in the CT-P16 and 162 [47.1%] patients in the EU-Avastin treatment group), which were mostly related to lung cancer. There were notable shifts from baseline from normal to abnormal in the head, ears, eyes, nose, throat system and the neurological system, mostly related to alopecia and numbness or neuropathy, respectively, with no notable differences between the 2 treatment groups.

The majority of patients had normal ECG findings. Minor changes from baseline, regarded as clinically non-significant, were observed in both groups. Altogether, 2 (0.6%) patients in the CT-P16 group and 1 (0.3%) patient in the EU-Avastin group was reported for clinically significant abnormal ECG results at any time point after study drug administration with normal ECG recording at baseline.

From hypersensitivity monitoring, the most commonly reported clinically notable vital sign result was high respiratory rate (≥ 20 breaths per minute). It was reported for a marked proportion at several time points throughout the hypersensitivity monitoring, with no notable differences between the CT-P16 and the EU-Avastin treatment groups.

Studies CT-P16 1.1 and 1.2

No notable differences across the treatment groups were seen in vital sign results, physical examinations and ECGs.

2.4.8.5. In vitro biomarker test for patient selection for safety

N/A

2.4.8.6. Safety in special populations

N/A

2.4.8.7. Immunological events

The applicant followed the EMA guideline "Guideline on immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1)" and the immunogenicity of CT-P16 was assessed in 1 primary PK similarity study conducted in healthy male subjects (Study CT-P16 1.1), in 1 supportive Japanese PK similarity study (Study CT-P16 1.2) and in 1 Phase 3 therapeutic similarity study conducted in patients with metastatic or recurrent nsNSCLC (Study CT-P16 3.1).

The drug tolerance of both ADA assays was sufficient to detect 50.0 ng/mL of ADA in most patients in study CT-P16 3.1 and in all patients after D15 in study CT-P16 1.1.

In Study CT-P16 3.1 most ADA positive subjects had drug concentrations > 25.0 µg/mL and NAb levels lower than 2000 ng/mL could not have been detected without interference of drug in any patient in Study CT-P16 3.1.

Frequencies and titres of ADA and NAb

Healthy subjects

In Study CT-P16 1.1 overall 7 subjects (5.0%) reported at least 1 positive ADA at any time point post dose; 2 subjects (4.3%), 2 subjects (4.3%) and 3 subjects (6.3%) in the CT-P16, EU-Avastin, and US-Avastin treatment groups, respectively. NAb results were negative for all these subjects.

No subject in study CT-P16 1.2 had a positive ADA test result on any day in either treatment group.

Study CT-P16 3.1

ADA and NAb frequencies in patients with nsNSCLC are summarised in Table 36. Post-treatment incidence of ADA formation was 74 (21.4%) and 80 (23.3%) in the CT-P16 and EU-Avastin treatment groups, respectively.

Table 36. Summary of Immunogenicity Results in Study CT-P16 3.1 (Safety Population)

Timepoint/Visit ADA Result NAb Result	CT-P16 (N=345)	EU-approved Avastin (N=344)	Total (N=689)
	Number (%) of patients		
Subject with at least 1 result at anytime during the Whole Study Period	**345 (100.0)**	**343 (99.7)[1]**	**688 (99.9)**
Positive	78 (22.6)	83 (24.1)	161 (23.4)
Positive	8 (2.3)	8 (2.3)	16 (2.3)
Subject with a result at baseline visit	**341 (98.8)**	**340 (98.8)**	**681 (98.8)**
Positive	5 (1.4)	7 (2.0)	12 (1.7)
Positive	1 (0.3)	0	1 (0.1)
Subject with at least 1 result after the first infusion	**323 (93.6)**	**304 (88.4)**	**627 (91.0)**
Positive	74 (21.4)	80 (23.3)	154 (22.4)
Positive	7 (2.0)	8 (2.3)	15 (2.2)

Abbreviations: ADA, anti-drug antibodies; NAb, neutralizing antibodies.
Note: The ADA test involves both screening and confirmatory assay to confirm positive results. Samples that are 'Potential Positive' in the screening assay would undergo further testing in the confirmatory assay to determine if patients are a true positive labeled 'Positive'. Only patients with a positive ADA result are included in the NAb summary.

The ADA titre results up to Induction Cycle 6 were presented in the Integrated Summary of Immunogenicity (Module 2.7). The mean and the median values of ADA titre were similar between the two treatment groups at each timepoint. The titres of ADA were generally low and the ADA titre kinetics were similar between the two treatment groups. Neither ADA progression over time nor transiency of ADA was seen in any of the treatment arms. A majority of subjects who were ADA positive on more than one occasion (n=63) were also ADA positive at the EOT visit if ADA was assessed (4/7 and 10/14 for CT-P16 and EU-Avastin, respectively).

Impact of ADA on clinical outcome

Impact of ADA on PK

In the subjects with negative ADA status, the mean serum concentrations are slightly higher in the EU-Avastin group at induction cycles 2 and 4 than in the CT-P16 group and at induction cycles 1 and 6 the mean serum concentration is slightly higher in the CT-P16 group than in the EU-Avastin group. In the subjects with positive ADA status, the trend in mean serum concentrations is similar as in the subjects with negative ADA status. The number of subjects with positive ADA status can be considered small (n = 3-10 per group depending on the cycle) and to draw conclusions of impact of ADAs on PK is not possible.

The applicant was asked to provide a figure, in which the mean serum concentrations (µg/L) at different cycles are shown by the visit-based ADA status of patients. The applicant provided in the response to the D120 questions, acceptable figures in relation to the mean serum concentrations by ADA status. Additionally, descriptive statistics of serum concentration in the maintenance study period by visit-based ADA status were presented. The number of ADA-positive patients was small in the study and it can be

agreed with the applicant that a definite conclusion could not be drawn on the impact of ADA on PK of bevacizumab.

Impact of ADA on efficacy

The objective response rate (ORR) during Induction Study Period by ADA status up to Induction Cycle 6 is presented in Table 37.

Table 37. ORR Result during Induction Study Period by ADA Status up to Induction Cycle 6 (PP Population)

	ADA-Positive		ADA-Negative	
ADA Status	**CT-P16 (N=16)**	**EU-Avastin (N=14)**	**CT-P16 (N=301)**	**EU-Avastin (N=289)**
Number of Responders (%)	5 (31.3)	7 (50.0)	139 (46.2)	136 (47.1)
CR	1 (6.3)	0	1 (0.3)	3 (1.0)
PR	4 (25.0)	7 (50.0)	138 (45.8)	133 (46.0)
Number of Non-Responders (%)	11 (68.8)	7 (50.0)	162 (53.8)	153 (52.9)
Objective Response Rate (%) (95% CI)	31.25 (8.54 - 53.96)	50.00 (23.81 - 76.19)	46.18 (40.55 - 51.81)	47.06 (41.30 - 52.81)

Objective response rate was defined as the proportion of patients whose best overall response was CR or PR (considered as the 'Responder'). All other patients except responders were considered as non-responder including patients without postbaseline disease assessment.
Abbreviation: ADA, anti-drug antibody; CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response

In the CT-P16 treatment group, the difference in ORR was observed for ADA-positive subgroup (31.25%) and ADA-negative subgroup (46.18%) with ORR appearing to decrease for the ADA-positive subgroup. In the EU-Avastin treatment group, ORR was similar regardless of ADA status as ORR was 50.00% for the ADA-positive subgroup and 47.06% for the ADA-negative subgroup. Although a difference was observed between the 2 treatment groups the results should be considered in context of the small and fragmented dataset. The trends in DOR and PFS by ADA status was the opposite of the observed trend in ORR during the Induction Study Period; thus, the comparison of Duration of Response (DOR) and Progression-Free Survival (PFS) showed no relevant effect of ADA on the efficacy endpoints in any treatment group.

Impact of ADA on safety

Within each treatment arm the incidence of serious treatment emergent adverse events is slightly lower among patients with positive ADA results than in those with negative results. The incidence of AEs seems comparable between treatment arms among both ADA positive and ADA negative subjects. ADA positivity does not seem to correlate with development of IRR.

2.4.8.8. Safety related to drug-drug interactions and other interactions

N/A

2.4.8.9. Discontinuation due to adverse events

Study CT-P16 3.1

Altogether 55 (15.9%) patients from the CT-P16 treatment group and 55 (16.0%) patients from the EU-Avastin treatment group experienced at least 1 TEAE leading to study drug discontinuation. The most frequently reported TEAE leading to study drug discontinuation was pulmonary embolism in 8 (2.3%) patients in the CT-P16 group and proteinuria in 5 (1.5%) patients in the EU-Avastin group (Table 38).

Table 38. Summary of TEAEs Leading to Study Drug Discontinuation (Reported for at Least 1% of Patients by PT in Either Treatment Group) by SOC and PT in Study CT-P16 3.1 (Safety Population)

Period	Induction Study Period		Maintenance Study Period		Whole Study Period[1]	
SOC PT	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)	CT-P16 (N=345)	EU-Avastin (N=344)
Number (%) of patients with ≥ 1 TEAE leading to study drug discontinuation	**34 (9.9)**	**35 (10.2)**	**21 (6.1)**	**19 (5.5)**	**55 (15.9)**	**55 (16.0)**
Related	12 (3.5)	15 (4.4)	10 (2.9)	6 (1.7)	22 (6.4)	21 (6.1)
Unrelated	22 (6.4)	20 (5.8)	11 (3.2)	13 (3.8)	33 (9.6)	34 (9.9)
Blood and lymphatic system disorders	**3 (0.9)**	**3 (0.9)**	**1 (0.3)**	**1 (0.3)**	**4 (1.2)**	**5 (1.5)**
Thrombocytopenia	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)	2 (0.6)	4 (1.2)
Related	0	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Unrelated	1 (0.3)	2 (0.6)	0	0	1 (0.3)	3 (0.9)
Renal and urinary disorders	**1 (0.3)**	**0**	**4 (1.2)**	**5 (1.5)**	**5 (1.4)**	**5 (1.5)**
Proteinuria	0	0	3 (0.9)	5 (1.5)	3 (0.9)	5 (1.5)
Related	0	0	3 (0.9)	4 (1.2)	3 (0.9)	4 (1.2)
Unrelated	0	0	0	1 (0.3)	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	**10 (2.9)**	**8 (2.3)**	**5 (1.4)**	**0**	**15 (4.3)**	**8 (2.3)**
Pulmonary embolism	5 (1.4)	2 (0.6)	3 (0.9)	0	8 (2.3)	2 (0.6)
Related	5 (1.4)	2 (0.6)	1 (0.3)	0	6 (1.7)	2 (0.6)
Unrelated	0	0	2 (0.6)	0	2 (0.6)	0

Note: At each level of summarization, patients are counted once if they reported one or more events and the most severe event is counted.
[1] Whole Study Period includes data from Follow-up Period in addition to Induction Study Period and Maintenance Study Period
Abbreviations: PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

Study CT-P16 1.1 and 1.2

In the healthy subjects of Studies CT-P16 1.1 and CT-P16 1.2, no subjects experienced a TEAE leading to treatment discontinuation.

2.4.8.10. Post marketing experience

N/A

2.4.9. Discussion on clinical safety

The applicant has provided safety data from three clinical studies; a pivotal Phase 3 study CT-P16 3.1 in patients with metastatic or recurrent nsNSCLC, Phase 1 PK study CT-P16 1.1 in healthy male subjects and a supportive PK study CT-P16 1.2 in healthy Japanese subjects.

The development of CT-P16 was discussed with DKMA and MPA in February 2016 and EMA Scientific Advice was received in July 2016 (EMA/CHMP/SAWP/476333/2016). Further, the global development of CT-P16 has been discussed with the FDA.

From the safety perspective, the design of the conducted Phase 3 study as well as the safety assessments included in the clinical studies are considered to be sufficiently aligned with the EMA Scientific Advice (EMA/CHMP/SAWP/476333/2016) and adequate. The Phase 3 study (CT-P16 3.1) is ongoing and has been completed up to 1 year from the last enrolled patient. Clinical data up to the cut-off date (21 September 2021) has been provided by the applicant that includes complete data for all patients through Induction Study Period and data for a total of 148 (21.5%) patients who have completed 1 year of treatment (≥ Maintenance Cycle 12).

The safety evaluations were planned according to the known safety profile of Avastin, considering the adverse reactions presented in the SmPC and AESIs identified for Avastin e.g. in the RMP for Avastin. The safety analyses were conducted on safety population, consisting of all subjects receiving at least 1 dose of either CT-P16 or Avastin. The safety data for the Phase 3 study CT-P16 is presented separately for the induction study period (combination with paclitaxel and carboplatin), maintenance study period (monotherapy), follow-up period and whole study period. In general, the safety data has not been pooled, but presented separately for the 3 clinical studies, which is acceptable.

In the Phase 3 study CT-P16 3.1, a total of 689 patients with nsNSCLC received at least one dose of the study drug, 345 patients in the CT-P16 treatment group and 344 patients in the EU-Avastin treatment group. In addition, 141 healthy subjects received a single dose of CT-P16 (n=46), EU-Avastin (n=47) or US-Avastin (n=48) in the pivotal PK study CT-P16 1.1 and 46 healthy subjects received a single dose of CT-P16 (n=22) or EU-Avastin (n=24) in the supportive PK study CT-P16 1.2.

In terms of drug exposure, some imbalances between the treatment groups were observed in number of patients that received the study drug after the first induction cycle. At cycle 1: 100% and 100%; at cycle 2: 95.7% and 92.2%; at cycle 3: 89.6% and 80.5%, and at the last induction cycle 6: 76.2% and 69.8% of the patients in CT-P16 and EU-Avastin treatment groups, respectively, received the study drug. This was also reflected in higher number of patients receiving concomitant paclitaxel and carboplatin in the CT-P16 group. Consequently, more patients in the CT-P16 than in the EU-Avastin group continued to receive the study drug during the maintenance period. The administered dose intensities were similar in both study groups, including chemotherapy during the induction period. In the PK studies CT-P16 1.1 and CT-P16 1.2, all subjects received full dose of the study drug.

Overall, the size of the safety population included in the clinical studies can be considered sufficient to allow a meaningful comparison of safety and immunogenicity between CT-P16 and EU-Avastin in the context of a biosimilar MAA.

In the Phase 3 study CT-P16 3.1, the patient demographics were comparable between the study groups (CT-P16 and EU-Avastin) in terms of mean age (61.3 and 61.5 years, respectively), gender (65.2% and 64.0% males), race (77.2% and 76.1% white) and other characteristics. The majority of patients had a metastatic disease (92.7% and 90.5%) and ECOG Grade 1 performance status (69.3% and 68.3%). The pathological diagnosis was adenocarcinoma in almost all cases (98.2% and 98.0%, respectively) and clinical stage in most cases either stage IVA (43.0% and 47.3%, respectively) or Stage IVB (49.7% and 42.9%, respectively). In general, the study groups were comparable in terms of medical history and

previous treatments, but some minor differences were observed between study groups (CT-P16 and EU-Avastin) e.g. in number of patients with previous lung lobectomy (5.8% and 9.2%) and previous cytotoxic chemotherapy (1.8% and 2.9%). Overall, the demographics and baseline characteristics were sufficiently balanced between the treatment groups in all three clinical studies.

Adverse events in the Phase 3 study CT-P16 3.1:

At least 1 TEAE was reported for 96.2% and 93.0% and treatment related TEAEs for 51.6% and 50.6% of patients in the CT-P16 and EU-Avastin groups, respectively.

In terms of common TEAEs by SOC, skin and subcutaneous tissue disorders were reported for 67.0% and 65.4%, nervous system disorders for 52.5% and 47.4%, blood and lymphatic system disorders for 50.4% and 42.2%, gastrointestinal disorders for 44.9% and 40.7%, and general disorders and administration site conditions for 41.2% and 34.9% of patients in the CT-P16 and EU-Avastin groups, respectively.

In terms of common TEAEs by PT, alopecia was reported for 63.8% and 63.4%, anaemia for 31.6% and 27.0%, neutropenia for 21.7% and 16.0%, nausea for 21.4% and 18.9%, asthenia for 18.3% and 15.7%, thrombocytopenia for 18.3% and 13.7% of patients in the CT-P16 and EU-Avastin groups, respectively. A vast majority of these TEAEs were reported during the induction period.

Of the common related TEAEs by PT, proteinuria was reported for 10.4% and 9.3%, anaemia for 7.2% and 8.4%, hypertension for 7.2% and 7.3%, alopecia for 6.7% and 6.1%, thrombocytopenia for 6.4% and 2.6%, and neutropenia for 3.8% and 5.2% of patients in the CT-P16 and EU-Avastin groups, respectively. The frequency of related TEAEs were comparable between the study groups, i.e. at least 1 related TEAE was reported for 51.6% and 50.6% of patients in the CT-P16 and the EU-Avastin treatment groups, respectively.

Overall, the frequency of common TEAEs was somewhat higher in the CT-P16 group compared to EU-Avastin group both during the induction (95.1% vs 91.6%) and maintenance periods (50.7% vs 45.1%). At least 5% difference was reported for CT-P16 vs. EU-Avastin in SOCs blood and lymphatic system disorders, general disorders and administration site conditions and nervous system disorders. TEAEs from these SOCs were analysed further by the applicant and it can be concluded that the higher frequency of TEAEs in the CT-P16 vs. EU-Avastin group was mainly driven by chemotherapy-related TEAEs during the induction period. As discussed above, more patients in the CT-P16 group than in the EU-Avastin groups received the study drug and chemotherapy after the first cycle during the induction period. Consequently, more patients in the CT-P16 group continued to receive the study drug during the maintenance period. Given that the frequencies (%) for the TEAEs were calculated from the total safety population (i.e. all subjects who received at least 1 dose of study drug), it is likely that the imbalance in drug exposure contributed to the observed numerical difference in the TEAEs between the study groups. Importantly, no major differences in the frequency of study drug-related TEAEs were observed during the induction or maintenance periods in the three SOCs analysed.

At least 1 ≥ Grade 3 TEAE was reported for 43.8% and 41.9% of patients in the CT-P16 and EU-Avastin groups, respectively. The most common ≥ Grade 3 TEAE was neutropenia, reported for 10.4% and 7.3% of patients in the CT-P16 and EU-Avastin groups, respectively. Dyspnoea was reported for 7 vs 0 patients (6 vs 0 during maintenance period) and pulmonary embolism for 6 vs 3 of patients (2 vs 0 during maintenance period) in the CT-P16 and EU-Avastin groups, respectively. When examining the risk factors for the patients that experienced dyspnoea during the maintenance period, most notably, 12 (75%) vs. 4 (40%) of the patients in CT-P16 and EU-Avastin treatment groups, respectively, reported dyspnoea already at screening. Some further imbalances in the risk factors were also observed, e.g. more unfavourable smoking history in CT-P16 group, and altogether these imbalances can be considered a plausible reason for the observed difference in the grade ≥ 3 cases between the study groups.

Importantly, all grade ≥ 3 events of dyspnoea were considered unrelated to the study drug by the investigator.

TEAEs leading to study drug discontinuation was reported for 15.9% and 16.0% of the patients in the CT-P16 and EU-Avastin groups, respectively. The most common reason for discontinuation was pulmonary embolism, in 8 (2.3%) and 2 (0.6%), proteinuria in 3 (0.9%) and 5 (1.5%), and thrombocytopenia in 2 (0.6%) and 4 (1.2%) patients in the CT-P16 and EU-Avastin groups, respectively. All other TEAEs that led to discontinuation, were reported for less than 1% of subjects in each group. Except for the numerical difference in the pulmonary embolism cases, the safety profile based on TEAEs that led to discontinuation was similar between the CT-P16 and EU-Avastin group.

In the Phase 3 study CT-P16 3.1, the number of patients that died was 23 (6.7%) and 24 (7.0%) in CT-P16 and EU-Avastin treatment groups, respectively. Number of patients with drug-related TESAE leading to death was higher in the EU-Avastin group, i.e. 3 (0.9%) and 7 (2.0%) of the cases were regarded as study drug-related in the CT-P16 and EU-Avastin groups, respectively. All, except one study-drug related death occurred during the induction study period.

TESAEs were reported in 20.0% and 21.2% and related TESAEs in 5.2% and 6.7% of patients in the CT-P16 and EU-Avastin treatment groups, respectively. The most common TESAEs were pneumonia in 2.3% and 2.9%, febrile neutropenia in 1.7% and 0.6%, COVID-19 pneumonia in 1.4% and 1.2%, neutropenia in 1.4% and 0.3% and pulmonary embolism in 1.4% and 0.3% of patients in the CT-P16 and EU-Avastin treatment groups, respectively.

Overall, the number of deaths, other TESAEs and related TESAEs were comparable between CT-P16 and EU-Avastin treatment groups in the Phase 3 study CT-P16 3.1. No deaths or other TESAEs were reported in the PK studies CT-P16 1.1 and 1.2. The applicant has provided full narratives of TESAEs and deaths, where the cases are adequately described.

The AESIs were adequately pre-defined based on known safety profile of Avastin as described in the SmPC of Avastin, as well as important identified and potential risks in the RMP of Avastin. In the Phase 3 study CT-P16 3.1, the following AESIs were included: hypersensitivity/infusion-related reactions (IRR), gastrointestinal perforations and fistulae, wound healing complications, hypertension, posterior reversible encephalopathy syndrome (PRES), proteinuria, arterial thromboembolism (ATE), venous thromboembolism (VTE), hemorrhages, congestive heart failure (CHF), and ovarian failure/fertility. Overall, apart from the numerical differences in pulmonary embolism discussed above, the frequency of most AESIs was similar between the CT-P16 and EU-Avastin treatment groups.

In general, no major differences were observed in the clinical laboratory evaluations between the study groups. The mean values over time in haematology laboratory parameters followed a similar pattern in both groups, with no major differences between the CT-P16 and EU-Avastin. By CTCAE grading, numerically slightly more (mainly grades 1-2) anaemia, neutrophil count decreased, platelet count decreased and white blood cell decreased was reported in CT-P16 vs. EU-Avastin group, which is in line with the observations related to the TEAEs under SOC Blood and Lymphatic System Disorders.

Data on vital signs, physical examination and ECG did not reveal any notable differences between the study groups.

In summary, the safety of CT-P16 was consistent with the known safety profile of Avastin with or without chemotherapy that was used during the induction phase in the Phase 3 study CT-P16 3.1. As discussed above, some numerical differences were observed in the TEAEs between the study groups, but considering the safety data as a whole, CT-P16 and EU-Avastin can be concluded to be biosimilar in terms of safety.

Adverse events in the PK Phase 1 studies CT-P16 1.1 and 1.2:

Of the 141 healthy subjects included in the safety population in Study CT-P16 1.1, at least 1 TEAE was reported for 50.0%, 72.3% and 54.2% of subjects, treatment related TEAEs for 19.6%, 42.6% and 33.3% and ≥ Grade 3 TEAEs for 4.3%, 4.3% and 0% of subjects in the CT-P16, EU-Avastin and US-Avastin groups, respectively.

In terms of common TEAEs by PT in Study CT-P16 1.1, diarrhoea was reported for 6.5%, 12.8% and 8.3%, blood CPK increased for 6.5%, 10.6% and 8.3%, CRP increased for 4.3%, 10.6% and 8.3%, nasopharyngitis for 8.7%, 2.1% and 12.5%, and IRR for 4.3%, 4.3% and 8.3% of subjects in the CT-P16, EU-Avastin and US-Avastin groups, respectively. All other TEAEs were reported for ≤3 subjects in each group. Of the common related TEAEs by PT, diarrhoea was reported for 6.5%, 12.8% and 4.2%, and CRP increased for 2.2%, 8.5% and 8.3% of subjects in the CT-P16, EU-Avastin and US-Avastin groups, respectively. TEAEs of ≥ Grade 3 was observed in 2 subjects (4.3%) in CT-P16 and EU-Avastin groups.

Of the 46 healthy subjects included in the safety population in study CT-P16 1.2, TEAEs were reported for 2 subjects (9.1%) in the CT-P16 groups and 3 subjects (12.5%) in the EU-Avastin group. Related TEAEs were reported for 1 subject in the CT-P16 group (drug eruption) and 1 subject in the EU-Avastin group (nausea and dizziness). Two TEAEs of ≥ Grade 3 were reported for 1 subject in the EU-Avastin group (AST increased and blood CPK increased).

In the PK studies CT-P16 1.1 and 1.2, no TEAEs leading to study drug discontinuation, deaths or other TESAEs were reported. Only individual grade ≥ 3 laboratory findings were seen, with no relevant differences between the study groups.

Overall, although some numerical differences in the TEAEs were seen in the single dose PK studies between study groups, there were no findings that were considered relevant in the context of similarity assessment of safety.

Immunological events:

The proportion of healthy subjects who had post-dose ADA positive results was 4.3% in both CT-P16 and EU-Avastin treated subjects in study 1.1. The low proportion of ADA positive subjects in this study is in line with historical studies with bevacizumab. NAb results were negative for all healthy subjects. Of note, due to weak drug tolerance of the NAb assay, no meaningful NAb detection was possible at Day 15 and Day 43 in these two studies.

In study CT-P16 1.2 no subject had a positive ADA test result on any day in either treatment group. The applicant pointed out that the lack of ADA detection in Study CT-P16 1.2 was probably due to the low sample size and the generally low incidence of anti-bevacizumab antibodies. The applicant further provided literature data from other phase 1 studies with similar results.

In the phase III study 3.1 no meaningful difference in post-treatment ADA or NAb incidence was observed between the two treatment groups. The prevalence of ADA positive patients at each time point was low (< 5%) and in line with historical studies. The overall ADA incidence was 78 (22.6%) and 83 (24.1%) for the CT-P16 and EU-Avastin treatment groups, respectively. The titres of ADA were generally low and the ADA titre kinetics were similar between the two treatment groups. Neither ADA progression over time nor transiency of ADA was seen in any of the treatment arms. As the number of ADA positive subjects in each treatment arm can be considered small (n = 1-17 depending on the cycle), it is not possible to draw conclusions on the impact of ADAs on PK. No relevant effect of ADA on the efficacy or safety endpoints could be determined in any treatment group.

2.4.10. Conclusions on the clinical safety

In summary, the safety and immunogenicity of CT-P16 was consistent with the known safety profile of Avastin with or without chemotherapy that was used during the induction phase in the Phase 3 study CT-P16 3.1. Considering the safety data as a whole, CT-P16 and EU-Avastin can be concluded to be biosimilar in terms of safety and immunogenicity.

2.5. Risk Management Plan

2.5.1. Safety concerns

The applicant identified the following safety concerns in the RMP version 0.2:

Table 39. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.5.2. Pharmacovigilance plan

There are no additional pharmacovigilance activities conducted or planned.

2.5.3. Risk minimisation measures

Since there are no safety concerns identified for the medicinal product, neither routine nor additional risk minimisation measures are considered applicable.

2.5.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Abevmy and Herzuma. The bridging report submitted by the applicant has been found acceptable.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vegzelma (bevacizumab) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Vegzelma has been developed as a proposed biosimilar to the reference product Avastin (bevacizumab). The applicant is claiming all of the approved indications for Avastin.

The proposed indications are:

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

VEGZELMA 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.

VEGZELMA 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 VEGZELMA in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1.

VEGZELMA, 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 (NSCLC) other than predominantly squamous cell histology.

VEGZELMA, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSCLC with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1).

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

VEGZELMA, 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).

VEGZELMA, 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 vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents.

VEGZELMA 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 (see section 5.1).

VEGZELMA, 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).

Summary of quality comparability data

A comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012) has been performed. Ten independent CT-P16 DP batches representative of the commercial scale and 10 EU-approved Avastin batches were included in the similarity study. The batches reflected a range of expiration dates and product ages. The DP material used in the analytical biosimilarity studies is considered representative of the material used in clinical trials. The similarity analyses were performed side-by-side using qualified in-house reference standard (P2-RF-JPP01). A ±3*SD quality range was set by analysis of 10 batches of EU-approved Avastin for key biological quality attributes. Results of physicochemical analyses were presented without statistical analysis; instead the mean and SD as well as the spread of the underlying distribution from quantitative analyses have been compared and differences have been highlighted and discussed. In addition, raw data has been provided to allow assessment of biosimilarity independently of statistical approach chosen.

Analytical comparability studies included primary and higher order structures, post-translational modifications, glycation and glycosylation, charge heterogeneity, purity/impurity, content, biological activity of Fab and Fc related functions, and comparative forced degradation studies.

Summary of nonclinical comparability data

A comprehensive *in vitro* similarity exercise included biological activity of Fab and Fc -related functions of bevacizumab presented and described under quality comparability data. A supportive four weeks of duration repeated toxicology study with toxicokinetic analysis in cynomolgus monkeys comparing CT-P16 to EU-Avastin of was conducted.

Summary of clinical comparability data

One pivotal PK study (i.e. CT-P16 1.1) was conducted: a single-dose (i.e. 5 mg /kg IV infusion for 90 min) randomised, double-blind, 3-arm, parallel study in healthy subjects comparing CT-P16, EU-Avastin and US-Avastin (N ~ 46-48 subjects administered/group). Supportive PK data was obtained from a study with healthy Japanese subjects (i.e. study CT-P16 1.2) and with nsNSCLC patients in the clinical efficacy and safety study CT-P16 3.1.

The main efficacy and safety study CT-P16 3.1 is an ongoing double-blind, randomised, active-controlled, parallel group Phase 3 study to compare the efficacy, PK, and overall safety of CT-P16 (15 mg/kg) and

EU-Avastin (15 mg/kg) when co-administered with paclitaxel and carboplatin as first-line treatment in patients with metastatic or recurrent nsNSCLC.

In general, the clinical programme for Vegzelma is consistent with relevant CHMP Guidance concerning development of biosimilars.

3.2. Results supporting biosimilarity

Quality data

Similarity between CT-P16 and EU-approved Avastin has been demonstrated for the following physico-chemical and biological properties:

- Primary structure
- Content
- Charge heterogeneity
- Glycan profile
- Size heterogeneity and purity/impurity profile
- Antiproliferation activity, and binding to VEGF-A165 and VEGF-A121
- Binding to FcγRIIIa (F-type, V-type), FcγRIIa, FcγRIIb, FcγRI, FcRn, C1q
- ADCC and CDC activity
- Inhibition of VEGFR2 RTK autophosphorylation
- Binding to VEGF-A isoforms (VEGF-A145, VEGF-A189, VEGF-A206) and VEGF family (VEGF-B, -C, -D, and -E; PlGF-1 and -2)
- Stability under forced degradation

Minor differences in the levels of post-translational modifications (deamidation, oxidation, N-terminal pyroglutamic acid, C-terminal lysine, proline amidation), free thiol groups, relative proportion of the charge variants, individual fucosylated glycan species, levels of glycation, and levels of monomer, HMW, LMW, HC+LC and NGHC were sufficiently justified to have no clinical impact.

Nonclinical data

Similarity between CT-P16 and EU-approved Avastin was demonstrated for the functional properties as described above under Quality data (antiproliferation activity, binding to VEGF-A165 and VEGF-A121, binding to FcγR subtypes, FcRn, C1q, ADCC and CDC activity, Inhibition of VEGFR2 RTK autophosphorylation and binding to other VEGF-A isoforms and VEGF family members). CT-P16 and EU-Avastin did not differ in cynomolgus monkeys on their toxicological and toxicokinetic characteristics.

Clinical data

Pharmacokinetics

In the comparison of PK data (pivotal PK study CT-P16 1.1) for the CT-P16 group with the EU-Avastin and US-Avastin treatment groups, the 90% CIs of the geometric LS mean ratios for the three primary PK parameters (i.e. C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) were all within 80% and 125% (including 100.00). In the comparison of the AUCs between EU-Avastin and US-Avastin, the 90% CIs were between the range 80% - 125% but the range did not include 100.00%. This is, however, not any concern. The sensitivity analysis supported the PK similarity between CT-P16 and EU-Avastin.

In the supportive PK study in Japanese subjects the 90% CIs of ratios of geometric LS means of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were entirely contained within the predefined equivalence margin of 80% to 125% which indicated that bevacizumab exposures from CT-P16 were similar to those from EU-Avastin.

The mean trough concentrations were comparable between CT-P16 group and EU-Avastin group (PK data up to induction cycle 6) in nsNSCLC patients in the study CT-P16 3.1.

Efficacy

In the clinical efficacy study CT-P16 3.1, CT-P16 and EU-Avastin were compared in a Phase III study in nsNSCLC patients. The design and other general characteristics of the study are considered fit for the purpose of demonstrating biosimilarity. The primary endpoint was ORR (based on BOR as per central review) during the Induction Study Period. For the ITT and the PP populations, the reported CT-P16 – EU-Avastin risk differences of 0.40 (95% CI -7.02, 7.83) and -1.90 (95% CI -9.80, 6.00), respectively, were entirely contained within the pre-specified equivalence margin of -12.5 to 12.5. Also based on the local investigators' response evaluation, the 95% CI for difference between CT-P16 and EU-Avastin in ORR during the Induction Study Period was within the equivalence margin of -12.5 to 12.5 (ITT: 4.87% [95 %CI: -2.53 to 12.26]; PP: 2.90% [95 % CI: -4.99 to 10.79]).

The post-hoc analysis of ORR by treatment cycle showed similar response rates between the treatment groups; at Induction Cycle 6, the reported ORR was 42.69% (95% CI 37.45, 47.93) for CT-P16 and 43.52% (95% CI 38.30, 48.73) for EU-Avastin in the ITT population, and 44.97% (95% CI 39.50, 50.44) for CT-P16 and 48.84% (95% CI 43.22, 54.47) for EU-Avastin in the PP population. Also in this analysis, the reported CT-P16 – EU-Avastin risk differences of -0.77 (95% CI -8.21, 6.68) and -3.79 (95% CI -11.69, 4.11), for the ITT and the PP populations respectively.

Data on time-dependent endpoints is also supportive of biosimilarity.

In the ITT population, median PFS was 7.9 [95% CI: 6.9 – 8.3] months and 7.2 [95% CI: 6.5 – 8.3] months for the CT-P16 and EU-Avastin treatment groups, respectively, with a hazard ratio of 0.92 (95% CI: 0.77 – 1.10). In the PP population, median PFS was 8.3 [95% CI: 7.2 – 8.5] months and 8.1 [95% CI: 6.8 – 8.6] months for the CT-P16 and EU-Avastin treatment groups, respectively, with a hazard ratio of 0.93 (95% CI: 0.76 – 1.12). With respect to the comparison between CT-P16 and EU-Avastin, similar results were observed in additional PFS analyses performed by the applicant in response to D180 LoQ.

In the ITT population, median OS was 17.1 [95% CI: 14.6 – 18.7] months and 15.6 [95% CI: 13.4 - 18.0] months for the CT-P16 and EU-Avastin treatment groups, respectively, with a hazard ratio of 0.95 (95% CI: 0.77 – 1.19). In the PP population, median OS was 17.5 [95% CI: 15.5 - 19.2] months and 17.0 [95% CI: 14.6 – 20.5] months for the CT-P16 and EU-Avastin treatment groups, respectively, with a hazard ratio of 0.96 (95% CI: 0.76 – 1.22).

Safety

The clinical Safety Population includes data from 689 nsNSCLC patients in Study CT-P16 3.1 that received CT-P16 (n=345) or EU-Avastin (n=344). In addition, 187 healthy subjects received a single dose (5 mg/kg) of CT-P16, EU-Avastin or US-Avastin in studies CT-P16 1.1 and 1.2.

The design of the clinical studies and the safety assessments were adequate, including AESIs, that were identified based on the known safety profile of Avastin. The safety data for the Phase 3 study CT-P16 3.1 was presented separately for the induction study period (combination with paclitaxel and carboplatin), maintenance study period (monotherapy), follow-up period and whole study period. The safety data was not pooled, but presented separately for the three clinical studies. Overall, the size of the safety population included in the clinical studies can be considered sufficient and the groups

comparable in terms of demographics and baseline characteristics to allow a meaningful comparison of safety between CT-P16 and EU-Avastin in the context of a biosimilar MAA.

In the Phase 3 study CT-P16 3.1, at least 1 TEAE was reported for 96.2% and 93.0%, treatment related TEAEs for 51.6% and 50.6% and ≥ Grade 3 TEAEs for 43.8% and 41.9% of patients in the CT-P16 and EU-Avastin groups, respectively. In terms of common TEAEs by SOC, similar frequencies were reported in several SOCs, e.g. skin and subcutaneous tissue disorders were reported for 67.0% and 65.4% and gastrointestinal disorders for 44.9% and 40.7% of patients in the CT-P16 and EU-Avastin groups, respectively. In terms of most common TEAEs by PT, alopecia was reported for 63.8% and 63.4% of patients in the CT-P16 and EU-Avastin groups, respectively. TEAEs leading to study drug discontinuation was reported for 15.9% and 16.0% of the patients in the CT-P16 and EU-Avastin groups, respectively. The number of deaths (6.7% vs 7.0%), other TESAEs (20.0% vs 21.2%) and related TESAEs (5.2% vs 6.7%), as well as AESIs were generally comparable between CT-P16 and EU-Avastin treatment groups.

Overall, although some numerical differences in the TEAEs were seen in the single dose PK studies (CT-P16 1.1 and 1.2) between study groups, there were no findings that were considered relevant in the context of similarity assessment of safety.

Immunogenicity

The proportion of healthy subjects who had post-dose ADA positive results was 4.3% in both CT-P16 and EU-Avastin treated subjects in study 1.1. In study CT-P16 1.2 no subject were ADA positive.

In the phase III study 3.1 the prevalence of ADA positive patients at each time point was low (< 5%) and in line with historical studies. The overall ADA incidence was 78 [22.6%] and 83 [24.1%] for the CT-P16 and EU- Avastin treatment groups, respectively.

3.3. Uncertainties and limitations about biosimilarity

Safety

- Overall, the frequency of common TEAEs was somewhat higher in the CT-P16 group compared to EU-Avastin group in the Phase 3 study CT-P16 3.1. At least 5% difference in the number of patients with TEAEs was reported in the CT-P16 vs. EU-Avastin group in SOCs blood and lymphatic system disorders (including neutropenia), general disorders and administration site conditions and nervous system disorders. However, more patients were exposed to the CT-16 + chemotherapy vs EU-Avastin + chemotherapy after the first treatment cycle during the induction phase and the numerical differences were largely driven by the chemotherapy-related TEAEs during the induction period. Importantly, no major differences in the frequency of study drug-related TEAEs were observed in the three SOCs analysed.
- The most notable difference between study groups were observed in the number of patients with ≥ Grade 3 dyspnoea which was reported for 7 vs 0 patients in the CT-P16 and EU-Avastin groups, respectively. Six (6) out of the 7 cases in the CT-P16 group occurred during the maintenance period. In a more thorough analysis of these cases, some imbalances in the baseline factors (e.g. presence of dyspnoea already at screening and smoking history) were identified that potentially could explain the differences. Further, pulmonary embolism was reported for 8 (2.3%) vs 3 (0.9%), and ≥ Grade 3 pulmonary embolism for 6 (1.7%) vs 3 (0.9%) patients in the CT-P16 and EU-Avastin groups, respectively, which could not be explained by imbalance of risk factors at baseline. On the other hand, e.g. drug related TESAEs leading to death was reported in 7 (2.0%) patients in EU-Avastin group and in 3 (0.9%) patients in CT-P16 group. Therefore, the numerical imbalances in these individual TEAEs were likely a chance finding.

- None of the findings described above are considered to be uncertainties that would have an impact on the conclusion of biosimilarity.

3.4. Discussion on biosimilarity

Quality

A comprehensive similarity exercise following the general principles outlined in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance; Quality issues (EMA/CHMP/BWP/247713/2012) has been performed. The comparability studies have been conducted by analysing CT-P16 DP and EU-approved Avastin side-by-side (as possible) with qualified state of-the-art physicochemical and biological methods.

For most physicochemical and biological quality attributes high similarity has been demonstrated. Minor difference were observed mainly in post-translational modifications, charge variants, glycation levels, and levels of monomer and aggregates, and were without implications to Fab and Fc -related functions. The differences were sufficiently justified to have no clinical impact.

Nonclinical

Comprehensive similarity exercise following the principles laid down in the guideline on similar biological medicinal products containing monoclonal antibodies -nonclinical and clinical issues (EMA/CHMP/BMWP/403543/2010) and containing biotechnology derived medicinal products as active substances: non-clinical and clinical issues (EMEA/CHMP/42832/2005 Rev 1) was performed. The functional comparability data was identical to *in vitro* comparative data presented under Quality section and was, in order to avoid repeating the data, assessed under Quality. This data demonstrated high similarity of CT-P16 and EU-Avastin in their functional characteristics. Toxicology and toxicokinetic analysis in cynomolgus monkeys did not reveal differences between CT-P16 and EU-Avastin, and can be considered as supportive data for the similarity.

Clinical

Biosimilarity in the pivotal PK study CT-P16 1.1 using healthy subjects has been formally demonstrated between CT-P16 and EU-Avastin and US-Avastin as in the primary PK parameters C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$, the 90% CI for the ratio of test-to-reference/comparator fell within the acceptance range of 80.00-125.00%. Also, in the supportive PK study in Japanese subjects in the primary PK parameters (i.e. C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$), the 90% CI for the ratio of test-to-reference fell within the acceptance range of 80.00-125.00%. The sensitivity analyses support the biosimilarity. Additional support for similarity between CT-P16 and EU-Avastin was obtained in the study in nsNSCLC patients (clinical study CT-P16 3.1). The mean C_{trough} concentrations were comparable between CT-P16 and EU-Avastin.

As indicated above, efficacy data from the nsNSCLC study CT-P16 3.1 can be considered to support biosimilarity. The primary endpoint was met, with the risk difference contained within the pre-specified equivalence margin, and available sensitivity analyses support this view. This position is supported by the analyses for relevant time-dependent endpoints (PFS, OS).

The safety of CT-P16 was consistent with the known safety profile of Avastin with or without chemotherapy that was used during the induction phase in the Phase 3 study CT-P16 3.1. Some numerical differences were observed in the TEAEs between the study groups, but considering the safety data as a whole, CT-P16 and EU-Avastin can be concluded to be biosimilar in terms of safety and immunogenicity.

3.5. Extrapolation of safety and efficacy

The applicant is claiming all indications approved for the reference product Avastin. In principle, it is agreed that the MoA of bevacizumab across its approved indications is to inhibit VEGF-induced angiogenesis and vascular permeability, and there is no evidence to support claims of a unique MoA in any specific indication. It is thus agreed that extrapolation to other indications is appropriate and authorisation can be granted for all indications approved for Avastin. This approach is also consistent with regulatory precedence for other previously authorised bevacizumab biosimilars.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Vegzelma is not similar to Zejula within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

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

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

Vegzelma 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.

Vegzelma 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 Vegzelma in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1.

Vegzelma, 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 (NSCLC) other than predominantly squamous cell histology.

Vegzelma, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent NSCLC with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1).

Vegzelma, in combination with interferon alfa-2a is indicated for first line treatment of adult patients

with advanced and/or metastatic renal cell cancer.

Vegzelma, 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).

Vegzelma, 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 vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor–targeted agents.

Vegzelma 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 (see section 5.1).

Vegzelma, 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 marketing authorisation holder (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.