30 May 2024
EMA/285021/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Avzivi

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/005574/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
AEX	Anion exchange chromatography
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase / alanine transaminase
AS	Active substance
AST	Aspartate aminotransferase / aspartate transaminase
AUC_{0-inf}	Area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from 0 hours to time (t)
BLA	Biologics license application
BOR	Best overall response
C1q	Complement component 1, q subcomponent
CCI	Container closure integrity
CD	Circular dichroism
CDC	Complement-dependent cytotoxicity
CDR	Complementarity-determining regions
CE-SDS	Capillary electrophoresis-sodium dodecyl sulphate
CEX	Cation exchange chromatography
cGE	Capillary gel electrophoresis
CHO	Chinese hamster origin
CI	Confidence interval
CIR	Central imaging review
CK	Creatine kinase
CL	Systemic clearance/total clearance
C_{max}	Maximum concentration
CMC	Chemistry, manufacturing and controls
CNS	Central nervous system
CPP	Critical process parameter
CQA	Critical quality attributes
CZE	Capillary zone electrophoresis

DLS	Dynamic light scattering
DoE	Design-of-experiment
DoR	Duration of response
DP	Drug product
DS	Drug substance
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EoT	End of treatment
EPCB	End-of-production cell bank
EU	European Union
FAS	Full analysis set
FcγRIa	Fc gamma receptor Ia
FcγRIIa	Fc gamma receptor IIa
FcγRIIb	Fc gamma receptor IIb
FcγRIIIa	Fc gamma receptor IIIa
FcγRIIIb	Fc gamma receptor IIIb
FCM	Flow cell microscopy
FcR	Fc receptor
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration
FDS	Formulated drug substance
FMEA	Failure mode and effects analysis
FP	Finished product
FTC	Fallopian tube cancer
GCP	Good clinical practice
GMP	Good manufacturing practice
HC	Heavy chain
HCP	Host cell protein
HILIC	Hydrophilic interaction chromatography
HMW	High molecular weight
HPLC	High performance liquid chromatography

HR	Hazard ratio
HUVEC	Human umbilical vein endothelial cells
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC-HPLC	Ion exchange chromatography-HPLC
IgG1	Immunoglobulin gamma subclass 1
IPC	In-process control
ITT	Intention-to-treat
IV	Intravenous(ly)
KPP	Key process parameter
LC	Light chain
LIVCA	Limit of in-vitro cell age
LMW	Low molecular weight
LTE	Long-term extension
MAA	Marketing authorisation application
max	Maximum
MCB	Master cell bank
mCRC	Metastatic colorectal cancer
Min	Minimum
MMC	Mixed mode chromatography
MMV/MVM	Mouse minute virus
mRCC	Metastatic renal cell cancer
MS	Mass spectrometry
MVM	see MMV
n	Number of subjects with observation
N	Total number of subjects
NADA	Neutralising anti-drug antibody
NMPA	National Medical Products Association
NOR	Normal operation range
NSCLC	Non-small-cell lung cancer
nsNSCLC	Non-squamous non-small-cell lung cancer
OC	Ovarian cancer
ORR	Overall response rate
ORR12	Overall response rate at week 12

ORR18	Overall response rate at week 18
ORR6	Overall response rate at week 6
OS	Overall survival
PAR	Process acceptable ranges
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PDE	Permitted daily exposure
PFS	Progression-free survival
PhEur	European Pharmacopeia
PK	Pharmacokinetic(s)
PP	Per protocol
PPC	Primary peritoneal cancer
PPQ	Process performance qualification
PRES	Posterior reversible encephalopathy syndrome
PS20	Polysorbate 20
PTM	Post-translational modifications
QA	Quality attributes
QOS	Quality overall summary
QTPP	Quality target product profile
RCB	Research cell bank
RCC	Renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
ROS1	Receptor tyrosine kinase 1
RP-UPLC	Ultra-performance liquid chromatography
RT-PCR	Reverse transciptase-polymerase chain reaction
RVLP	Retrovirus-like particles
SAE	Serious adverse event
SD	Standard deviation
SD	Standard deviation
SEC-HPLC	Size exclusion HPLC
SFUV	Safety follow-up visit
SoC	Standard of care
SSM	Small scale model

t1/2	Terminal elimination half-life
TEAE	Treatment emergent adverse event
TE-SAE	Treatment emergent serious adverse event
TFF	Tangential flow filter
TGI	Tumour growth inhibition
TKI	Tyrosine kinase inhibitor
T_{max}	Time to maximum measured concentration
TOR	Time out of refrigeration
TSE	Transmissible spongiform encephalopathy
US	United States
UV	Ultraviolet spectrophotometry
v	Version
VEGF	Vascular endothelial growth factor
VEGF-A	Vascular endothelial growth factor A
VEGFR	Vascular endothelial growth factor receptor
WCB	Working cell bank
WCX	Weak cation exchange chromatography
xMULV	Xenotropic murine leukaemia virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant FGK Representative Service GmbH submitted on 22 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Avzivi, through the centralised procedure falling within the Article 3(1) and point 1of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

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

Avzivi 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.

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

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

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

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

Avzivi, 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).

Avzivi, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

Avzivi 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).

Avzivi, 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

The legal basis for this application refers to:

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

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

The chosen reference product is: Avastin

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

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

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

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

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

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

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 did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Tomas Radimersky

The application was received by the EMA on	22 November 2020
The procedure started on	24 December 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 March 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 March 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	07 December 2021
– A GMP inspection at one drug substance and drug product manufacturing site in China between 23-27 October 2023. The outcome of the inspection carried out was issued on	19 March 2024
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	31 January 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 February 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	24 February 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	02 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	15 May 2024
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 Avzivi on	30 May 2024

2. Scientific discussion

2.1. Problem statement

2.2. About the product

BAT1706 has been developed as a biosimilar to Avastin (bevacizumab), a recombinant humanised monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor (VEGF).

The applicant applied for the same therapeutic indications for BAT1706 as granted for Avastin in the EU. For all proposed indications for BAT1706, the recommended posology and method of administration correspond to those of Avastin.

Bevacizumab is a recombinant humanised monoclonal antibody, which specifically binds to human vascular endothelial growth factor (VEGF), preventing its interaction with VEGF receptors (VEGFRs) on the surface of endothelial cells. As a result, the VEGFR-dependent signalling pathways required to promote and maintain blood vessel formation (angiogenesis) are inhibited. Through this mechanism, bevacizumab can potentially reduce tumour size by promoting regression of existing tumour vasculature and inhibit tumour growth by inhibiting the formation of new tumour blood vessels.

2.3. Type of application and aspects on development

This application is submitted under Article 10(4) of Directive 2001/83/EC relating to applications for biosimilar medicinal products. The reference product is Avastin (25mg/ml Concentrate for solution for infusion, Roche Registration GmbH). Avastin was authorised in the EU on 12/01/2005.

The clinical development programme included two Phase I studies in healthy male subjects to compare PK with EU-Avastin and US-Avastin (BAT1706-001-CR conducted in New Zealand) and with EU-Avastin conducted in China (BAT1706-002-CR). In addition, a single, Phase III clinical study BAT1706-003-CR to compare the efficacy, safety, PK and immunogenicity of BAT1706 plus paclitaxel and carboplatin vs. EU-Avastin plus paclitaxel and carboplatin in patients with advanced nsNSCLC was conducted in 5 countries (China, Turkey, Ukraine, South Africa, and Mexico).

According to the applicant the studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines ICH E6(R2) and the applicable drug and data protection laws and regulations of the countries where the clinical study was conducted.

2.4. Quality aspects

2.4.1. Introduction

Avzivi has been developed as a biosimilar for the EU reference medicinal product Avastin. The finished product (FP) is presented as concentrate for solution for infusion containing 25 mg/mL of bevacizumab as active substance (AS).

Other ingredients are: trehalose dihydrate, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate monohydrate, polysorbate 20 and water for injections.

The product is available in single-use vials in two presentations, 100 mg/4 mL and 400mg/16 mL, as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The International non-proprietary name (INN) of the active substance is bevacizumab. The development code is BAT1706.

BAT1706 is a recombinant humanised immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (93% human, 7% murine sequences) with a molecular weight of approximately 149 kDa. BAT1706 is composed of two heavy chains (HC) (gamma 1) and two light chains (LC) (kappa). Each heavy chain (fully reduced) has 453 amino acids (AA); each light chain (fully reduced) includes 214 amino acids.

BAT1706 contains a total of 16 disulfide bonds, among which 12 are intra-chain and 4 inter-chain. The glycosylation site is N303 on the heavy chain and post-translational modifications mainly include C-terminal lysine truncation, N-terminal pyroglutamic acid formation, oxidation and deamidation.

BAT1706 selectively binds with high affinity to all isoforms of human VEGF-A and neutralises VEGF-A's biologic activity through a steric blocking of the binding of VEGF-A to its receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2) on the surface of endothelial cells, therefore inhibiting tumour growth and reducing tumour size.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturers

All sites involved in the manufacturing and control of the active substance operate in accordance with EU GMP.

The review of the manufacture information in Module 1 is within the remit of the EMA Inspections Sector. No issues that would trigger a GMP inspection have been identified by CHMP during the assessment of the information in Module 3 of the dossier.

Description of manufacturing process and process controls

The manufacturing process of BAT1706 Active Substance involves the upstream and downstream manufacturing processes. BAT1706 is produced in a recombinant Chinese Hamster Ovary (CHO) cell line. One batch of bevacizumab active substance refers to the specific quantity of the product that is produced from the same batch of raw materials according to a single manufacturing order during the same manufacturing cycle of the AS manufacturing process. Each batch of active substance production is designated with a specific and unique batch number for identification.

The upstream manufacturing process consists of different process steps, including cell line thawing, expansion, production and harvest.

The downstream process is divided into purification and separation steps, including filtration, chromatography purifications, and virus removal processes.

Information on process parameters and process controls is provided in the dossier. Where relevant, the hold times for respective pools are defined. The upstream and downstream processing steps are found acceptably described.

It is clearly stated that reprocessing and reworking are not permitted during the manufacture of BAT1706 AS. It is noted that AS and FP are manufactured at the same site, and therefore AS transport is not described.

Control of materials

Raw materials and reagents from upstream and downstream production are listed with supplier, quality grade, use and production stage. Cell culture media, raw materials for preparing buffers and solutions are included. Some materials are stated to be of pharmaceutical grade quality and compliant to Chinese Pharmacopeia. For these materials there are also internal specifications provided. Disposable consumables for upstream and downstream production with chromatography resins are included. The compositions of the buffers and solutions used were briefly described, some additional information was asked for on compositions and also raw materials used for generation of cell banks which was satisfactorily provided.

There are no substances originating from animal sources and certificates on safety from TSE risk were provided as part of the dossier.

The composition of commercial cell culture media and feeds used in the cell cultivation process was not defined, this is acceptable provided there is a quality agreement between the applicant and suppliers to ensure that the applicant is informed about any changes in the proprietary media in order to assess potential impact on the product. The applicant confirmed that such a quality agreement is in place.

Microbial and endotoxin tests on main raw materials have been validated and found to meet the standards for intended use. Raw materials used for final formulation comply to corresponding Ph. Eur.

The host cell line used for antibody expression is CHO-BAT, derived from the CHO-K1 cell line. A description is provided on the source of the cell substrate and the manufacture of BAT1706 with design and purpose of elements and analysis of the expression construct to manufacture the master cell bank (MCB) (E-M1-20120626). The amino acid sequence is presented.

The preparation and establishment of the MCB and characterisation is presented.

Both the MCB and WCB were verified for expression product. A protocol for the generation of a new WCB was asked for and provided. Further information on how the end-of-production cell bank (EoPC) was generated and sampled for testing was asked for and provided. More information was asked for on the genetic characterisation and this was satisfactorily provided.

The MCB have been characterised with respect to identity and purity for mycoplasma, sterility, *in vitro* adventitious virus, *in vivo* assays, and retroviruses, this and additional testing for purity, including the WCB and EOPC, is further discussed in the section of Adventitious agents. Short descriptions of the tests are included.

As regards to the characterisation and testing of MCB and WCB, tabulated specifications, analytical methods and detailed results was asked for to demonstrate the viability, identity, and purity of the cell banks and this was satisfactorily provided.

Long term storage stability testing is found in line with the ICH Q5B, Q5D and Q5A.

Control of critical steps and intermediates

The process parameters were classified according to their criticality as being critical process parameters (CPPs), key process parameters (KPPs) or non-key process parameters (non-KPPs). A table defining the process parameters, the control item, process range, range justification and criticality is provided. The applicant explains that each one of the process parameters was classified depending on its effect over the product's critical quality attributes (CQAs) and process performance, and its ranges

were defined according to the results obtained during process characterisation and process validation, virus clearance studies or based on process development studies or prior experience. The approach was found acceptable.

The in-process controls and corresponded specifications are listed. The applicant clarified how non-conformities are handled and terminology was harmonised throughout the dossier. The methods are briefly described and validated. Validation summaries of all methods are provided in the dossier. The information provided is found sufficient to confirm the suitability of the in-process controls.

Intermediate hold times and storage conditions for all process steps are listed.

Process validation

The manufacturing process validation of BAT1706 active substance was carried out.

Commercial process set points or ranges are listed and adequate. Data on the down scale experiments and a comparison to full-scale manufacturing has been provided and is satisfactory.

Process validation batches were controlled according to set points or normal operating conditions. The information regarding process development and characterisation is found adequate. The outcome of the risk assessment and process characterisation studies, supported by appropriate data are found in the dossier. The CQAs are justified and linked to risk assessment and characterisation.

Parameters included in the characterisation are listed for up- and downstream process. No design space is claimed. Virus clearance and virus validation studies are presented in the section of adventitious agents. Robustness of excipient levels was studied. No reprocessing of steps is allowed.

The process performance qualification (PPQ) included upstream and downstream consistency studies. The results were consistent and within the specification set. Results is provided for the validation batches. The microbial control during downstream processing is acceptable.

For process-related impurities, a risk-analysis to demonstrate the consistent clearance capability of the manufacturing process was provided.

Manufacturing process development

The upstream process was developed following a screen of different culture media and feed solutions.

The downstream process was developed. A traditional univariate study approach was used. Basic results and chromatographic profiles are presented. Final process parameter set points with ranges are presented. It is found that sufficient information on the manufacturing process development is found in the dossier.

Three different processes have been used throughout development. Process A was used in the initial pre-clinical studies, process B was used in the initial phase I clinical studies and for comparability studies. Process C corresponds to the commercial scale and was used for comparability and Phase III clinical studies.

A comparability study on process B and process C batches was performed on the finished product lots derived from the respective active substance batches. The comparability is sufficiently demonstrated between processes B and C. Overall, the commercial manufacturing is considered validated.

Characterisation

Elucidation of structure

Characterisation studies were performed using the primary reference standard. Additional BAT1706 FP lots were included in the characterisation studies and corresponding data also permits to demonstrate

manufacturing consistency. The proposed approach is considered acceptable. Results on batches are presented and it is noted that all FP batches included in the study were derived from different AS lots.

The characterisation studies were performed in accordance with ICH Q6B using state-of-the-art analytical procedures for confirming the structural, physicochemical, and immunochemical properties and the biological activity of the active substance.

The results from the characterisation studies are adequately presented, and most relevant characteristics have been evaluated. Relevant chromatograms, electrophoretograms and dose-response curves have been provided, where applicable.

Primary structural analysis

Primary structure was confirmed. The results show that observed average masses are consistent with those calculated from the amino acid sequence. Peptide mapping confirmed a 100% sequence coverage.

The expected 16 pairs of disulfide bonds were confirmed.

The presence of post-translational modifications was investigated. The levels are found acceptable.

The isoelectric point and the extinction coefficient were determined.

Higher order structures

Several assays were conducted to obtain information on higher order structure. Characterisation of the thermal stability was determined. The results demonstrated consistent spectra for the batches included in the study and acceptable higher order structures.

Glycosylation

The N-glycosylation site was confirmed. The N-linked glycans were sufficiently characterised. The levels of NGNA were acceptably low.

Characterisation of the monosaccharide profile is presented.

Heterogeneity and product-related variants

Size heterogeneity and purity was investigated and is found acceptable.

Biological functions and activity

A thorough biological characterisation is presented and the proposed mode of action of bevacizumab is briefly described.

As a conclusion, BAT1706 could bind to VEGF-A with high specificity and inhibit VEGF-A-induced proliferation of human umbilical vein endothelial cells (HUVEC), but did not bind to VEGF-B, VEGF-C, and VEGF-D. BAT1706 could bind to multiple Fcγ receptors and C1q but showed no ADCC activity nor CDC activity.

Impurities

The product-related impurities were identified and is found acceptable.

Clearance of the process-related impurities was successfully demonstrated at large scale these process-related impurities are determined in the AS specifications, which is considered appropriate. In conclusion, results presented in the sections describing process validation and batch analyses, respectively, confirm efficient removal of all investigated process-related impurities. This is found acceptable.

2.4.2.3. Specification

The active substance release and stability specifications are identical.

An active substance specification including methods to evaluate identity, purity, impurities, biological activity, strength, and a few general characteristics is presented. For compendial methods, references are made to the Ph. Eur chapters. For non-compendial method, in-house method numbers are referred to. This is acknowledged.

The specification limits for the general characteristics tests, i.e. appearance, colour and clarity are based on results obtained on commercial scale AS batches manufactured to date and Ph. Eur requirement. This is found acceptable. The acceptance criteria for pH and protein concentration are also found acceptable, and it is noted that these attributes are further controlled by the FP specification.

Regarding identity by peptide mapping, the acceptance criterion is found acceptable.

The glycosylation profile is analysed by HILIC. It is pointed out that the mode of action of bevacizumab does not involve ADCC or CDC. The acceptance criteria are found acceptable.

The tests used to monitor AS purity are SEC-HPLC, IEC-HPLC and reduced and non-reduced CE-SDS. The methods selected are sufficiently justified, and the impurities have been characterised. The AS and FP specifications are aligned. This is found acceptable.

Potency is evaluated by the relative binding assay ELISA and the reporter gene bioassay and is found acceptable.

The tests used to detect process-related impurities and the proposed acceptance criteria are found sufficiently justified.

The specification limits for bacterial endotoxin and bioburden are found acceptable.

Overall, the specification is considered acceptable.

Analytical methods and reference standards

The tests for clarity, pH, bacterial endotoxin, and microbial limit are stated to comply with Ph. Eur. Method descriptions for all non-compendial procedures are provided. For all methods, the method principle is described, the critical equipment and critical materials are listed, a brief description of the procedure and system suitability criteria is provided, and determination and reporting of the results is addressed.

Validation reports confirming that the methods are properly validated, in line with ICH Q2, have been provided for all non-compendial methods. This is found acceptable.

Reference standards have been used throughout the development of BAT1706. Adequate information on the reference standard usage is provided. The methods used for characterisation and qualification of the historical batches are listed, and the strategy is found acceptable. The overall strategy for biological activity calibration is described and found acceptable.

A protocol describing qualification of future reference standards is provided.

Batch analysis

Results from batch analyses presented. All results complied with the proposed specification limits. The provided release data from the commercial process is in support of a consistent manufacture of active substance.

The history of analytical methods is presented and rationales for method replacement and bridging studies are provided.

Container closure

BAT1706 active substance is stored in storage bag. The components of the bag are clearly stated and specifications for the bag is provided. The storage bags comply with Ph. Eur and USP requirements with respect to endotoxins and particulates and the product contact layer material conforms with Ph. Eur 3.1.7. Extractables and leachables studies were performed using the primary packaging materials, and the results of the studies are found acceptable.

2.4.2.4. Stability

The stability programme is presented for BAT1706 active substance. All batches included in the study are manufactured at commercial scale and stated to be stored in containers representative of those used for commercial batches. The container for stability samples is sufficiently demonstrated to be representative of the AS storage container.

Based on the obtained stability data, the proposed shelf-life is found acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

BAT1706 finished product (FP) is a sterile, clear, preservative-free solution for intravenous infusion. BAT1706 is presented as a single-use 6 mL vial containing 100 mg of active substance in 4 mL and a single use 20 mL vial containing 400 mg of active substance in 16 mL. Both presentations share the same formulation and only differ in the size of the container and filled volume. All excipients comply with the applicable requirements of USP and Ph. Eur. Monographs.

The section on description and composition of the finished product is found acceptable.

Formulation development

The formulation development studies described justifies the chosen formulation and are found comprehensive. The studies described included selection of formulation/excipient screening, pH optimisation and surfactant screening. In addition, forced degradation tests were performed and studied the sample stability by relevant test methods.

The excipients and the formulation composition used for BAT1706 FP are the same as the ones used in the EU-authorised reference medicinal product Avastin (RMP). All the excipients comply with Ph. Eur. requirements.

The final formulation was used during all clinical studies.

There are no formula overages in the BAT1706 finished product.

Manufacturing process development

The manufacturing process for the proposed commercial manufacturing process of finished product consists of the following standard steps: AS thawing, compounding (including bioburden reduction), sterile filtration, filling, capping, visual inspection, packaging, and storage at 2-8°C.

The development studies were performed according to the quality target product profile (QTTP) with the aim to develop a robust commercial process with consistent manufacturing of FP, with acceptable control of the product's CQAs, when run within the prescribed operating ranges.

Furthermore, the control strategy of the proposed manufacturing process is found acceptably justified.

Comparability

Detailed process changes have been provided and the changes classified as minor or major based on the expected potential impact on finished product quality. Furthermore, comparability has been sufficiently demonstrated as judged from batch-data and the tests included in the finished product specification provided in the section on control of FP with a high degree of similarity and only a minor difference noted.

In addition, a comparability study has been performed between the 100 mg per 4 mL presentation and the 400 mg per 16 mL presentation of BAT1706 FP. Both presentations are prepared in the same type of container closure system, differing only in fill volume and vial size, keeping all the other features identical. The process differences between the presentations have been described. Process validation studies have been performed for both presentations as described in the manufacturing section. An analytical comparability exercise has been performed including a large number of commercial scale batches of both presentations and testing was performed. All quality attributes studied showed a high degree of similarity and very few and minor differences are noted. The presented data demonstrate comparability between the 100 mg/4 mL- and the 400 mg/16 mL-presentations for the attributes tested.

Hold times

All the claimed hold times are mentioned in the process description.

Container closure system

The development of the container closure system is found sufficiently presented. The primary packaging is composed of Type I glass vials and butyl rubber stoppers, and these are compliant with compendial requirements of Ph. Eur. and are very similar to the RMP Avastin.

Microbiological attributes

The information provided on microbiological attributes is found acceptable.

Compatibility

Primary packaging material: The compatibility of the BAT1706 FP with the primary packaging material has been acceptably demonstrated by development studies.

BAT1706 FP should be diluted in aqueous 0.9% NaCl in an infusion bag to a concentration within the range 1.4 mg/ml to 16.5 mg/mL. In-use stability has been studied to simulate in-use conditions and verify the chemical and physical stability of BAT1706 FP as well as to confirm the compatibility of FP to the material of the infusion bag.

As previously requested, a report on extractables and leachables has been provided for assessment and the results are found acceptable.

2.4.3.2. Manufacture of the product and process controls

Manufacturers

Information and evidence of GMP compliance have been provided on the manufacturers for BAT1706 finished product.

As previously requested, a revised and acceptable QP declaration has been provided for the batch release site Eurofins Pharma Quality Control.

Description of manufacturing process, process controls of critical steps, and intermediates

Flow diagrams for the manufacturing process of the finished product and acceptable ranges are provided for process parameters and in-process controls are defined with acceptance criteria.

The finished product is manufactured by aseptic technique. Bioburden is tested. A

No reprocessing has been described in the dossier.

The description of manufacturing process and process controls and control of critical steps and intermediates is sufficiently described also including all claimed hold times.

Differences in the manufacturing process of the two presentations 100 mg/4 mL and 400 mg/16 mL result from the difference in strength.

Process validation

The process validation studies for finished product were conducted.

All validation batches complied with the established validation acceptance criteria for all process parameters and in-process controls as well as with the proposed finished product specifications. The validation was run at set points while the ranges of some process parameters were challenged during the manufacturing process development. The currently approved process hold time limits were challenged during the execution of some of the manufacturing runs to obtain data that supports current limits. The homogeneity of buffer preparation was assessed. The homogeneity of the finished product during the filling process was assessed. This is acceptable.

As previously requested, validation data have been provided for the minimum batch size for both of the two presentations, and the results found acceptable. In addition, the minimum batch size has been stated in the batch formula within the dossier.

Overall, the FP commercial process is considered validated.

Media fills, filter validation and transportation validation

The media fill validation demonstrates that aseptic conditions are maintained during the filling process.

As previously requested, reports on filter validation have been provided for assessment and the results therein found acceptable.

Transportation validation studies have been initiated. In addition, and as requested, acceptable results have been provided from additional transport validation studies performed to cover different transportation conditions using the packaging and containers proposed for commercialisation.

2.4.3.3. Product specification

The release and stability specification for BAT1706 finished product is provided.

A broad set of relevant tests is included in the finished product specifications document. The acceptance criteria in the specifications document applies for both release and stability testing (end-of-shelf-life). The specifications proposed comply with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008 guideline. The specifications include tests for appearance (appearance, clarity and colour of the solution), general tests (i.e. pH, extractable volume, osmolality), tests for identity (CZE-CE), tests for purity/product-related impurities (purity by CE-SDS reduced/non-reduced, SEC-HPLC, IEC-HPLC), biological activity (reporter gene assay, binding by ELISA), quantity (protein by UV, stabilisers trehalose and Polysorbate 20), and tests for contaminants (bacterial endotoxins, sterility, visible and subvisible particulate matter). Integrity is tested.

Overall, the FP release and shelf-life specifications are considered acceptable.

Analytical methods

The following non-compendial methods are used for both release testing and stability testing of finished product and active substance: SEC-HPLC, IEC-HPLC, CE-SDS (reduced and non-reduced), protein concentration, biological assay, and relative binding assay. These methods and validation results are presented and assessed in the section on AS. The compendial methods have been tested in accordance with the applicable monographs.

As previously requested, validation reports have been submitted for assessment. The analytical methods have been adequately validated.

Batch analysis

Batch analysis data for BAT1706 FP have been provided. All the batches for both presentations compiled well with the acceptance criteria in the FP specification and demonstrate a satisfactory batch-to-batch consistency.

Characterisation of impurities

Potential process-related impurities and product-related impurities are sufficiently addressed in the section on characterisation of active substance. No new impurities have been observed in FP compared to the ones identified in AS. Furthermore, visible particles, subvisible particles and sterility are tested at the level of FP and are included in the FP specification.

A risk assessment and control strategy for elemental impurities in the finished product in accordance with ICH Q3D has been provided and the results therein are found acceptable. The risk of elemental impurities contamination in the finished product is low. No additional specific control is considered necessary.

Reports on risk assessments and control strategies for N-nitrosamine contamination in the BAT1706 finished product have been provided for assessment. According to the provided reports, the overall risk of N-nitrosamine contamination in BAT 1706 active substance and finished product is found low. No additional specific control is considered necessary.

Container closure system

The primary packaging has been acceptably described and includes specifications and schematic drawings. The vials and rubber stoppers are in compliance with the Ph. Eur. monographs for primary containers (Ph. Eur. 3.2.1) and closures (Ph. Eur. 3.2.9).

As stated in the manufacturing section, the vials, rubber stoppers and caps are sterilised during the manufacturing process.

The secondary packaging (cardboard boxes and cartons) is listed.

The information provided in this section is deemed sufficient and acceptable.

2.4.3.4. Stability of the product

The proposed shelf-life for BAT1706 finished product is 12 months when stored at the recommended storage condition of 2°C to 8°C.

Stability data has been provided for up to 30 months at 2°C to 8°C for the 100 mg/4 mL-presentation and up to 24 months at 2°C to 8°C for the 400 mg/16 mL-presentation.

In addition, stability data has been provided at accelerated (25 ± 2°C) and stressed conditions (40 ± 3°C or mechanical stress) as well as in-use stability testing.

All stability results for both presentations stored at 2°C to 8°C for up to 30 months for the 100 mg/4 ml-presentation and up to 24 months for 400 mg/16 mL-presentation comply with the end-of-shelf-life specification.

During the stability study performed for the presentation 100 mg/ 4 mL, an out-of-specification (OOS) occurred for one batch as regards visible particles at timepoint 30 months. Investigations into the OOS visible particles identified two types of particles, process-related and stability-related, and the uncertainty as regards the root-cause of occurrence of visible particles have now been solved. In addition, the applicant has proposed different corrective and preventive actions (CAPAs) to reduce the occurrence of visible particles in the finished product and these are acknowledged. However, to demonstrate the effectiveness of the CAPAs, data from additional batches manufactured after implementation of the corrective actions should be submitted after granting of the marketing authorisation. If despite the CAPAs, visible particles are still present in the finished product, an alternative to avoid visible particles should be considered. **(REC-1).**

Degradation pathways have been evaluated in forced degradation studies. The applied stress conditions included high temperature, light, and mechanical agitation. Based on these studies, it can be concluded that BAT1706 is sensitive to exposure to high temperatures (40°C ± 2°C), and light. Therefore, BAT1706 should be stored protected from light. Appropriate protection is afforded by the secondary packaging. This is in line with section 6.4 in the SmPC.

Freeze-thaw studies have been performed between -60°C and +25°C and for 5 repeated freeze-thaw cycles without any degradation observed.

In-use stability testing has been performed for diluted solutions of BAT1706 finished product in isotonic sodium chloride solutions. Chemical and physical in-use stability has been demonstrated for 30 days at 2°C to 8°C plus an additional 48 hours at 2°C to 30°C in sodium chloride 9 mg/mL (0.9%), in line with section 6.3 in the SmPC.

Post-approval stability protocol and stability commitment

The applicant commits to continue all the ongoing stability studies at long-term condition through the proposed shelf-life. In addition, one commercial batch for each presentation will be added annually to the on-going post-approval stability programme under real-time storage conditions at 2°C to 8°C.

Proposed shelf-life and storage conditions

The proposed shelf-life for the BAT1706 finished product is 12 months at the recommended storage condition of 2°C to 8°C for both the 100 mg/4 mL- and the 400 mg/16 mL-presentations, is acceptable.

2.4.3.5. Adventitious agents

No materials of animal and/or human origin are used in the manufacture of BAT1706 active substance, and it is stated that the process materials are in compliance with the "Note for Guidance" on minimizing the Risk of Transmitting Spongiform Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products EMA/410/01 current version. TSE/BSE certificates are provided, and it is agreed that the risk for presence/transmission of TSE is very low.

In accordance with ICH Q5D the cell substrates, MCB, WCB and EoPC used for manufacturing of BAT 1706 were assessed for sterility and mycoplasma. Compendial methods were used. Cell banks complied with the established acceptance criteria.

The applicant states that the viral testing of the MCB, WCB and EoPC is in compliance with ICH Q5A. However, a recommendation is raised for the applicant to provide reports for the testing of the new EoPC that was generated, and the dossier updated accordingly (**REC-2**).

Overall adventitious agents' safety is considered sufficiently assured.

2.4.3.6. GMO

Not applicable.

2.4.3.7. Biosimilarity

An analytical biosimilarity assessment is presented for the biosimilar candidate BAT1706. The analytical panel is found acceptable, evaluating relevant quality attributes. Several concerns related to the overall approach to assess biosimilarity identified in the initial submission are now considered solved, and analytical biosimilarity is found demonstrated.

The reference product is defined to be EU-approved Avastin. The BAT1706 finished product lots included in the analytical similarity assessment are presented. Comparability between the two presentations has been successfully demonstrated and the approach is found acceptable.

The analytical similarity acceptance criteria were established based on the criticality of the product quality attributes (tier groups), method capability and lot-to-lot variability of the RMP. Three tier groups were defined, where Tier 1 includes the most clinically relevant attributes, Tier 2 attributes not directly related to clinical presentation, quantitative properties of higher abundance and Tier 3 attributes of lower abundance, and the qualitative results of sample.

For product quality attributes placed in Tier 1, an equivalence test was used where the proposed biosimilar is considered equivalent to the RMP if the calculated 90% two-sided confidence interval of the mean of the proposed biosimilar product is within ±δ. The δ is based on the standard deviation of all the RMP lots tested and multiplied by 1.5. For Tier 2 attributes, the similarity acceptance criterion is that more than 90% of the biosimilar candidate lots must fall within RMP mean±3SD RMP. For Tier 3, the acceptance criteria are qualitative comparisons of e.g. chromatograms and gels.

The strategy to assign attribute criticality is sufficiently described. An extensive analytical panel is used for biosimilarity assessment of physiochemical properties and biological functions. In line with the guideline EMA/CHMP/BWP/247713/2012, it is demonstrated that the selected methods used in the biosimilar comparability exercise are capable of detecting slight differences in all aspects pertinent to the evaluation of quality (e.g. ability to detect relevant variants with high sensitivity). The validation status of the methods is confirmed, and corresponding validation reports or qualification summaries are provided.

Summary of the methods applied and results obtained

A summary of the attributes investigated, the analytical methods used for characterisation and the key findings of the biosimilarity evaluation is provided in Table 1. The results are further presented in the subsequent sections.

Table 1: Summary of the Analytical Biosimilarity Exercise

Molecular parameter	**Attribute**	**Methods for control and characterisation**	**Key findings**
Primary structure	Intact mass	ESI-TOF-MS	Match with the theoretical mass Intact mass highly similar
	Reduced and de-N-glycosylated (LC and HC)	ESI-qTOF-MS	The major peaks correspond to the expected theoretical masses of reduced and deglycosylated HC and LC. Masses highly similar
	Primary structure confirmation by reduced peptide mapping with trypsin and chymotrypsin	Reducing peptide mapping by UPLC-qTOF-MS (LC-MS/MS)	100% sequence coverage, identical
	pI value	cIEF	Similar charge distribution, no new peak observed. Same pI value for the main peak
	Extinction coefficients	Edelhoch method	Same extinction coefficient
Higher order structure	Disulphide bonds	Non Reduced Peptide mapping	Comparable mapping profile
	Free Thiols	Ellman method	Similar content
	Secondary Structure	FTIR spectroscopy	Similar FTIR spectra
	Tertiary and secondary structure	Near and far circular dichroism	Similar far and near UV-CD profiles
	Higher Order Structure	Intrinsic fluorescence	Similar intrinsic fluorescence spectra
	Thermal stability	Differential Scanning Calorimetry	Similar thermal stability (Tm)

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
	Protein Conformational Array	ELISA	Similar with regard to epitope exposure and higher order structure
Post-translational modifications	Charge variants	IEC-HPLC	Lower level of acidic variants and slightly higher level of basic variants in BAT1706 compared to EU-Avastin. No impact in clinical studies
	Oxidation/Deamidation/Aspartate isomerisation	Peptide mapping (LC-MS)	Similar levels of deamidation, oxidation, pyroglutamate(pE), Lys truncation
	Site of N-glycosylation	Peptide mapping	Identical site of N-glycosylation on N303
	Sialic Acids content	RP-HPLC-fluorescence labelling of DMB	Slightly higher sialic acids content for BAT1706; levels are very low; difference is not significant from clinical perspective
	Glycan map	HILIC-HPLC	Similar N-glycans identity and distribution, higher percentage of afucosylation, galactosylation, and sialylation; differences are not clinically meaningful Slight difference of the high mannose content (higher in BAT1706) but no impact observed in the comparative PK study
Purity	Size heterogeneity	SEC-HPLC	Similar profile, Same level of aggregates
	Size heterogeneity	nrCE-SDS and rCE-SDS	Similar profiles Non-reduced: The raw data for %main peak and pre-main peak in BAT1706 showed that just one lot of BAT1706 was outside of the EU-Avastin QR

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
			Reduced: slightly higher levels of HC+LC and lower levels of NGHC and LMW+MMW
	Hydrophobic purity	HIC-HPLC	Similar profiles
	RP-HPLC purity	RP-HPLC	Higher % main peak for BAT1706
	Subvisible particles	Light obscuration	Higher count of subvisible particles except for the ≥25 µm ones
	Subvisible particles	Flowcam	Higher count of spherical particles ≥ 5 µm
	Submicron (≤1µm) size particles	DLS	Similar submicron size particle distribution
	Mass determination of aggregates	SEC-MALS	Similar profiles. The polymer peak mass is lower for BAT1706
General properties	pH value	Compendial method	Highly similar
	Protein concentration	UV 280 nm	Higher protein concentration
	Osmolality	Compendial method	Highly similar
	Extractable volume	Compendial method	Lower volume for BAT1706
	Trehalose content	HPLC-CAD	Highly similar
	Polysorbate 20 content	HPLC-FLR	Highly similar
Process-related impurities	Residual HCP	Sandwich ELISA	Higher level of HCP
	Protein A	ELISA	Higher level of protein A
	Residual DNA	qPCR	Highly similar
Biological activity (Fab region)	Binding to VEGF-A_{165}	ELISA	Highly similar relative binding
	Binding to VEGF-A_{165}	SPR	Highly similar relative affinity and KD

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
	Binding to VEGF-A_{121}	ELISA	Highly similar relative binding
	Binding to VEGF-A_{121}	SPR	Highly similar relative affinity and KD
	VEGF-A neutralisation	NFAT-*luc* reporter gene assay	Similar relative potency
	Antiproliferation bioassay	HUVEC assay	Similar relative potency
	Inhibition of VEGFR-2 RTK Autophosphorylation	Electrochemical luminescence immunoassay	Similar dose dependent decrease in the amount of VEGFR-2 phosphorylation. Similar inhibitory activity of VEGFR-2 RTK autophosphorylation
	VEGF B, C and D variants and PlGF	SPR	Absence of binding for both BAT1706 and Avastin for VEGF-B, VEGF-C, VEGF-D. extremely weak binding to PIGF (No data provided in the dossier)
Biological activity (Fc region)	ADCC and CDC activity	ADCC and CDC bioassays using 3 different cell lines (DLD-1, Calu-6 and SKOV-3)	No ADCC and CDC activity (No data provided in the dossier)
	Binding to C1q	BLI	Highly similar binding affinity
	Binding to FcγRIa	SPR	Highly similar binding affinity
	Binding to FcγRIIa (131H/R)	BLI	Highly similar binding affinity
	Binding to FcγRIIb	BLI	Highly similar binding affinity
	Binding to FcγRIIIa 158V	SPR	Differences in relative binding (lower for BAT1706); minor differences not clinically meaningful

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
	Binding to FcγRIIIa 158F	SPR	Highly similar binding affinity
	Binding to FcγRIIIb	BLI	Highly similar binding affinity
	Binding to FcRn	BLI	Highly similar binding affinity

Primary structure including glycosylation pattern

The primary structure was evaluated. Analysis of finished product samples confirmed that the predominant species of BAT1706 are similar to those of EU-Avastin and US-Avastin.

The applicant concludes that the same modifications and sites were observed for both BAT1706 and EU- and US-Avastin, and that the levels were similar.

Higher order structure

The secondary structure of BAT1706 was demonstrated to be similar to EU- and US-Avastin. Tertiary structure was demonstrated to be similar. Furthermore, the stability profile was demonstrated to be similar.

A further investigation demonstrates that BAT1706, EU- and US-Avastin were similar with respect to epitope exposure and higher order structure.

Particles, Aggregates, Purity and Product Related substances

The levels of subvisible particles and aggregates were evaluated by appropriate methods. The levels were found to be acceptably low and comparable between BAT1706 and the RMP.

Several analytical tests have been applied to compare batches of BAT1706 and EU-Avastin for their purity and product-related substances.

Purity analysis supported the biosimilarity claim with respect to hydrophobic purity and polarity, respectively.

General properties and process-related impurities

A few general properties were investigated with respect to biosimilarity.

Furthermore, process-related impurities were assessed.

The levels and content of host cell proteins were evaluated.

Biological and functional biosimilarity

Several analytical tests have been applied to compare batches of BAT1706, EU-Avastin, US-Avastin and CN-Avastin for their Fab-related biological activity. This is found acceptable.

Biosimilarity with respect to neutralizing activity to VEGF-A was evaluated. The results confirm that the neutralising activity is similar. Inhibition of VEGFR-2 RTK autophosphorylation was also demonstrated to be similar between BAT1706, EU-, US- and CN- Avastin.

Binding specificity was investigated. It was demonstrated that BAT1706, EU-, US- and CN-Avastin specifically binds to VEGF-A, but fails to bind VEGF-B, - C and -D and shows very weak binding to PIGF.

Several analytical tests have been applied to compare BAT1706, EU-Avastin, US-Avastin and CN-Avastin with respect to Fc-related bio-functional properties. Binding towards C1q, FcRn, FcγRIa, FcγRIIa(131H), FcγRIIa(131R), FcγRIIb, FcγRIIIa(158V), FcγRIIIa(158F) and FcγRIIIb was evaluated.

As compared to EU-Avastin, biosimilarity was demonstrated for all but one of the receptors, FcγRIIIa(158V). It is agreed that the binding affinities are on the same level, and that these differences are not considered to preclude biosimilarity.

ADCC and CDC effector function of BAT1706, EU and US-Avastin were evaluated. Lack of ADCC and CDC was demonstrated for all products. This is found acceptable and in line with prior knowledge on Bevacizumab.

Comparative Stability Study

A comparative stability study was included as part of the analytical similarity assessment. Overall, BAT1706 and Avastin share the same degradation profiles and pathways under the conditions applied.

Overall, the results obtained in the stability study support the biosimilarity claim.

Overall, the biosimilarity with EU-Avastin is considered demonstrated.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and finished product has been presented in a satisfactory way. The presented documentation indicates that the active substance and finished product is manufactured in a well-controlled and validated process.

The applicant has analysed the biosimilarity between BAT1706 and Avastin in an extensive comparability exercise. The analytical biosimilarity assessment has been performed with a combination of methods assessing the primary and higher order structures, particles and aggregates, purity and product-related substances, process-related impurities, post-translational modifications including charge variants and glycosylation profile assessments, and biological activity including Fab and Fc-related functions as well as comparative stability testing. From the obtained results, BAT1706 is considered to be similar to EU approved Avastin at the quality level. Some minor differences are noted, for instance, in the N-glycans profile, charged forms and purity. The applicant sufficiently justifies the differences and give arguments related to bevacizumab mode of action and information in the literature as well as *in vitro* data generated that no impact is expected and that these differences are not clinically meaningful.

From the quality perspective, the marketing authorisation application for Avzivi is approvable as a biosimilar to EU-Avastin.

2.4.5. 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.

The CHMP has identified Recommendations (see below).

2.4.6. Recommendation(s) for future quality development

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

Area	Number	Description	Classification
Quality	1	The applicant is recommended to submit data from additional batches manufactured after implementation of the CAPAs to provide assurance regarding visible particles in the finished product. If, despite the CAPAs, visible particles are still present in the finished product, an alternative to avoid visible particles should be considered.	REC
Quality	2	The applicant is recommended to provide the reports on the new studies for virus safety.	REC

2.5. Non-clinical aspects

2.5.1. Pharmacology

***In vitro* studies**

In vitro primary pharmacodynamic studies comparing biological activity and specific binding were conducted as a part of the analytical similarity studies.

Comparability of BAT1706 and Avastin was demonstrated in *in vitro* studies that measured the binding ability of BAT1706 and Avastin to VEGF-A. BAT1706 and Avastin exhibited specific binding with VEGF-A121 and VEGF-A165. The biological activity of BAT1706 and Avastin were compared *in vitro* by measuring the effect on cell growth in human umbilical vein endothelial cells (HUVEC). The details of *in vitro* pharmacodynamic studies are provided in Module 3.

***In vivo* studies**

In vivo pharmacodynamic studies were conducted to determine the effect of BAT1706 and Avastin on tumour growth in mice xenograft models of human NSCLC, ovarian cancer, and rhabdomyosarcoma. These models were selected as VEGF is highly expressed in all these 3 models. The *in vivo* comparative pharmacodynamic studies were conducted using Avastin sourced from China.

Tumour cells were subcutaneously inoculated in mice and allowed to grow to size ranging from 126 to 131 mm3 followed by treatment with test or reference products via tail vein twice/thrice weekly for 2 to 3 weeks. Doses of 0.5 and 5 mg/kg were used in NSCLC and rhabdomyosarcoma models while doses of 1 and 10 mg/kg were used in the ovarian cancer model. Efficacy was measured by tumour weight, tumour volume, and tumour growth inhibition (TGI). Tumour latency was also observed, but not assessed for statistical significance.

BAT1706 and Avastin showed dose-dependent efficacy in these models. Higher IV doses (5 mg/kg in NSCLC and rhabdomyosarcoma and 10 mg/kg in ovarian cancer) were found to be effective (≥60% TGI) in all three tumour models. The pharmacodynamic effects of BAT1706 and Avastin were similar, and the tumour growth curves showed a high degree of coincidence, except for the 0.5 mg/kg dose in the rhabdomyosarcoma model where variable results were seen in the two studies conducted using this model.

2.5.2. Pharmacokinetics

A comparative evaluation of the pharmacokinetic profiles of BAT1706 and Avastin has been conducted in cynomolgus monkeys. Four groups of cynomolgus monkey (n= 5/sex/group), were respectively given a single IV injection at three dose levels: low (2 mg/kg), intermediate (4 mg/kg) and high (8 mg/kg) of BAT1706 and 4 mg/kg of Avastin. No differences in pharmacokinetic parameters were observed.

2.5.3. Toxicology

A comparative repeat-dose, 3-month IV study with 1-month recovery was performed in cynomolgus monkey to compare the toxicity profile of BAT1706 versus Avastin. The test and reference products were administered twice weekly with BAT1706 doses of 2, 10 and 50 mg/kg and Avastin doses of 50 mg/kg. The irritation potential of BAT1706 was also tested as part of the acute and repeat-dose toxicity studies. The repeat-dose toxicity study also included comparative assessment of immunogenicity and immunotoxicity. Toxicokinetics was also evaluated in a 3-month study but was non-comparative. Results of the repeat-dose study showed that toxicity profile, immunogenicity and local irritant effects of BAT1706 and Avastin were comparable. The effects of BAT1706 and Avastin on *in vitro* haemolysis and red blood cell agglutination in rabbit were investigated and both were found to be compatible without any haemolytic effects. Tissue cross-reactivity of BAT1706 and Avastin with normal adult human and cynomolgus monkey tissues were found to be negative for immunogenic cross-reactivity.

2.5.4. Ecotoxicity/environmental risk assessment

Bevacizumab is a monoclonal antibody and is consequently classified as a protein. According to th Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment.

2.5.5. Discussion on non-clinical aspects

Pharmacology

For a biosimilar product, evaluation of nonclinical pharmacology is not warranted.

A number of *in vitro* biological assays have been performed as part of the biosimilarity exercise, and these are presented in Module 3 of the dossier. The results of these assays and the assessment of the biosimilarity claim are presented in the quality part of the report.

The applicant has performed *in vivo* studies in mouse xenograft tumour models. No difference was seen when comparing BAT1706 and Avastin sourced from China in these models. These data are not considered to add support to the biosimilarity evaluation. These nonclinical pharmacology models are not considered sufficiently sensitivity for this purpose.

Pharmacokinetics

For a biosimilar product, evaluation of nonclinical pharmacokinetics is not warranted. Comparative pharmacokinetics in cynomolgus monkeys has been performed. While no differences were observed, these data are not considered supportive of the biosimilarity evaluation.

Toxicology

In vivo studies of toxicity are not considered necessary to substantiate a claim of biosimilarity. This is in accordance with the guidance contained in Guideline on similar biological medicinal products containing monoclonal antibodies–nonclinical and clinical issues EMA/CHMP/BMWP/403543/2010, which states that *in vivo* toxicity studies are generally not required to support marketing authorisation of such products.

In order to fulfil regulatory requirements in other regions, a comparative repeat dose toxicity study, including TK analysis, was conducted in cynomolgus monkeys. The study was performed in a facility not compliant with OECD GLP. Since *in vivo* toxicity studies are not pivotal for the biosimilarity evaluation, this deficiency has no further consequences.

2.5.6. Conclusion on the non-clinical aspects

In vitro pharmacodynamic and analytical similarity studies establishing comparability between BAT1706 and EU-approved Avastin are available. *In vivo* nonclinical studies showed no difference in the pharmacodynamic, pharmacokinetic and toxicological effects of BAT1706 compared to the EU/China-sourced Avastin.

2.6. Clinical aspects

2.6.1. 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 2: Reports of Clinical Studies

Study No. study centers Location	Report location (Module)	Study status Study period	Design	Objectives	Treatment regimen	Main inclusion criteria	Enrolled / completed
BAT1706-001-CR 1 New Zealand	5.3.3.1	Completed 15Mar2016-14Nov2016[a]	Phase I, randomized, double-blind, single-dose, 3-arm parallel design study	PK, safety, tolerability and immunogenicity,	1 mg/kg as a single 90-minute infusion: • BAT1706 • EU-Avastin • US-Avastin	Healthy adult male subjects	128 / 122
BAT1706-002-CR 1 China	5.3.3.1	Completed 17Aug2016-06Feb2017	Phase I randomized, double-blind, single-dose, 2 parallel group study	PK, safety, tolerability and immunogenicity	1 mg/kg as a single 90-minute infusion: • BAT1706 • EU-Avastin	Healthy adult male subjects	82 / 79
BAT1706-003-CR 86 China, Turkey, Ukraine, South Africa, and Mexico	5.3.5.1	Completed 11Dec2017- Primary data cut [a]: 05Nov2019	Phase III, randomized, double blind, multicenter, active comparator, parallel 2-arm study	Efficacy, safety, immunogenicity, PK	15 mg/kg as a 60 or 90-minute infusion: • BAT1706 + C/P • EU-Avastin + C/P Dosing was every 3 weeks for up to 6 cycles of combination therapy, followed by maintenance therapy every 3 weeks with test drug up to 12 months.	Patients with previously untreated advanced nsNSCLC	651 / 218

C/P = carboplatin and paclitaxel; EU = European Union; nsNSCLC = non-squamous non-small cell lung cancer; PK = pharmacokinetic(s); US = United States

(a) Treatment ongoing at the time of the primary data cut. The data cut for the primary CSR in support of this submission = last patient enrolled evaluated at Week 18 and where there are safety and immunogenicity data for 1 year from enrollment for at least one-third of the study population enrolled.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical development programme comprised of two Phase I studies (BAT1706-001-CR and BAT1706-002-CR) and one Phase III study (BAT1706-003-CR).

The pivotal Phase I study BAT1706-001-CR in healthy male subjects was carried out in New Zealand to establish the pharmacokinetic (PK) equivalence of BAT1706 bevacizumab to the marketed Avastin bevacizumab (EU-sourced Avastin ["EU-Avastin"] and US-sourced Avastin ["US-Avastin"]).

In addition, a Phase I study BAT1706-002-CR was carried out in China to confirm PK equivalence of BAT1706 to EU-Avastin.

These were single dose studies. The dose selected for these studies was 1.0 mg/kg, which is at the lower end of the linear range (bevacizumab PK is linear in the 1.0 to 10 mg/kg dose range). As these studies were conducted in healthy subjects, the lowest dose that provided sufficient PK data for a scientifically valid comparison was selected. The 1.0 mg/kg dose is one 15^{th} of the dose used for the clinical treatment of nonsquamous nonsmall cell lung cancer (nsNSCLC), and one-fifth of the dose for metastatic colorectal cancer, which minimised the potential harm caused by the study drug to healthy subjects.

In the Phase III study BAT1706-003-CR, PK analyses were planned for a subgroup of approximately 200 patients from samples collected only at designated sites in China, Turkey, and Ukraine. Trough bevacizumab concentrations were measured at the end of each cycle of treatment with BAT1706 and EU-Avastin in patients with previously untreated advanced nsNSCLC. Blood samples for anti-drug antibody (ADA) tests were collected for all patients at similar time points to the PK blood sampling.

Analytical Methods

Bioanalysis

The quantification of bevacizumab in human serum samples was performed using a validated ELISA.

Each clinical study had its own method. Method ALM-200 was applied in the Phase I PK study BAT1706-001-CR; Method 16BASM162V3 was applied in the Phase I PK study BAT1706-002-CR and Method ICSH 18-022 was applied in the Phase III study BAT1706-003-CR.

The methods were based on the binding of bevacizumab to the capture antigen biotinylated human VEGF165. Bound bevacizumab was detected with an anti-human IgG (Fc specific)-peroxidase antibody produced in goat. Following addition of a chromogenic substrate and spectrophotometric measurement of the reaction product generated. The colour intensity was directly proportional to bevacizumab quantity.

Immunogenicity

A multitiered strategy (screening, confirmation, titer, neutralisation) was applied. Each clinical study had its own assays, as detailed below.

Method 16BASM161V3 (WuXi) for antidrug antibodies (ADA) was used for samples from the Phase I study BAT1706-001-CR. ADA in samples was extracted with BAT1706-coupled CNBr-activated sepharose. Then the extracted ADAs were tested in the bridge assay format (biotinylated BAT1706 and ruthenylated BAT1706) with the MSD platform. Additionally, anti-VEGF was added in the extraction step and in the bridging step to inhibit VEGF present in the samples. Excess BAT1706 was added in the

bridging step to inhibit the signal in the confirmatory assay. A full validation was performed, with all parameters falling within acceptance criteria.

ADA method ICSH 18-047 (Covance) was used for samples from the Phase III study BAT1706-003-CR (VR 8370-436, study report 8370-439). Samples were acidified at ambient temperature and then neutralised and captured by BAT1706 coated on an ELISA plate in the presence of VEGFR to bind endogenous VEGF. After incubation and subsequent elution by acid treatment, ADAs were allowed to coat a second plate, which was later incubated with Ruthenium-BATl706/EU-Avastin and VEGFR to avoid false positive signals from binding to endogenous VEGF. Unbound material was washed away before detection via chemiluminescence. The confirmation assay was based on use of excess un-labelled drug in a competitive binding format to demonstrate the specificity of the binding interactions in the antibody-labelled drug complex. A full validation was performed, including interchangeability of reagents to support the use of the single assay format using labelled BAT1706 for ADA against both BAT706 and EU Avastin.

An in-study cut point analysis was performed with 30 pre-dose individual samples. Both a Levene test for equality of variance (p 0.3324) and an ANOVA test for equality of means (p 0.405) showed a lack of statistical difference between the normal and the patient population. Thus, the cut-point from the validation was used also in the study.

The neutralizing ADA (nAb) Assay (Method ICSH 18-048, Covance) was used for samples from the Phase III study BAT1706-003-CR (VR, 8370-438, study report 8370-439). The method was identical to the ADA method ICSH 18-047 up to the elution step by acid treatment. Supernatant were then incubated with Sulfo Tag labelled BAT1706 to allow to form nAb and Sulfo-Tag labelled BAT1706/EU-Avastin complexes. After incubation. the antibody complex was added to a streptavidin coated plate which has been pre-coated with VEGF. Sulfo-Tag labelled BAT1706/EU-Avastin would bind to the VEGF coated plate which was not bound to neutralised antibody complex. The plate was then washed before readout by chemiluminescence. The luminescence signal was indirectly proportional to the concentration of nAbs present in serum. A full validation was performed, including interchangeability of reagents to support the use of the single assay format using labelled BAT1706 for ADA against both BAT706 and EU Avastin. No interference by VEGF up to 500 ng/mL was demonstrated, but the assay tolerates only 150 µg/mL bevacizumab at positive control levels ≥ 2000 ng/mL, and 300 µg/mL bevacizumab at positive control levels ≥ 4000 ng/mL

Study BAT-1706-001-CR

Study Title: Randomized, Double-blind, Single-dose, 3-arm Parallel Design Comparative Pharmacokinetic and Safety Phase I Study of BAT1706 versus EU-sourced Avastin and US-sourced Avastin Administered in Healthy Subjects.

Study Design: This study was a Phase I, randomised, double-blind, single-dose, 3-arm parallel group study to compare the PK and to evaluate the safety, tolerability and immunogenicity of BAT1706, EU-Avastin and US-Avastin after a single IV infusion in healthy adult male subjects.

A total of 129 healthy male subjects who met the required entry criteria were planned to be randomly assigned to one of 3 treatment groups in a 1:1:1 ratio to receive a single IV infusion of BAT1706, EU-Avastin or US-Avastin. Of the 128 subjects randomised subjects, 122 subjects completed the study. Of the 6 subjects who discontinued, 5 subjects withdrew consent and 1 subject was discontinued.

Subjects received a single dose of 1 mg/kg administered as a 90-minute infusion.

Subjects were admitted to the study centre on Day -1 (i.e. the day prior to dosing) and were discharged on Day 3. Thereafter, subjects attended the study centre on an outpatient basis on Days 5, 8, 11, 15, 22, 29, 36, 43, 57, 71, 85 and 99.

PK blood samples were collected at pre-infusion (within 1 hour prior to the start of infusion or 0 hour), 0.75 hours from the start of infusion, the end of infusion (1.5 hours from the start of infusion), at 1, 2, 4, 8, 12 hours from the end of infusion, and at 24 (Day 2), 48 (Day 3), 96 (Day 5), 168 (Day 8), 240 (Day 11), 336 (Day 15), 504 (Day 22), 672 (Day 29), 840 (Day 36), 1008 (Day 43), 1344 (Day 57), 1680 (Day 71), 2016 (Day 85), and 2352 hours (Day 99) from the start of infusion.

The measurement of the serum concentrations of bevacizumab was performed using a validated immune-assay method.

Subjects were tested for ADA, and ADA-positive samples were analysed for NADA.

Anti-bevacizumab antibodies, neutralizing antibodies and anti-VEGF antibodies were tested at screening, at pre-dose on Day 1, on Day 15, Day 43, Day 71 and follow-up (Day 99). Subjects confirmed positive for anti-bevacizumab antibodies were followed for 12 months after study drug administration or until 2 consecutive samples were negative for ADA. Blood samples were collected at 6, 9 and 12 months post dose.

Studied Population: All the subjects enrolled in the study were male. The mean age of study subjects was 24.6 years and ranged from 18 to 48 years. Mean age, weight and BMI were similar between BAT1706 group and the Avastin groups.

Results:

There were 14 subjects who had quantifiable pre-dose concentrations of bevacizumab. One subject had pre-dose concentration which was >5% of C_{max} and was excluded from the PK analysis.

A summary of key PK parameters for all 3 products (BAT1706, EU-Avastin and US-Avastin) is presented in the below Table.

Table 3. Summary of Geometric Mean (Geometric CV%) Pharmacokinetic Parameters (Pharmacokinetic Analysis Population)

Parameter (unit)	BAT1706 (n = 39)	EU-Avastin (n = 43)	US-Avastin (n = 42)
$AUC_{0\text{-}inf}$ (µg·h/mL)	7330 (15.9)	6970 (16.6)	7120 (19.5)
$AUC_{0\text{-}t}$ (µg·h/mL)	7180 (14.9)	6850 (16.3)	6980 (19.0)
C_{max} (µg/mL)	22.1 (15.1)	22.3 (15.7)	22.2 (16.2)
t_{max} (h)	2.50 (1.50, 9.50)	1.50 (1.50, 24.00)	1.50 (1.50, 9.50)
$t_{1/2}$ (h)	389 (30.2)	358 (27.8)	384 (24.7)
CL (L/h)	0.0106 (16.2)	0.0110 (17.3)	0.0107 (18.3)
V_Z (L)	5.97 (24.4)	5.67 (22.9)	5.94 (19.9)
V_{ss} (L)	5.92 (15.0)	5.80 (15.3)	5.79 (14.4)

Source: Table 2.2

Note: t_{max} is presented as median (minimum, maximum); EU-Avastin = EU-sourced Avastin; US-Avastin = US-sourced Avastin.

The 90% confidence interval (CI) for the ratios of the geometric means of the primary ($AUC_{0\text{-}inf}$) and secondary PK parameters ($AUC_{0\text{-}t}$ and C_{max}) met the predefined acceptance criteria (80.00% to 125.00%) for PK equivalence for all 3 pairwise comparisons.

Table 4. Statistical Comparison of Key Pharmacokinetic Parameters (Pharmacokinetic Analysis Set)

					Pairwise Comparison		
Parameter (units)	**Treatment**	**n**	**Geometric LS Means**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
Primary							
AUC_{0-inf} (h*µg/mL)	BAT1706	39	7329	(6938, 7742)	BAT1706 / EU-Avastin	105.13	(98.64, 112.05)
	EU-Avastin	42	6971	(6613, 7350)	BAT1706 / US-Avastin	102.91	(96.56, 109.69)
	US-Avastin	42	7122	(6755, 7508)	EU-Avastin /US-Avastin	97.89	(91.95, 104.21)
Secondary							
AUC_{0-t} (h*µg/mL)	BAT1706	37	7180	(6798, 7584)	BAT1706 / EU-Avastin	104.77	(98.32, 111.64)
	EU-Avastin	40	6853	(6502, 7223)	BAT1706 / US-Avastin	102.90	(96.63, 109.56)
	US-Avastin	42	6978	(6629, 7346)	EU-Avastin / US-Avastin	98.21	(92.35, 104.44)
C_{max} (µg/mL)	BAT1706	39	22.09	(21.03, 23.21)	BAT1706 / EU-Avastin	99.07	(93.57, 104.90)
	EU-Avastin	43	22.30	(21.28, 23.38)	BAT1706 / US-Avastin	99.71	(94.14, 105.61)
	US-Avastin	42	22.16	(21.13, 23.24)	EU-Avastin /US-Avastin	100.64	(95.16, 106.45)

Source: Table 2.3

Note(s): CI = confidence interval; LS = least-squares; EU-Avastin = EU-sourced Avastin; US-Avastin = US-sourced Avastin.

Immunogenicity Summary:

All subjects in all 3 treatment groups were negative for anti-bevacizumab antibodies at all study visits and negative for anti-VEGF antibodies at baseline.

One subject (Subject 001001) did not provide a baseline sample for anti-VEGF antibody testing.

Study BAT-1706-002-CR

Study Title: A Randomized, Double-blind, Single-dose, Two Parallel Groups Study to Compare the Pharmacokinetics and Safety of BAT 1 706 Injection with Bevacizumab (European Product) in Healthy Subjects.

PK blood samples and ADA samples were collected up to 2352 h (Day 99) after the administration of the study drugs. Subjects were tested for anti-vascular endothelial growth factor (VEGF) antibody during the screening period.

Studied Population: A total of 82 adult healthy male subjects aged 18-45 years were enrolled. Of the 82 randomised subjects, 2 subjects who were assigned to the BAT1706 group withdrew from the study before the administration. Mean age, weight and BMI were similar between BAT1706 injection group and Bevacizumab group.

Results:

The pharmacokinetic parameters are summarised in the below Table.

Table 5. Pharmacokinetic Parameters

PK Parameters	BAT1706 Injection Group (N = 39)	Bevacizumab Group (N = 40)
AUC_{0-inf} (h*ng/mL)	6127083.616 ± 1070221.9516	6066172.773 ± 1352673.1899
AUC_{0-t} (h*ng/mL)	6058563.248 ± 1060900.4595	5984408.466 ± 1303258.7911
C_{max} (ng/mL)	21513.8 ± 3415.32	20657.9 ± 3993.57
T_{max} (h)	2.963 ± 0.9126	4.514 ± 10.9767
$T_{1/2}$ (h)	318.271 ± 48.4126	315.738 ± 47.1809
V_z (mL)	5016.865 ± 767.4851	5218.975 ± 738.5503
V_{ss} (mL)	4993.703 ± 612.0443	5366.820 ± 633.8293
CL (mL/h)	11.092 ± 1.9617	11.624 ± 1.9633

The GMR and 90% CI of the PK parameters (AUC_{0-inf}, AUC_{0-t} and C_{max}) were in the acceptable equivalent range (0.8 to 1.25), indicating that BAT1706 was equivalent to Bevacizumab. There was no statistically significant difference in T_{max} between the two groups.

Table 6. Geometric Mean and Geometric Mean Ratio

	Geometric Mean			
PK Parameters	BAT1706 Injection Group (N = 39)	Bevacizumab Group (N = 40)	GMR (BAT1706/Bevacizumab)	90% CI
AUC_{0-inf} (h*ng/mL)	6038153.343	5942484.190	1.016	0.947-1.090
AUC_{0-t} (h*ng/mL)	5970102.473	5865794.141	1.018	0.949-1.091
C_{max} (ng/mL)	21250.704	20194.998	1.052	0.976-1.134

During the study period, no subjects developed positive ADA in the two groups.

Study BAT-1706-003-CR

Title of Study: A Multicenter, Randomized, Double-blind, Phase III Study of BAT1706 versus EU-Avastin plus Chemotherapy in Patients with Advanced Non-squamous Non-Small Cell Lung Cancer.

Number of Patients: Approximately 632 patients were planned to be enrolled including a subgroup of 200 patients for PK. A total of 218 (33.5%) patients were included in the PK population.

Pharmacokinetic Results:

Bevacizumab PK parameters summarised by cycle and treatment are presented below. Geometric mean bevacizumab exposure parameters AUC_{0-t} and C_{max}, and median t_{max} were similar across treatments for both Cycle 1 and Cycle 6.

Table 7. Pharmacokinetic Parameter Summary (PK Population)

	Cycle 1		Cycle 6	
Parameter/Statistic	**BAT1706**	**EU-Avastin**	**BAT1706**	**EU-Avastin**
AUC_{0-t} (µg*h/mL)				
n	102	93	82	55
Geometric Mean	56340	56510	98940	112400
Geometric CV%	23.7	28.4	27.5	26.8
C_{max} (µg/mL)				
n	108	106	89	66
Geometric Mean	293.0	285.2	409.4	436.3
Geometric CV%	27.8	28.2	22.7	18.6
t_{max} (h)				
n	108	106	89	66
Median	1.75	1.74	1.23	1.22
Minimum, Maximum	1.25, 474.32	1.02, 597.65	0.00, 98.95	0.55, 597.55

Source: Table 14.4.2.1

Abbreviations: AUC_{0-t} = area under the concentration-time curve from 0 hour to time of the last quantifiable concentration; C_{max} = maximum serum concentration; CV = coefficient of variation; t_{max} = time of C_{max}.

Immunogenicity:

The incidence rates of positive ADA results were similar in the 2 treatment arms. Twelve [3.7%] patients in the BAT1706 group and 10 [3.1%] patients in the EU-Avastin group had negative ADA results at baseline and positive ADA results at a postbaseline visit. The overall incidence rates of positive ADA results at each visit were low (≤ 5%) and did not increase over time and were similar between treatment groups.

No patient had a positive NADA result detected during the study.

Bevacizumab systemic exposure was similar when stratified by positive or negative ADA for both the BAT1706 and EU-Avastin groups.

2.6.2.2. Pharmacodynamics

No pharmacodynamic data has been submitted as part of this application. This is acceptable.

2.6.3. Discussion on clinical pharmacology

Analytical methods

Bioanalysis

The quantification of bevacizumab in human serum samples was performed using a validated ELISA.

Method ALM-200:

Method ALM-200 was applied in the Phase I PK study BAT1706-001-C. Sufficient selectivity could not be demonstrated at LLOQ. The lowest level with acceptable selectivity was 300 ng/mL.

Interference by VEGF was not investigated in the validation of the analytical method for bevacizumab. The level of VEGF in healthy subjects is low and no relevant interference with bevacizumab is presumed.

Parallelism was demonstrated for method ALM-200.

For the pivotal Phase I pharmacokinetic study BAT1706-001-CR two observations were identified by FDA in May 2021 with regards to selectivity experiment and cross-validation comparability study in method validation VAL200. Further details about the observations and the additional experiments and analyses performed regarding selectivity and potential bias of the assay have been presented. Method ALM-200 is acceptable for the quantification of BAT1706 and Avastin in human serum of healthy subjects.

Method ICSH 18-022:

Method ICSH 18-022 was applied in the Phase III study BAT1706-003-CR.

For method ICSH 18-022, four out of six samples failed to demonstrate parallelism and were reanalysed and then eight out of nine samples met the predefined acceptance for parallelism. Parallelism data is not considered reliable for method ISCH 18-022. It cannot be concluded that study samples behave in the same way as validation samples. However, since method ICSH 18-022 was only applied in the Phase III study BAT1706-003-CR and PK data from this study are not considered pivotal, this issue was not further pursued.

An update on the ongoing long-term stability study for both methods has been provided, and the available stability data cover the actual storage period and conditions of study samples prior to analysis.

In-study quality control samples seem to have been prepared in normal human serum from healthy subjects although it would have been more appropriate to use a disease-state matrix to better simulate matrix of study samples (patients of Phase III study).

Selectivity, accuracy and precision of the assay should have been validated using QC samples prepared in disease-state serum as well. Although the first selectivity run failed for Avastin on both levels, LLOQ and ULOQ, repeated run showed that Avastin can be measured reliably in disease-state matrix too. Selectivity test for BAT1706 passed well at both concentration levels. ISR results indicate that assay worked reliably while analysing samples of patients.

Although some effect of ADAs (especially of their high levels) on the recovery of a drug (especially at low levels) is assumed, it is agreed that the incidence of ADA in study BAT1706-003-CR was very low that it there was no merit doing the test for potential ADA interference impact. Furthermore, drug concentration data of the study BAT1706-003-CR were analysed following stratification by cycle and antibody status (positive or negative). There was no discernible difference comparing antibody-positive and antibody-negative subjects.

Numerous batches of BAT1706 and Avastin were used in the study BAT1706-003-CR. This would have required a verification of the analytical performance of the methods to ensure that the performance was not altered compared with the original or previous batch. No verification of the performance of the method was performed, yet since method ICSH 18-022 was only applied in the Phase III study BAT1706-003-CR and PK data from the study is not considered pivotal, this issue is not further pursued.

Immunogenicity

Different positive controls were used in the different ADA methods, and no cross-validation has been performed. Although it would have been preferable to cross-validate the methods, this is acceptable in view of the fact that the data from study BAT1706-003-CR with multiple dosing to the patient population is considered most relevant for the investigation of immunogenicity. Additionally, no ADAs were detected in study BAT1706-001-CR. The interchangeability of mastermix between BAT1706 and EU Avastin (to support for the single assay format) has been investigated only for the ADA and nAb methods used for study BAT1706-003-CR. This is accepted on similar grounds.

The WuXi method 16BASM161V3, used for samples from study BAT1706-002-CR is considered adequately validated, with sufficient drug and target tolerance. Method 16BASMI61V2, used in study BAT1706-002-CR, was poorly described. From the available information, no differences to the 16BASM161V3 method could be identified, suggesting the method may also be adequate. No concerns were raised since study BAT1706-002-CR is not pivotal for this application.

In the ADA method ICSH-18-047, used in study BAT1706-003-CR, the target and drug tolerance (300 µg/mL BAT1706 at 100 ng/mL positive control) were adequate. The cut point was established in the validation study using 54 pre-dose samples from the clinical study. Hence, it is agreed that the cut point established in the assay validation is suitable for sample analysis.

The nAb method (ICSH 18-048) has insufficient drug tolerance. Only very high nAb levels are detected (from 2000 ng/mL) in presence of 150 µg/mL bevacizumab, which is approximately the concentration reached at C_{trough}. No study sample was nAb positive. This is considered to be a consequence of the poor drug tolerance. Thus, potentially nAb positive samples may have been missed. Nevertheless, only 3.7% of patients had treatment emergency ADA, indicating an overall low immunogenicity in line with data from the reference product. The lack of a sensitive nAb method may be acceptable.

Studies

Pharmacokinetic data were obtained from two Phase I single-dose parallel group studies in healthy volunteers comparing BAT1706 with the reference product (Avastin) at a dose of 1 mg/kg as a 90-minute infusion.

Considering the long half-life of bevacizumab, the proposed parallel-group study design applied in the Phase I studies is acceptable and in line with the recommendations as outlined in the Guideline "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010).

A single dose of 1 mg/kg bevacizumab is acceptable since the pharmacokinetics of bevacizumab is linear from 1-10 mg/kg and it could also be less toxic in healthy volunteers.

Assessment of PK in a single-dose study in healthy volunteers is expected to be the most sensitive setting possible to detect differences in PK between BAT1706 and Avastin. The use of healthy volunteers avoids factors that can confound the interpretation of PK, safety and tolerability results in patient studies, including varying tumour burden and complications arising from the disease state, comorbidities and concomitant therapies and medications.

For the purpose of investigating the pharmacokinetic properties of BAT1706 in comparison to the reference product Avastin, the study design of the Phase I studies is acceptable.

For $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} the 90% confidence interval for the ratio of the test and reference product fell within the conventional bioequivalence acceptance range of 80.00-125.00% when comparing BAT1706 to the reference product Avastin. The ratios were close to one for all three parameters in both studies.

Results from both studies BAT1706-001-CR (N=128) and BAT1706-002-CR (N=82) in healthy male subjects demonstrates that the PK of BAT1706 injection was equivalent to that of bevacizumab (Avastin).

Fourteen subjects in study BAT1706-001-CR had quantifiable pre-dose concentrations of bevacizumab most likely due to endogenous anti-VEGF antibodies being detected in the assay as clarified by the applicant. The analytical method was properly validated and selectivity, sensitivity are deemed adequate. The justification of pre-dose levels detected in the study is acceptable.

Two interim analyses (IAs) were performed in the study BAT-1706-001-CR (Data not shown). The first interim analysis contained data from 87/91 subjects, 3 were excluded due to database issues, and one due to higher pre-dose concentration. Second interim analysis was planned to be performed before the end of study when 39 evaluable subjects were available per treatment. After sample size re-estimation it was determined no additional subject enrolment was necessary. Thus, second interim analysis formally agrees with final analysis.

A small discrepancy between the expected number of subjects for individual treatments for the primary endpoint $AUC_{0\text{-}inf}$ (39 subjects for BAT1706, 42 subjects for EU-Avastin and 42 subjects for US-Avastin) was noted, however, this discrepancy is small and number of subjects for each IA is described sufficiently.

Although, in general, blinded sample size reassessments in equivalence studies do not preserve the type one error, see for example Friede and Kieser (2003), in this case, the increase in type I error is however not expected to change the overall conclusions given the results of the sample size reassessment and the bioequivalence results.

A single dose study in healthy volunteers is generally recommended as target-mediated clearance may be less important than in patients. In case a PK study in healthy volunteers is conducted to support bioequivalence, supportive PK data from clinical studies in patients are encouraged and could provide highly supportive evidence of a similar PK behaviour. Additional pharmacokinetic data were obtained from the Phase III study BAT1706-003-CR in patients with advanced non-squamous non-small cell lung cancer (using EU reference product).

In the Phase III study BAT1706-003-CR, the geometric mean bevacizumab exposure parameters $AUC_{0\text{-}t}$ and C_{max},and median t_{max} were similar across treatments for both Cycle 1 and Cycle 6 which supports similar exposure in this patient population.

Immunogenicity

Both Phase I studies had no occurrence of ADAs, thus similarity of immunogenicity in healthy subjects given a single dose of BAT1706/EU Avastin can be concluded.

In patients, the incidence of ADA was similar and the effect of ADA on the PK of BAT1706 and EU-Avastin appears to be minimum, but it should be considered that the incidence of positive ADA was very low during the study. Overall, similarity of immunogenicity has been demonstrated.

2.6.4. Conclusions on clinical pharmacology

Similarity in pharmacokinetics and immunogenicity is considered sufficiently demonstrated between Avzivi (BAT1706) and the reference product EU-Avastin.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

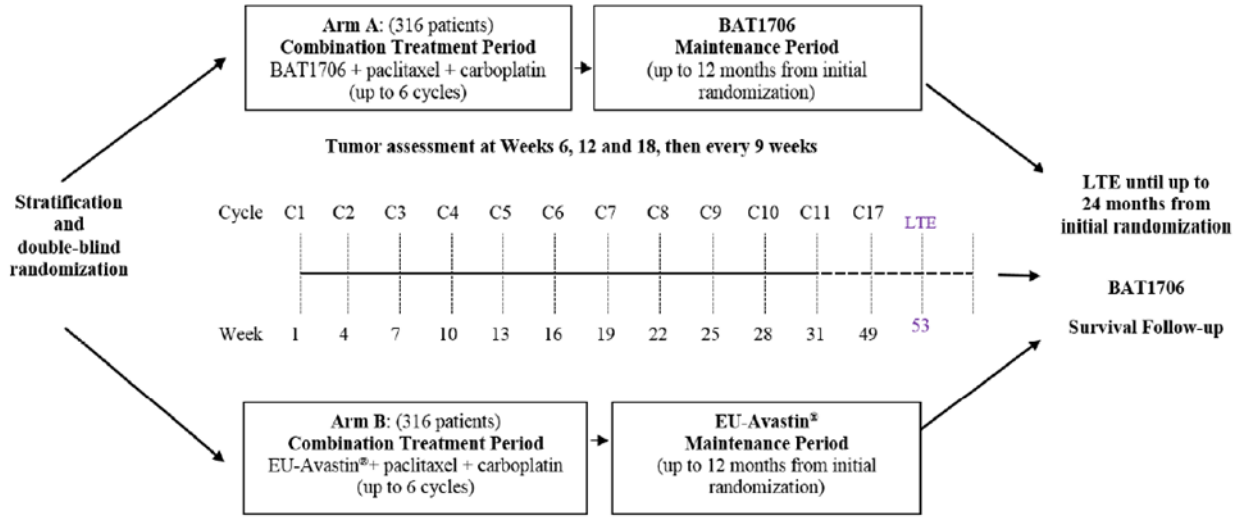
No dose response study was conducted.

2.6.5.2. Main study

Study BAT-1706-003-CR

A single randomised, double-blind, parallel group, multicentred study (Study BAT-1706-003-CR) was conducted to compare the efficacy, safety, and immunogenicity between BAT1706 and EU-sourced Avastin in patients with newly diagnosed advanced non-squamous non-small cell lung cancer (nsNSCLC).

Figure 1. Study design (Study BAT-1706-003-CR)



Combination treatment period up to Week 18 (maximum 6 cycles), and maintenance period for a maximum of 12 months from initial randomization (up to a total of 17 cycles); then maintenance with BAT1706 in the LTE study up to 24 months from initial randomization.

Abbreviations: ALK = anaplastic lymphoma kinase; CIR = central imaging review; EGFR = epidermal growth factor receptor; EU = European Union; I/E = inclusion/exclusion; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; LTE = Long-term Extension.

Note: To be eligible, a patient had to meet all I/E criteria requirements. Patients had to have at least 1 measurable lesion per CIR according to RECIST v1.1 and no known EGFR mutation/ALK receptor alteration. If a patient had positive or unknown EGFR mutation/ALK receptor alteration, the patient was eligible only if chemotherapy was the standard first line therapy for the patient.

Methods

651 subjects with newly diagnosed or recurrent stage IV non-squamous NSCLC were randomised to receive either BAT1706 (n=325) or EU-Avastin (n=326).

Study Participants

Main Inclusion Criteria

1. Age ≥18 years.

2. Stage IV nsNSCLC or recurrent disease (any stage at initial diagnosis) no longer amenable to curative surgery or local therapy (histologically or cytologically confirmed).

3. No prior systemic therapy for metastatic disease. Prior systemic therapy and/or radiotherapy for locally advanced disease was permitted if completed ≥ 6 months prior to the diagnosis of relapsing disease.

4. Tumours without EGFR mutation or ALK receptor alteration. Patients with unknown mutation status or known EGFR mutation or ALK receptor alteration could be included provided the corresponding

targeted agent was not available and chemotherapy was the standard of care of the study centre for the treatment option of the patient.

5. At least 1 unidimensional measurable lesion per RECIST v1.1 as confirmed by CIR; bone only and brain-only metastases were not allowed. Lesions previously treated with radiotherapy had to be non-target lesions unless clear progression was documented.

6. ECOG performance status of 0 or 1 and life expectancy > 3 months based on Investigator's judgment.

7, 8 and 9. Adequate hepatic, renal and hematologic function

10. Women of childbearing potential (WOCBP), and their partners, must have agreed to adhere to pregnancy prevention methods throughout the duration of the study.

Exclusion criteria

1. Small cell carcinoma of the lung or squamous cell carcinoma of the lung. Mixed tumours were categorised according to the predominant histology (> 50% of tumour cells).

2. Known receptor tyrosine kinase 1 (ROS-1) positive tumour.

3. Tumour cavitation, tumour invading into large blood vessels or close to large vessels with an increased risk of bleeding, according to Investigator's judgment.

4. Prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or vascular endothelial growth factor receptor (VEGFR), including Avastin.

5. Previous systemic therapy for metastatic disease and previous systemic anticancer therapy, or radiotherapy for locally advanced nsNSCLC if completed < 6 months prior to the diagnosis of relapsing disease.

6. Known brain metastasis or other central nervous system (CNS) metastasis that was either symptomatic or untreated. Metastases that had been treated by complete resection and/or radiotherapy demonstrating stability or improvement was not an exclusion criterion provided they were stable as shown by computed tomography (CT) or magnetic resonance imaging (MRI) scan for at least 4 weeks before screening without evidence of cerebral oedema. Patients on stable dose of corticosteroids or anticonvulsants were permitted.

Treatments

In this study, the study drugs consisted of test drugs (investigational drug BAT1706 and reference drug EU-Avastin) and associated concomitant drugs for combination therapy (paclitaxel + carboplatin).

BAT1706 was supplied as 100 mg/4 mL. The dose administered was 15 mg/kg.

EU-Avastin was supplied as 100 mg/4 mL. The dose administered was 15 mg/kg.

Combination Therapy: Paclitaxel/carboplatin

Dose: Paclitaxel 200 mg/m2 followed by carboplatin (target area under the curve [AUC] 6 mg/mL·minute). However, for Chinese patients (according to local label), paclitaxel was given at a dose of 175 mg/m2. For all patients in case of anticipated excessive toxicity (e.g., elderly patients, prior toxicity during chemo-radiotherapy), the Investigator could start the first course of chemotherapy using paclitaxel at a dose of 175 mg/m2 (or use a paclitaxel dose of 200 mg/m2 after prophylactic administration of granulocyte-colony stimulating factor [G-CSF]), and/or carboplatin AUC 5 mg/mL·minute).

Mode of administration: Paclitaxel was administered intravenously over 3 hours or according to local standard practice or package insert after adequate premedication before carboplatin was administered. Carboplatin was administered intravenously according to local standard practice or package insert. The schedule was every 3 weeks (21 days) for up to 6 cycles of combination therapy. The drug sequence was as follows: Only BAT1706 or EU-Avastin was administered on Day 1 of Cycle 1, and paclitaxel and carboplatin were given on Day 2. As of Cycle 2, BAT1706 or EU-Avastin was given first, then paclitaxel followed by carboplatin on the same day. During the combination treatment period, any chemotherapy delay mandated a BAT1706/Avastin administration delay and vice-versa.

Patients intolerant to chemotherapy after 2 dose reductions could start monotherapy with BAT1706 or EU-Avastin or start another line of anticancer therapy after Investigator's judgment. BAT1706 or EU-Avastin dose modification for intolerance was not permitted during this study.

Duration of Treatment:

The duration of participation for each patient was expected to be about 12 months. There was a 21-day screening period, followed by the administration of study drugs over a maximum of 12 months. A SFUV/EoT visit took place 28 days ± 2 days after the last dose during the study with a maximum at Week 53. Patients who were still benefiting of bevacizumab after 12 months of treatment had the option to continue treatment with BAT1706 as of Week 53 (regardless of the arm they were assigned to at randomisation) in a LTE study until disease progression, excessive toxicity, withdrawal of consent, Investigator's decision, or for a maximum of 12 additional months (i.e., for up to 24 months from initial randomisation). The end of study was set at 24 months after the Last Patient In (LPI).

Allowed Medications

Patients were allowed to continue with concomitant medication for pre-existing disease as long as they were not part of the list of excluded medicines. In the interest of patient safety and acceptable standards of medical care, the Investigator was permitted to prescribe treatment(s) at his/her discretion for treatment-emergent adverse events (TEAEs). All treatments administered during the patient's participation in the study (prescription or over the counter, including vitamins and/or herbal supplements) were recorded in the source documents and patients' eCRF (medication, dose, treatment duration, and indication).

Allowed Radiotherapy

A short course of local radiotherapy for bone metastasis with palliative intent was allowed during participation in the study, but radiotherapy for relapsing or new brain metastases was not allowed. In such case, the patient was to be withdrawn from study.

Excluded Medications

• no anticancer or immune-stimulating agents were allowed (either standard, investigational, or Chinese herbal medicines).

• Anti-infectives from Chinese herbal medicines were not allowed as the drug-drug interaction was unknown but standard antibiotics had to be used any time as required from screening to end of LTE.

• Any NSAIDs (including aspirin in doses over 325 mg/day) within 10 days prior to administration of the study drug and for the duration of the study; paracetamol, up to 4 g per day, was allowed.

• Any live/attenuated virus vaccination within 12 weeks before Screening, and during study participation until the final Follow-Up Visit.

• Any oral anticoagulation (e.g., warfarin, rivaroxaban, dabigatran, acenocumarol, etc.) treatment.

Objectives

Primary objective

The primary objective of the study was to compare the efficacy of BAT1706 and EU-Avastin given with chemotherapy as first line treatment using the ratio or the difference in ORR to show clinical equivalence.

Primary hypothesis

For the EMA submission the difference in ORR18 is used as the primary efficacy analysis. For the equivalence analysis a statistical hypothesis testing if 95% CI of the difference in the ORR18 between treatments is entirely contained within the asymmetrical equivalence margin of (-0.12, 0.15) was performed.

- H0: (ORRBAT1706 - ORRAvastin $\leq$ -12%) or (ORRBAT1706 - ORRAvastin $\geq$ +15%)
- H1: -12% < (ORRBAT1706 - ORRAvastin) < +12%,

Secondary Objectives

• To further evaluate the efficacy of BAT1706 and EU-Avastin given with chemotherapy using ORR at different time points, duration of response (DoR), PFS, and OS (time and rate) at 12 months.

• To evaluate the safety and immunogenicity of BAT1706 and EU-Avastin.

• To characterise bevacizumab exposure after administration of BAT1706 and EU-Avastin.

Exploratory Objective

• To explore the population pharmacokinetics (popPK) of BAT1706 and EU-Avastin.

Outcomes/endpoints

Primary endpoint

Overall response rate (ORR) based on tumour response at Week 18 (ORR18) in ITT as assessed by CIR. The response was evaluated according to RECIST v1.1. The primary analysis was based on the ITT population, and the supportive analysis was based on the PP population.

Primary Efficacy Endpoint Assessment

The ORR18 was calculated as the proportion of patients achieving a PR or a CR at Week 18. Each patient was assigned to 1 of the following RECIST v1.1 category based on independent CIR, irrespective of protocol deviations or missing data:

• CR: complete response.

• PR: partial response.

• SD: stable disease.

• PD: progressive disease.

• NE: not evaluable (insufficient data).

Patients underwent tumour assessment at Weeks 6, 12, and 18, regardless of the number of cycles actually completed (with a visit window of 1 week maximum during the first 18 weeks), then after every 3 cycles (approximately every 9 weeks) and at Safety Follow-up Visit (SFUV)/End of Treatment (EoT). During the trial, tumour response was assessed by local radiologist/investigator for immediate

therapeutic decision. To comply with the different statistical approaches of each regulatory agency, the main efficacy analyses (difference and ratio of ORR) were based upon tumour response at different time points as determined by CIR according to RECIST v1.1.

Patients who discontinued study drug without disease progression continued to undergo tumour assessments every 9 weeks until disease progression or a maximum of 12 months. Tumour assessment at the EoT visit was only necessary if more than 4 weeks had passed since the previous assessment (window for these assessments was within 1 week of the EoT visit).

A schedule of events is presented below:

Table 8. Schedule of Events in Study BAT-1706-003-CR

Assessments	Screening	Treatment Period[a]						Maintenance Period[a]	SFUV[b]/ EoT Visit[b]	LTE Study[c] EoT Visit[b]
Cycle	NA	1	2	3	4	5	6	7 to 17	28 days from last dose or Week 53 at the latest	Cycle 18 onward
Week	-3 to -1	1-3	4-6	7-9	10-12	13-15	16-18	19 to 49		Week 53 up to 104
Day	-21 to -1	1-21	22-42	43-63	64-84	85-105	106-126	127 to 343		
Previous/concomitant medications[o]	X	Continuous assessment								
DISEASE ASSESSMENTS										
Tumor Assessment (RECIST v1.1)[p]	X	Weeks 6, 12, 18						Weeks 27, 36, 45	X[q]	X[r]
ECOG performance status	X			X		X		Day 1 Q6W	X	
Survival[s]										Every 3 months
OTHER ASSESSMENTS										
Serum PK sampling[t]		X						Day 1 Q9W	(X)	
ADA/NADA[u] before therapy		X						Day 1 Q9W	(X)	(X)
STUDY TREATMENT										
Randomization[v]		X								
BAT1706 or EU-Avastin[w]		X	X	X	X	X	X	Day 1		Day 1 (BAT1706 only)
Carboplatin/Paclitaxel after premedication and after BAT1706 or EU-Avastin		X[x]	X	X	X[y]	(X[y])	(X[y])			

a. Day 1 of each cycle was planned on Day 22 after the previous cycle was given (i.e., an interval of 21 days) with a maximum window of -1 up to +3 days. During the combination treatment period, efforts were made to conduct study visits on the day scheduled with a maximum time window of -1 up to + 3 days for Day 1 of each cycle (except Cycle 1), and for Day 8 of each cycle. During the maintenance period, visits occurred as scheduled with a maximum window of -1 up to + 3 days for Day 1 of each cycle.

b. Patients who received at least 1 infusion of BAT1706 or EU-Avastin attended the SFUV/EoT visit while on main study 28 days ± 2 days after last dose. For patients continuing in the LTE study after 1-year therapy, an SFUV was conducted at Week 53 before they started therapy in the LTE study. During the LTE study, the EoT visit took place 28 days ± 2 days after last dose was administered and at the latest at Week 104.

c. Patients who were still benefiting of therapy after 12 months of treatment were transferred to an LTE study to receive BAT1706 treatment up to a total of 24 months as of randomisation in initial study. The visit window for LTE visits was -1 to +7 days. All tests were to be performed as indicated until the patient starts another anticancer therapy.

d. Demographics included the collection of date of birth, gender, and ethnicity.

e. Medical history included lung cancer history and other past and current medical disease with clinical significance. Prior anticancer treatments, including adjuvant chemo and/or radiotherapy, were also recorded in the eCRF.

f. All clinical laboratory tests (hematology [complete blood cell count (CBC) including hemoglobin, hematocrit, platelets, lymphocytes, neutrophils with differential]; serum chemistry [creatinine, AST, ALT, ALP, gamma-glutamyl transpeptidase, total bilirubin, direct bilirubin, glucose, total cholesterol, total protein, albumin, sodium, potassium, chloride, calcium], coagulation [INR and aPTT or P.T.], and urinalysis [protein, glucose, and blood]) were performed at the local laboratory. Laboratory samples were drawn prior to infusion of premedication and study treatment. In case therapeutic doses of anticoagulants were started during the treatment period, coagulation tests were to be repeated no more than 3 days prior to each cycle. Urine dipstick was assessed 7 days prior to randomisation and then every 6 weeks during the treatment period. In case proteinuria was observed, 24-hour urine test was to be

performed. Written informed consent was required for performing any study-specific tests or procedures. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 could be used for screening assessments rather than repeating such tests.

g. Infection screen included serum virology of Hepatitis B and C, HIV, syphilis, and tuberculosis to be performed according to local practice and local regulatory guidance. Infection screen within -21 days of patient consent of screening was acceptable.

Secondary endpoints

- Progression-free survival rate at 12 months, defined as the proportion of patients being alive without documented progression 12 months after randomisation using Kaplan-Meier method.
- Progression-free survival time defined as the time from the date of randomisation to the date of documented clinical or radiological progression or death due to any cause using Kaplan-Meier method.
- Overall survival rate at 12 months, defined as the probability of being alive 12 months after randomisation using Kaplan-Meier method.
- Overall survival time defined as the time from randomisation to death of any cause using Kaplan-Meier method.
- ORR at Week 6 (ORR6) and at Week 12 (ORR12), based on tumour response as assessed by CIR, and best ORR of confirmed responses at end of study assessed by local radiologist/Investigator if after Week 18 according to RECIST v1.1.
- Duration of response defined as the time from first documentation of a response (complete response [CR] or partial response [PR]) and the first documentation of progression (assessed by local radiologist/ Investigator if after Week 18) according to RECIST v1.1.

Safety endpoint

The safety profile of the study drugs as measured by the incidence and severity of adverse events, clinical laboratory assessments, vital signs, physical examination, and electrocardiogram (ECG) parameters.

All outputs for safety outcomes were based on the SAF. There was no statistical comparisons between the dosing cohorts for safety data.

Pharmacokinetics endpoint

Bevacizumab serum exposure following treatments of BAT1706 or EU-Avastin.

Immunogenicity variable

Serum level of anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (NADA) correlated with bevacizumab serum level.

Exploratory Endpoint

Population PK:

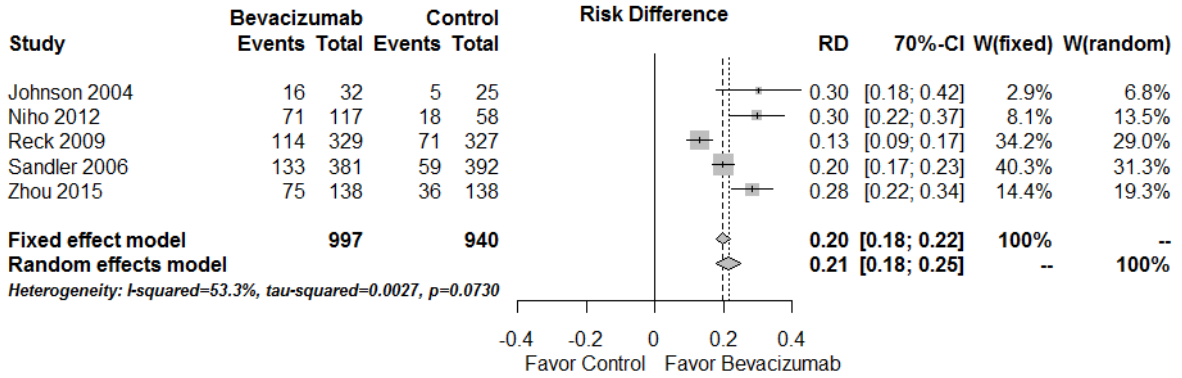
Bevacizumab serum exposure following treatment with BAT1706.

Sample size

Equivalence was demonstrated using the risk difference method (Figure 2). The net treatment effect of Avastin as measured by the difference between ORRs was 0.21 with 70% CI of [0.17, 0.26].

Preserving 29% net effect of Avastin, the equivalence margin would be set to (-0.12, +0.15) for the difference of ORRs.

Figure 2. Fixed Effect and Random Effects Models by Risk Difference



Abbreviations: CI = confidence interval; RD = risk difference.

The null hypothesis was that either (1) BAT1706 was inferior to EU-Avastin or (2) BAT1706 was superior to EU-Avastin based on a pre-specified asymmetrical equivalence margin of (-0.12, 0.15). The alternative hypothesis was that BAT1706 was equivalent to EU-Avastin, which could be demonstrated by showing that the true treatment difference was likely to lie between a lower and an upper equivalence margin of clinical acceptable difference. In other words, equivalence was to be declared if the 2-sided 95% CI of the difference in the ORR between treatments (BAT1706 and EU-Avastin) was entirely contained within the equivalence margin of (-0.12, 0.15). Based on that margin and a reference effect size of 40% at Week 18, 316 patients per arm (632 patients total) could achieve 85% power and 2-side control type I error within 5%. The primary analysis was based on the ITT population, and the supportive analysis was based on the PP population. With an expected ORR of 42% in the PP set, 84% power could be achieved.

Randomisation

Eligible patients were randomly assigned in a blinded manner to either Arm A or Arm B with a 1:1 ratio. The randomisation was performed using the Interactive Web Response System (IWRS) based on the following stratification factors:

- The NSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV).
- Gender (male or female).
- Ethnicity (Asian or non-Asian).

Randomisation were performed with a block size of 4.

Blinding(masking)

This was a randomised, double-blind, active comparator study with limited access to the randomisation code. The treatment each patient received was not disclosed to the Investigator, study centre staff, patient, Sponsor or Sponsor designee or the DSMB. The treatment codes were held by the Sponsor.

Blinding was ensured with the identical appearance of the study drug packaging for the IP and reference drug, except for unique identifying information specific to local regulations and information essential for patient randomisation. Inside of the package, the cap of the vials had a different colour for each of the two study treatments (BAT1706 vs. EU-Avastin); however, this difference (apparent only after opening the packages) was considered unlikely to have compromised the blinding.

The process for breaking the blind was handled through the IWRS. Investigators were strongly discouraged from requesting the blind be broken for an individual patient, unless there was a patient safety issue that required unblinding and would change patient management. Any centre that broke the blind under inappropriate circumstances may have been asked to discontinue its participation in the study. If the blind was broken, it may be broken for only the patient in question.

The DSMB could assess unblinded data if needed**.**

Statistical methods

This section presents statistical methods used in the analyses as described in the final statistical analysis plan (Version 2.0, dated 28 November 2019).

The significance level was 5%, the CIs were 95%, and all tests were 2-sided, unless otherwise specified in the description of the analyses.

Analysis sets

- Screen analysis set (SCR) consisting of all patients who signed the informed consent.
- Intention-to-Treat (ITT) population consisting of all randomised patients in accordance with the intended treatment arm, regardless of the treatment actually received. For the primary efficacy analysis of the ITT population, patients who discontinued prior to Week 18 for any reason were counted as non-responders.
- Per-protocol (PP) population defined as patients who had received at least 3 cycles of study drugs as allocated (BAT1706 or EU-Avastin and paclitaxel/carboplatin) or less due to early progression, death, or excessive toxicity and had one tumour assessment with no major protocol deviations that could significantly impact on primary efficacy or safety outcomes. All decisions to exclude patients from PP population were made prior to database release. For the PP efficacy analysis, patients for whom the efficacy endpoint was missing, i.e., patients without at least 1 valid post treatment evaluation, were excluded from the PP population, except those who were withdrawn due to excessive toxicity, early progression or death, in which case the patients were classified as non-responders. In the case that the PP population included at least 90% of patients in the ITT population, additional efficacy analyses on the PP population were to be omitted as the differences in the results based upon these 2 analysis sets were expected to be negligible.
- Safety population (SAF) consisted of all randomised patients who received at least one dose of study drug (BAT1706 or EU-Avastin) and allocated to the treatment actually received. The safety population was used as the basis for all safety analyses.

Primary efficacy analysis

The efficacy analyses were to be applied for both the PP and ITT population. The primary efficacy endpoint was ORR at Week 18 (ORR_{18}) based on tumour response evaluated according to RECIST v1.1 as assessed by CIR.

To demonstrate the clinical equivalence between BAT1706 and EU-Avastin arms, the ratio of, as well as the difference between ORR_{18} were to be analysed. Equivalence could be declared if the 90% CI of the ratio of ORR_{18} (BAT1706/EU-Avastin) was entirely contained within the equivalence margin of (0.75, 1.33) to comply with China NMPA requirements, and within the equivalence margin of (0.73, 1.36) to comply with US FDA requirements. The difference in ORR_{18} was to be calculated, and equivalence could be declared if the 95% CI of the difference in the ORR18 between treatments was entirely

contained within the asymmetrical equivalence margin of (-0.12, 0.15) to comply with EMA requirements.

The Risk Difference was given by "BAT1706 – EU-Avastin". The asymmetric margins of the 95% CI for the RD of ORR18 with a slightly higher upper margin of 0.15 chosen, were justified as there was no medical concern that slightly higher ORR18 of BAT1706 would result in higher toxicity.

The 2-sided 90% CI of risk ratio or 95% CI of risk difference was estimated including covariates of stratification factors: NSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), gender (male or female), and ethnicity (Asian or non-Asian) for the ITT population as primary analyses and for the PP population as supportive analyses.

The multivariate-adjusted risk ratio and the 90% CI were to be estimated by the log-binomial regression model including stratification factors. If the log-binomial model failed to converge, the Poisson regression with robust error variance was to be used. The multivariate-adjusted risk difference and the 95% CI were to be estimated by the binomial regression model including stratification factors. If this binomial model for the risk difference failed to converge, the modified Poisson approach could be used as above.

The primary efficacy analyses took place after all patients had been evaluated for response at Week 18.

Evaluation of secondary efficacy endpoints

Progression-free survival (PFS)

Progression-free survival was defined as the time from the date of randomisation to disease progression or death whichever occurs first in subjects. Subjects without event (no disease progression or death) were censored at the date of 'last tumour assessment'. Subjects for whom no post-baseline tumour assessments were available were censored at the time of first dose. Kaplan Meier methodology was used to estimate median PFS and its 95% confidence interval. Kaplan Meier curves was constructed to provide a visual description of the PFS change with time. PFS was analysed based on Investigator assessment.

Define date of PFS event / censoring:

Status		Censoring	Date of event / censoring
Progressed or died	Within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD or randomization	Event	Minimum(Date of PD, Date of death)
	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of randomization, whatever is later
Neither progressed nor died		Censored	Date of last tumor assessment with outcome CR, PR or SD or date of randomization, whatever is later

Overall Survival (OS)

Overall survival is defined as the time from randomisation to the date of death (any cause). Subjects who were alive at the time of analysis or end of study were censored at the date of the last available visit. Kaplan-Meier methodology was used to estimate the median survival time and its 95% confidence interval. Kaplan Meier curves were constructed to provide a visual description of the OS change with time. OS was analysed based on Investigator assessment.

Define date of OS event / censoring:

Survival Status		Censoring	Date of event/censoring
Died	Before cut-off	Event	Date of death
	After cutoff	Censored	Date of cutoff
Alive (no date of death)	Alive after cut-off	Censored	Date of cut-off
	Otherwise	Censored	Last date known to be alive

Duration of Response (DoR)

Duration of response for responders (CR or PR) is defined as the time interval between the date of the earliest qualifying response and the date of disease progression of death for any cause, whichever occurs earlier. For subjects who were alive without disease progression following the qualifying response, duration of response was censored on the date of last evaluable tumour assessment or last follow-up for progression of disease. Kaplan Meier methodology was used to estimate median duration of response or duration of stable disease and its 95% confidence interval. Kaplan Meier curves were constructed to provide a visual description of the DoR. DOR was analysed based on CIR assessment before week 18 and investigator assessment after week 18.

ORR6 and ORR12 were analysed based on CIR assessment.

Best Overall Response (BOR)

The BOR rate is defined as the number of subjects, whom BOR was either Complete Response (CR) or Partial Response (PR), confirmed at end of treatment (EoT) assessed by local radiologist/Investigator if after Week 18 according to RECIST 1.1. BOR was analysed based on CIR assessment before week 18 and investigator assessment after week 18.

Missing data

For the primary efficacy analysis as well as all analyses of responder/survivor proportion endpoints performed on ITT and PP population, patients who do not provided data for the responder/survivor endpoint were considered non-responders/censor, i.e., assigned to the less favourable outcome for the endpoint. Sensitivity analyses to assess the robustness of conclusions to missing data were carried out if there are more than 5% of patients missing evaluations in either treatment arm.

For imputing missing parts of dates for the efficacy analyses (except OS) the missing day in a date were imputed as the 15th of the month, if month and year is documented. If the imputation is earlier than the date of randomisation, the day of randomisation was taken. In all other cases missing or incomplete dates were not imputed.

For imputing missing day of death date, if month and year was available, the day was imputed by 15, unless this results in a date not later as a date the subject is known to be alive. In that case the date of death was imputed by the last date known to be alive + 1.

Results

Participant flow

Table 9. Patient Disposition Status - Screened Analysis Set

	BAT1706 + Carboplatin + Paclitaxel (Arm A)	EU-Avastin + Carboplatin + Paclitaxel (Arm B)	Total
Number of Screened Patients, n			891
Patients Discontinued prior to Randomization, n			240
Patient did not meet all eligibility criteria			239
Death			1
Randomized Patients, n (%)	325 (100.0)	326 (100.0)	651 (100.0)
Received no Treatment, n (%)	0	2 (0.6)	2 (0.3)
Received Treatment, n (%)	325 (100.0)	324 (99.4)	649 (99.7)
Treatment Ongoing, n (%)	116 (35.7)	102 (31.3)	218 (33.5)
Number of Patients who Stopped Treatment n (%)	209 (64.3)	222 (68.1)	431 (66.2)
Number of Patients who Received Combination Treatment during Study, n (%)	325 (100.0)	324 (99.4)	649 (99.7)
1 cycle	13 (4.0)	27 (8.3)	40 (6.1)
2 cycles	24 (7.4)	25 (7.7)	49 (7.5)
3 cycles	12 (3.7)	18 (5.5)	30 (4.6)
4 cycles	61 (18.8)	75 (23.0)	136 (20.9)
5 cycles	14 (4.3)	22 (6.7)	36 (5.5)
6 cycles	201 (61.8)	157 (48.2)	358 (55.0)
Number of Patients who Received Maintenance Treatment, n (%)	236 (72.6)	209 (64.1)	445 (68.4)
1-4 cycles	99 (30.5)	89 (27.3)	188 (28.9)
5-9 cycles	92 (28.3)	88 (27.0)	180 (27.6)
10-14 cycles	45 (13.8)	32 (9.8)	77 (11.8)
Number of Patients who Received BAT1706 in LTE, n (%)	25 (7.7)	17 (5.2)	42 (6.5)
Primary Reason for End of Treatment, n (%)	209 (64.3)	222 (68.1)	431 (66.2)
Disease progression	133 (40.9)	120 (36.8)	253 (38.9)
Adverse events	27 (8.3)	30 (9.2)	57 (8.8)
Surgical procedures	0	2 (0.6)	2 (0.3)
Treatment delay of > 6 weeks	1 (0.3)	3 (0.9)	4 (0.6)
Lack of compliance with protocol	0	1 (0.3)	1 (0.2)
Death	22 (6.8)	25 (7.7)	47 (7.2)
Withdrawal by patient	17 (5.2)	27 (8.3)	44 (6.8)
Symptomatic deterioration	2 (0.6)	5 (1.5)	7 (1.1)
Other	7 (2.2)	9 (2.8)	16 (2.5)
Reason for End of Study, n (%)	116 (35.7)	130 (39.9)	246 (37.8)
Death	99 (30.5)	102 (31.3)	201 (30.9)
Lost to follow-up	3 (0.9)	4 (1.2)	7 (1.1)
Withdrawal by patient	13 (4.0)	21 (6.4)	34 (5.2)
Other	1 (0.3)	3 (0.9)	4 (0.6)

Source: Table 14.1.1.1a
Abbreviations: LTE = long-term extension.
Note: Percentage was based on randomized patients.

Baseline data

Table 10. Patient Demographics, ITT Population

		BAT1706 + Carboplatin + Paclitaxel (Arm A) N=325	EU-Avastin + Carboplatin + Paclitaxel (Arm B) N=326	Total N=651
Age, years	Mean ± SD	59 ± 9.7	61 ± 9.0	60 ± 9.4
	Median	60	61	61
	Min, max	27, 84	26, 88	26, 88
Age categories, n (%)	<65 years	233 (71.7)	208 (63.8)	441 (67.7)
	≥ 65 years	92 (28.3)	118 (36.2)	210 (32.3)
	65 to <75 years	79 (24.3)	105 (32.2)	184 (28.3)
	75 to <85 years	13 (4.0)	12 (3.7)	25 (3.8)
	≥ 85 years	0	1 (0.3)	1 (0.2)
Gender, n (%)	Male	228 (70.2)	229 (70.2)	457 (70.2)
	Female	97 (29.8)	97 (29.8)	194 (29.8)
Race, n (%)	White	172 (52.9)	171 (52.5)	343 (52.7)
	Asian	141 (43.4)	140 (42.9)	281 (43.2)
	American Indian or Alaska native	11 (3.4)	13 (4.0)	24 (3.7)
	Black or African American	1 (0.3)	1 (0.3)	2 (0.3)
	Native Hawaiian or Other Pacific Islander	0	1 (0.3)	1 (0.2)
	Other	0	1 (0.3)	1 (0.2)
ECOG performance status, n (%)	0	69 (21.2)	103 (31.6)	172 (26.4)
	1	256 (78.8)	223 (68.4)	479 (73.6)
Weight (kg)	Mean ±SD	67.80 ±14.703	68.98 ±14.508	68.39 ±14.606
	Median (Min, Max)	65.00 (38.00, 136.00)	67.00 (40.00, 115.20)	66.00 (38.00, 136.00)
BMI (kg/m^2)	Mean ±SD	24.4 ±4.49	24.9 ±4.49	24.7 ±4.49
	Median (Min, Max)	24.0 (15.8, 45.2)	24.2 (16.0, 42.6)	24.2 (15.8, 45.2)

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; ITT = intention to treat; Max = maximum; Min = minimum; N = number of patients; n (%) = number (percent) of patients with event; SD = standard deviation

Lung Cancer History, ITT population

Table 11. Lung Cancer History Characteristics, ITT Population

	BAT1706 + Carboplatin + Paclitaxel (Arm A) N=325 (100%)	EU-Avastin + Carboplatin + Paclitaxel (Arm B) N=326 (100%)	Total N=651 (100%)
Time since Initial nsNSCLC Diagnosis (months)			
n (%)	325 (100.0)	326 (100.0)	651 (100.0)
Mean ±SD	3.93 ±9.951	4.24 ±13.918	4.08 ±12.093
Median	0.82	0.79	0.82
Q1; Q3	0.43; 1.84	0.33; 1.61	0.36; 1.71
Min; Max	0.03; 73.07	0.00; 143.80	0.00; 143.80
Stage of the Disease at the Time of Initial Diagnosis, n (%)			
Stage I	17 (5.2)	8 (2.5)	25 (3.8)
Stage II	8 (2.5)	8 (2.5)	16 (2.5)
Stage III	16 (4.9)	11 (3.4)	27 (4.1)
Stage IV	284 (87.4)	297 (91.1)	581 (89.2)
Missing	0	2 (0.6)	2 (0.3)
nsNSCLC Pathology Classification, n (%)			
Adenocarcinoma	315 (96.9)	310 (95.1)	625 (96.0)
Large cell carcinoma	2 (0.6)	8 (2.5)	10 (1.5)
Adenosquamous NSCLC mixed predominant Adenocarcinoma	0	0	0
Other	8 (2.5)	8 (2.5)	16 (2.5)
nsNSCLC Stage at Enrollment, n (%)			
Stage IV	303 (93.2)	305 (93.6)	608 (93.4)
Recurrent disease	22 (6.8)	21 (6.4)	43 (6.6)
Metastasis n (%)			
Yes	319 (98.2)	313 (96.0)	632 (97.1)
No	6 (1.8)	13 (4.0)	19 (2.9)
Time since First Metastasis (months) (a)			
n (%)	319 (98.2)	313 (96.0)	632 (97.1)
Mean ±SD	1.22 ±2.063	1.27 ±2.066	1.24 ±2.063
Median	0.66	0.79	0.72
EGFR Mutation Status, n (%)			
Positive	8 (2.5)	9 (2.8)	17 (2.6)
Negative	193 (59.4)	201 (61.7)	394 (60.5)
Unknown	5 (1.5)	7 (2.1)	12 (1.8)
Not done	119 (36.6)	109 (33.4)	228 (35.0)
ALK Mutation Status, n (%)			
Positive	1 (0.3)	6 (1.8)	7 (1.1)
Negative	194 (59.7)	202 (62.0)	396 (60.8)
Unknown	9 (2.8)	7 (2.1)	16 (2.5)
Not done	120 (36.9)	111 (34.0)	231 (35.5)
Missing	1 (0.3)	0	1 (0.2)
ROS-1 Mutation Status			
Positive	0	1 (0.3)	1 (0.2)
Negative	135 (41.5)	155 (47.5)	290 (44.5)
Unknown	69 (21.2)	58 (17.8)	127 (19.5)
Not done	120 (36.9)	111 (34.0)	231 (35.5)
Missing	1 (0.3)	1 (0.3)	2 (0.3)

Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; ICF= informed consent form; Min = minimum; Max = maximum; nsNSCLC = non-squamous non-small cell lung cancer; ROS = receptor tyrosine kinase; SD = standard deviationN: Number of patients in population. n: Number of patients with data available. %: Percentage based on N.

Time since Initial nsNSCLC Diagnosis (months) = (date of ICF – date of Initial nsNSCLC Diagnosis + 1)/30.4375.

(a) Time since First Metastasis (months) = (date of ICF – date of First Metastasis + 1)/30.4375.

(b) Time since First Metastasis (months) = (date of Randomisation – date of First Metastasis + 1)/30.4375.

Non-NSCLC medical history, ITT population

In summary, 202 (31.0%) patients had at least one past medical or surgical history (100 [30.8%] patients in Arm A and 102 [31.3%] patients in Arm B). The most common past medical or surgical history by SOCs were surgical and medical procedures in 147 (22.6%) patients (72 [22.2%] in Arm A and 75 [23.0%] in Arm B), and infections and infestations in 35 (5.4%) patients (16 [4.9%] in Arm A and 19 [5.8%] in Arm B). The 3 most common past medical or surgical histories by PT were appendicectomy in 26 (4.0%) patients (12 [3.7%] in Arm A and 14 [4.3%] in Arm B); hysterectomy in 16 (2.5%) patients (8 [2.5%] in both Arm A and Arm B), and cholecystectomy in 15 (2.3%) patients (4 [1.2%] in Arm A and 11 [3.4%] in Arm B).

Concurrent Illnesses

Overall, 544 (83.6%) patients had at least one concurrent medical or surgical condition with 280 (86.2%) patients in Arm A and 264 (81.0%) patients in Arm B. The most common concurrent medical or surgical condition by SOCs were respiratory, thoracic and mediastinal disorders in 228 (35.0%) patients (137 [42.2%] in Arm A and 91 [27.9%] in Arm B), and vascular disorders in 196 (30.1%) patients (88 [27.1%] in Arm A and 108 [33.1%] in Arm B). The 3 most common medical histories by PT were hypertension in 162 (24.9%) patients (69 [21.2%] in Arm A and 93 [28.5%] in Arm B); cough in 110 (16.9%) patients (65 [20.0%] in Arm A and 45 [13.8%] in Arm B), and dyspnoea in 74 (11.4%]) patients (43 [13.2%] in Arm A and 31 [9.5%] in Arm B).

Prior and Concomitant Medications/Procedures

Prior anticancer radiotherapy: In the ITT population the median total radiotherapy dose was 30 Gy in Arm A and 36 Gy in Arm B. The median time between end of radiotherapy and disease progression was 8.6 months (ranging from 0.2 to 9.6 months) in Arm A and 8.5 months (ranging from 0.7 to 23.5 months). The most common anatomical site in both groups was the brain (17 [2.6%] patients: 6 [1.8%] in Arm A and 11 [3.4%] in Arm B). A similar number of patients had stable disease after radiotherapy in the 2 treatment arms.

Prior anticancer therapy: A total of 44 (6.8%) patients had at least one prior anticancer therapy (22 [6.8%] patients in Arm A and 22 [6.7%] patients in Arm B), given as neoadjuvant or adjuvant therapy. The most common prior anticancer drug was cisplatin given in 22 (3.4%) patients (12 [3.7%] in Arm A and 10 [3.1%] in Arm B). Similar characteristics were found in the 2 treatments arms in terms of the intent of prior systemic anticancer therapy and best response. A difference was found in the median time between end of prior systemic anticancer therapy and disease progression (24.8 months in Arm A and 14.0 months in Arm B).

Prior cancer-related surgery/procedure: A total of 333 (51.2%) patients received at least one prior cancer-related surgery/procedure (167 [51.4%] patients in Arm A and 166 [50.9%] patients in Arm B) with a similar distribution of surgery/procedure site between the 2 treatment arms. The median time since last surgery/procedure to ICF signing was 1.31 months (ranging from -0.36 to 143.80 months). The most common prior cancer-related surgery/procedure by PT was biopsy lung in 79 (12.1%) patients (37 [11.4%] in Arm A and 42 [12.9%] in Arm B), followed by bronchoscopy in 78 (12.0%)

patients (38 [11.7%] in Arm A and 40 [12.3%] in Arm B), and lung lobectomy in 57 (8.8%) patients (32 [9.8%] in Arm A and 25 [7.7%] in Arm B).

Concomitant medication: A total of 629 (96.6%) patients received at least one concomitant medication. The most common concomitant medication was recombinant human granulocyte-colony stimulating factor given in 201 (30.9%) patients (100 [30.8%] in Arm A and 101 [31.0%] in Arm B), followed by dexamethasone given in 120 (18.4%) patients (60 [18.5%] in Arm A and 60 [18.4%] in Arm B).

Concomitant procedure: A total of 197 (30.3%) patients underwent at least one concomitant procedure. Among them, 29 (4.5%) patients underwent concomitant procedures prior to the first dose of study drugs; and 185 (28.4%) patients within 28 days after the last dose of study drugs. The primary reason to undergo a concomitant procedure was due to an AE (133 [20.4%] patients). The most common concomitant procedure by PT in Arm A was chest X-ray (15 [4.6%] patients) and computerised tomogram thorax (13 [4.0%] patients). The most common concomitant procedure by PT in Arm B was MRI brain (9 [2.8%] patients) and drug delivery device implantation (8 [2.5%] patients). The most common concomitant procedures within 28 days after last dose of study treatment were chest X-ray (21 [3.2%] patients) and computerised tomogram thorax (19 [2.9%] patients).

Demographic characteristics per study site and race shows a balanced distribution of ITT population per arm. The overview of the enrolment for the main study sites (> 20 patients overall) showed a balanced distribution between the treatment arms. According to the tables on Demographic and Baseline Data in CSR, the distribution of prior and concurrent medical history and prior and concurrent medication/procedures, specifically those related to the prophylaxis of adverse events is balanced between the arms, which is reassuring.

Treatment Compliance

Compliance was defined as the actual dose intensity divided by the planned dose intensity.

Almost all patients received the study drugs as planned. Overall, the median compliance was 96.9% for BAT1706 and 97.7% for EU-Avastin; median compliance for carboplatin was 95.3% in Arm A and 95.4% in Arm B; and median compliance for paclitaxel was 95.9% in Arm A and 96.5% in Arm B.

The median compliance to the study drugs and chemotherapeutics was high and balanced between arms.

Numbers analysed

Table 12. Analysis Sets

	BAT1706 + Carboplatin + Paclitaxel (Arm A) n (%)	EU-Avastin + Carboplatin + Paclitaxel (Arm B) n (%)	Total n (%)
Number of patients in Screened Analysis Set (a)			891
Number of patients in Intent-To-Treat Population (b)	325 (100.0)	326 (100.0)	651 (100.0)
Number of patients in Per-Protocol Population (c)	289 (88.9)	283 (86.8)	572 (87.9)
Number of patients in Safety Population (d)	325 (100.0)	324 (99.4)	649 (99.7)
Number of patients in Pharmacokinetic Population (e)	110 (33.8)	108 (33.1)	218 (33.5)

Source: Table 14.1.1.3

Notes: Percentage was based on randomized patients.

(a) All patients who signed the informed consent.

(b) The ITT population were all randomized patients in accordance with the intended treatment arm, regardless of the treatment actually received.

(c) The PP population was defined as patients who had received at least 3 cycles of study drugs as allocated (BAT1706 or EU-Avastin and paclitaxel/carboplatin) or less due to early progression, death, or excessive toxicity and had one tumor assessment with no major protocol deviations that would have a significant impact on primary efficacy or safety outcomes.

(d) The safety population consisted of all randomized patients who received at least one dose of study drug (BAT1706 or EU-Avastin) and allocated into actual received treatment arm.

(e) All patients received at least one dose of study drug, had at least one measured concentration at a scheduled postdose PK time point, and had no major protocol deviations that might significantly affect the PK assessment.

Table 13. Reasons for Exclusion from the PP Population-ITT Population

	BAT1706 + Carboplatin + Paclitaxel (Arm A) N=325 (100%) n (%)	EU-Avastin + Carboplatin + Paclitaxel (Arm B) N=326 (100%) n (%)	Total N=651 (100%) n (%)
Number of Patients Excluded from the PP Population (a)	36 (11.1)	43 (13.2)	79 (12.1)
Reason for Exclusion			
Response evaluability			
Received less than 3 cycles of study drugs and did not discontinue due to PD, death or AE	6 (1.8)	19 (5.8)	25 (3.8)
Not have at least one tumor assessment and did not discontinue due to PD, death or AE	3 (0.9)	13 (4.0)	16 (2.5)
Major protocol deviation			
Randomization Criteria	20 (6.2)	11 (3.4)	31 (4.8)
Eligibility and Entry Criteria	8 (2.5)	7 (2.1)	15 (2.3)
Concomitant Medication Criteria	3 (0.9)	6 (1.8)	9 (1.4)
IP Compliance	1 (0.3)	1 (0.3)	2 (0.3)
Other Criteria	0	1 (0.3)	1 (0.2)

Source: Table 14.1.2.2

Abbreviations: AE = adverse events; IP = investigational product; PD= progressive disease.

(a) Patients might have more than one reason for exclusion from the PP population.

Outcomes and estimation

Primary endpoint

Table 14. Overall Response Rate, Risk Ratio and Multivariate-Adjusted Risk Ratio, Risk Difference and Multivariate-Adjusted Risk Difference at Week 18 (ITT population) - Cutoff date: 25 June 2020)

	BAT1706 + Carboplatin + Paclitaxel (Arm A) N=325 (100%)	EU-Avastin + Carboplatin + Paclitaxel (Arm B) N=326 (100%)
Objective Tumor Response		
Overall Response Rate at Week 18 (ORR_{18}), n (%) (a)	156 (48.0)	145 (44.5)
95% CI (exact) (b)	[42.5; 53.6]	[39.0; 50.1]
Risk Ratio [90% CI] (c)	1.08 [0.94, 1.24]	
Multivariate-Adjusted Risk Ratio [90% CI] (d)	1.07 [0.93, 1.22]	
Risk Difference [95% CI] (e)	0.03 [-0.04, 0.11]	
Multivariate-Adjusted Risk Difference [95% CI] (f)	0.03 [-0.04; 0.11]	

Source: Table 14.2.1.1.1.1, Table 14.2.1.1.1.2, Table 14.2.1.1.2.1, Table 14.2.1.1.2.2

Abbreviations: CI = confidential interval; CR = complete response; ITT = intention-to-treat; ORR= overall response rate; PR = partial response.

(a) The ORR_{18} was calculated as the proportion of patients achieving a PR or a CR at Week 18.

(b) The method of Clopper and Pearson was used to calculate Confidence Intervals.

(c) The risk ratio was estimated including covariates of stratification factors: nsNSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), Gender (male or female), and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system.

(d) The multivariate-adjusted risk ratio and the 90% CI were estimated by the log-binomial regression model including stratification factors. Stratification factors were from IWRS system.

(e) The risk difference was estimated including covariates of stratification factors: nsNSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), Gender (male or female), and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system.

(f) The multivariate-adjusted risk difference and the 95% CI were estimated by the binomial regression model including stratification factors. Stratification factors were from IWRS system.

Table 15. Overall Response Rate, Risk Ratio and Multivariate-Adjusted Risk Ratio, Risk Difference and Multivariate-Adjusted Risk Difference at Week 18 (PP population)

	BAT1706 + Carboplatin + Paclitaxel (Arm A) N=289 (100%)	EU-Avastin + Carboplatin + Paclitaxel (Arm B) N=283 (100%)
Objective Tumor Response		
Overall Response Rate at Week 18 (ORR_{18}), n (%) (a)	143 (49.5)	135 (47.7)
95% CI (exact) (b)	[43.6; 55.4]	[41.8; 53.7]
Risk Ratio [90% CI] (c)	1.04 [0.90, 1.19]	
Multivariate-Adjusted Risk Ratio [90% CI] (d)	1.02 [0.89, 1.17]	
Risk Difference [95% CI] (e)	0.02 [-0.06, 0.10]	
Multivariate-Adjusted Risk Difference [95% CI] (f)	0.02 [-0.07; 0.10]	

Source: Table 14.2.1.1.4.1, Table 14.2.1.1.4.2, Table 14.2.1.1.5.1, Table 14.2.1.1.5.2

Abbreviations: CI = confidential interval; CR = complete response; ORR= overall response rate; PP = per-protocol; PR = partial response.

(a) The ORR_{18} was calculated as the proportion of patients achieving a PR or a CR at Week 18.

(b) The method of Clopper and Pearson was used to calculate CIs.

(c) The risk ratio was estimated including covariates of stratification factors: nsNSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), Gender (male or female), and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system.

Secondary efficacy endpoints

Progression-Free Survival

Table 16. Progression-Free Survival, Week 52 Data Set (25 June 2020) – ITT Population, BAT1706-003-CR

	BAT1706 + Carboplatin + Paclitaxel N = 325	EU-Avastin + Carboplatin + Paclitaxel N = 326
Number of Events (progressive/Deaths), n (%)	231 (71.1)	223 (68.4)
Number of Censored, n (%)	94 (28.9)	103 (31.6)
Hazard Ratio (primary, stratified) (a)	0.932	
95% CI	[0.770, 1.127]	
P-Value (Log rank, primary, stratified) (a)	0.464	
Hazard Ratio (unstratified)	0.927	
95% CI	[0.771, 1.115]	
P-Value (Log rank, unstratified)	0.419	
Progression-Free Survival Time (b)		
Median (months)	8.214	8.115
95% CI	[7.984, 8.345]	[6.965, 8.345]
Min, Max (c)	0.03, 23.85	0.03, 22.21
Number of Patients at Risk/Failed/Progression-Free Survival Rates (d) (%) up to [95% Confidence Interval]		
12 months	30/217/24.817 [19.461; 30.525]	30/206/24.692 [19.192; 30.570]
24 months	0/231/0.000 [-; -]	0/223/0.000 [-; -]

CI = confidence interval; IWRS = interactive web response system; Min = minimum; Max = maximum; nsNSCLC = nonsquamous non-small cell lung cancer. (a) Hazard Ratio BAT1706/EU-Avastin with the 95% CI were from a stratified Cox regression model with treatment as the explanatory variable and nsNSCLC stage (recurrent disease or Stage IV), gender (male or female) and ethnicity (Asian or non-Asian) as stratification factors. A less than 1 hazard ratio favors BAT1706 arm. P-value was calculated using Log Rank test stratified by nsNSCLC stage (recurrent disease or Stage IV), gender (male or female) and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system. (b) Product-limit (Kaplan-Meier) estimates. Confidence Intervals for the median were calculated according to Brookmeyer and Crowley. (c) Minimum and maximum of all observations. (d) Based on Kaplan-Meier estimates.

Figure 3. Kaplan-Meier Curve of Progression-Free Survival, Week 52 Data Set (25 June 2020) – ITT Population, BAT1706-003-CR

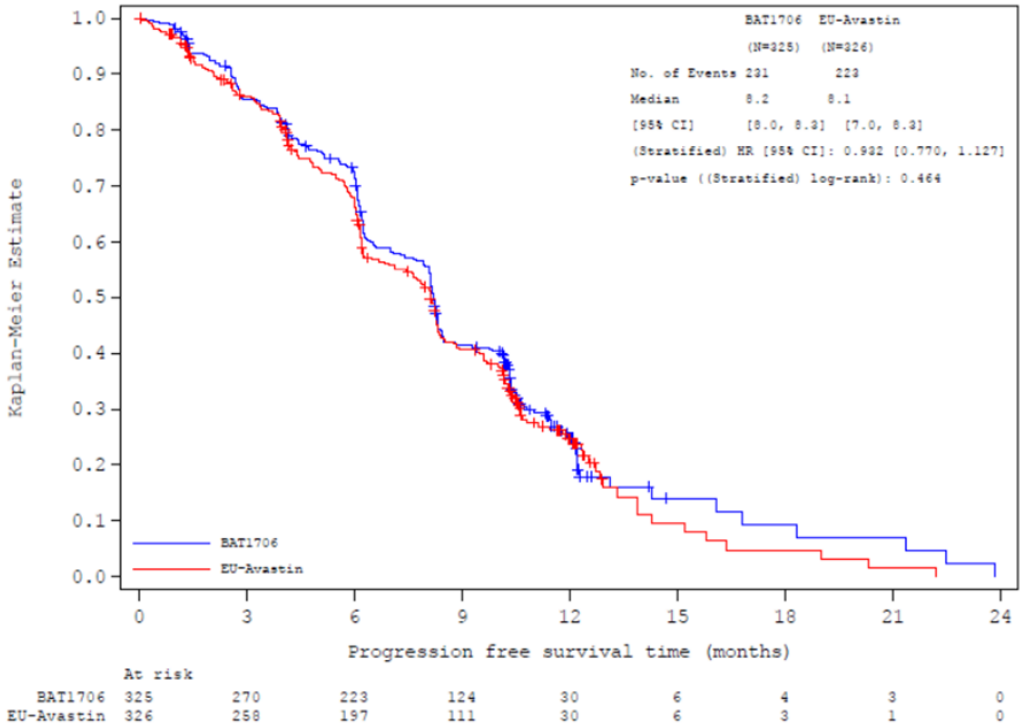


Table 17. Progression-Free Survival: Censoring/Event Status – ITT Population, Week 52 Data Set (25 June 2020) – ITT Population, BAT1706-003-CR

	BAT1706 + Carboplatin + Paclitaxel N = 325	EU-Avastin + Carboplatin + Paclitaxel N = 326
Number of Patients with:		
Event	231 (71.1)	223 (68.4)
Radiological PD*	183 (79.2)	160 (71.7)
Radiological PD based on existing lesions only*	69 (37.7)	68 (42.5)
Radiological PD based on new lesions only*	51 (27.9)	35 (21.9)
Radiological PD based on both existing and new lesions*	63 (34.4)	57 (35.6)
Death*	48 (20.8)	63 (28.3)
Censoring	94 (28.9)	103 (31.6)
Censored at randomization (a)	4 (4.3)	12 (11.7)
Lost to follow-up/withdraw of consent (b)	6 (6.4)	13 (12.6)
Due to data cut-off (c)	84 (89.4)	78 (75.7)

Abbreviation: PD = Progressive disease.
(a) Patients who did not die and had no tumor assessment after start of treatment were censored at time of randomization.
(b) Patients who had no PD and did not die before they were lost to follow-up/withdrew consent.
(c) Patients who had no PD and did not die before the trial data cutoff.
* The percentage of radiological PD and death were based on the number of patients with events.
Source: CSR BAT1706-003-CR Addendum 1 Table 14.2.2.1.2.

By the latest data cutoff date (Week 52, 25 June 2020), 94 (28.9%) patients were censored in the BAT1706 group, and 103 (31.6%) patients were censored in the EU-Avastin group, with data cutoff being the primary reason for censoring (84 [89.4%] patients in the BAT1706 group and 78 [75.7%] patients in the EU-Avastin group).

Similar results for PFS were found in the PP population (data not shown).

Overall Survival (OS)

Table 18. Overall Survival, Week 52 Data Set (25 June 2020) – ITT Population, BAT1706-003-CR

	BAT1706 + Carboplatin + Paclitaxel N = 325	EU-Avastin + Carboplatin + Paclitaxel N = 326
Number of Events (Deaths), n (%)	153 (47.1)	158 (48.5)
Number of Censored, n (%)	172 (52.9)	168 (51.5)
Hazard Ratio (primary, stratified) (a)	0.974	
95% CI	[0.779, 1.218]	
P-Value (Log rank, primary, stratified) (a)	0.819	
Hazard Ratio (unstratified)	0.949	
95% CI	[0.760, 1.185]	
P-Value (Log rank, unstratified)	0.644	
Total Survival Time (b)		
Median (months)	16.394	15.507
95% CI	[14.686, 18.957]	[13.963, 19.713]
Min, Max (c)	0.23, 27.70	0.03, 29.54
Number of Patients at Risk/Failed/Survival Rates (d) (%) up to [95% Confidence Interval]		
12 months	155/116/63.733 [58.180; 68.754]	165/123/61.669 [56.102; 66.747]
24 months	13/152/38.648 [30.905; 46.316]	17/158/37.074 [29.030; 45.112]

CI = Confidence interval; IWRS = Interactive web response system; Min = Minimum; Max = Maximum; nsNSCLC = non-squamous non-small cell lung cancer. (a) Hazard Ratio for BAT1706/EU-Avastin with the 95% CI were from a stratified Cox regression model with treatment as the explanatory variable and nsNSCLC stage (recurrent disease or Stage IV), gender (male or female) and ethnicity (Asian or non-Asian) as stratification factors. A less than 1 hazard ratio favoured BAT1706 arm. P-value was calculated using Log Rank test stratified by nsNSCLC stage (recurrent disease or Stage IV), gender (male or female) and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system. (b) Product-limit (Kaplan-Meier) estimates. Confidence Intervals for the median are calculated according to Brookmeyer and Crowley. (c) Minimum and maximum of all observations. (d) Based on Kaplan-Meier estimates.

Figure 4. Kaplan-Meier Curve of Overall Survival, Week 52 Data Set (25 June 2020) – ITT Population, BAT1706-003-CR

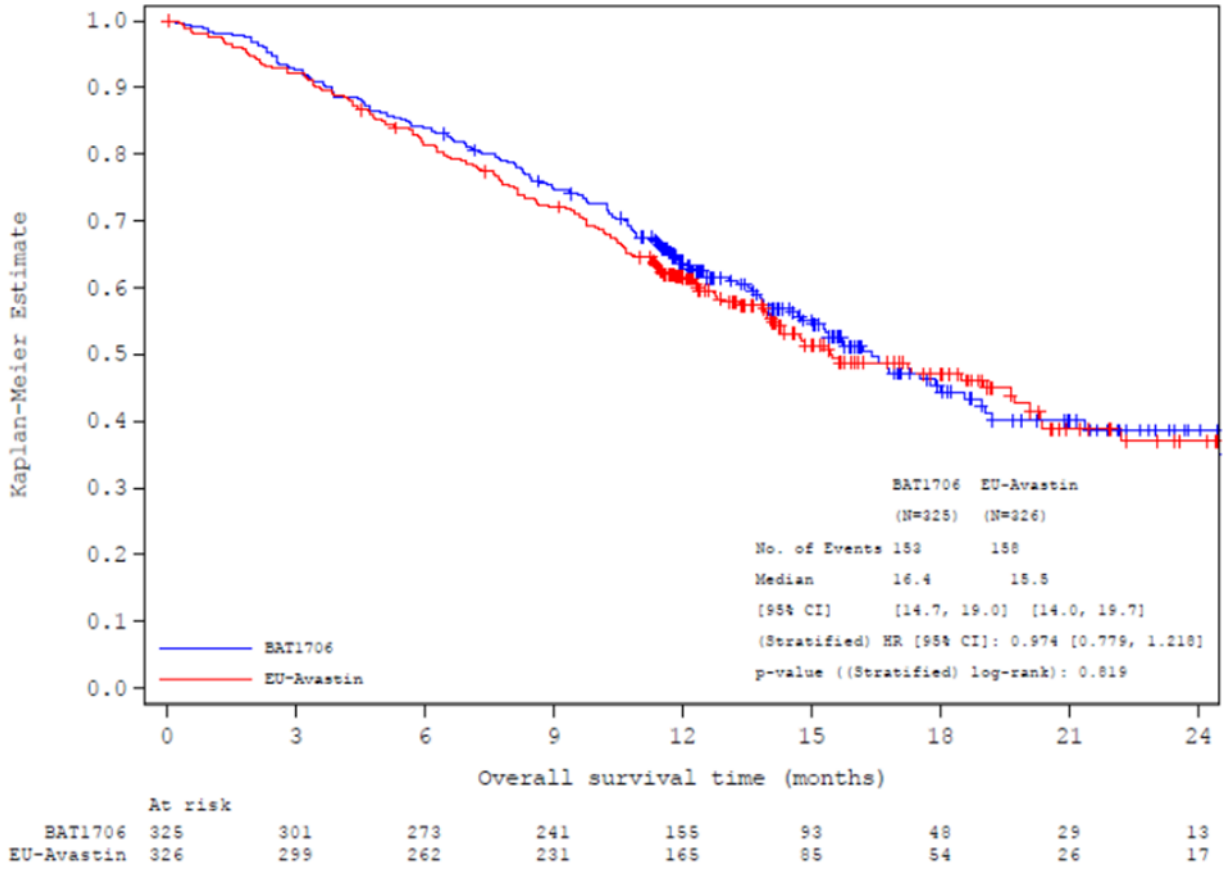


Table 19. Overall Survival: Censoring/Event Status – ITT Population Week 52 Data Set (25 June 2020), BAT1706-003-CR

	BAT1706 + Carboplatin + Paclitaxel N = 325	EU-Avastin + Carboplatin + Paclitaxel N = 326
Number of Patients with:		
Event (death)	153 (47.1)	158 (48.5)
Censored	172 (52.9)	168 (51.5)
Censored at data cut-off (Administrative censoring)	130 (75.6)	117 (69.6)
Censored before data cut-off (non-administrative censoring)	42 (24.4)	51 (30.4)

Censored included lost to follow-up, withdrawal by patient, alive at last contact.

By the latest data cut-off date (Week 52, 25 June 2020), 172 (52.9%) patients were censored in the BAT1706 group, and 168 (51.5%) patients were censored in the EU-Avastin group, with data cutoff being the primary reason for censoring.

Similar results for OS were found in the PP population (data not shown).

Duration of Response (DoR)

For patients who were alive without disease progression following the qualifying response, DoR was censored at the date of last available tumour assessment.

By the latest data cutoff date (Week 52, 25 June 2020), 206 patients in the BAT1706 group and 176 patients in the EU-Avastin group had a response. The hazard ratio stratified for DoR was 1.124 (95% CI [0.861, 1.466], p = 0.388). The number (%) of patients with an event (PD/death) was 129 (62.6%) in the BAT1706 group and 106 (60.2%) in the EU-Avastin group. The median DoR was 7.1 months in the BAT1706 group and 7.8 months in the EU-Avastin group.

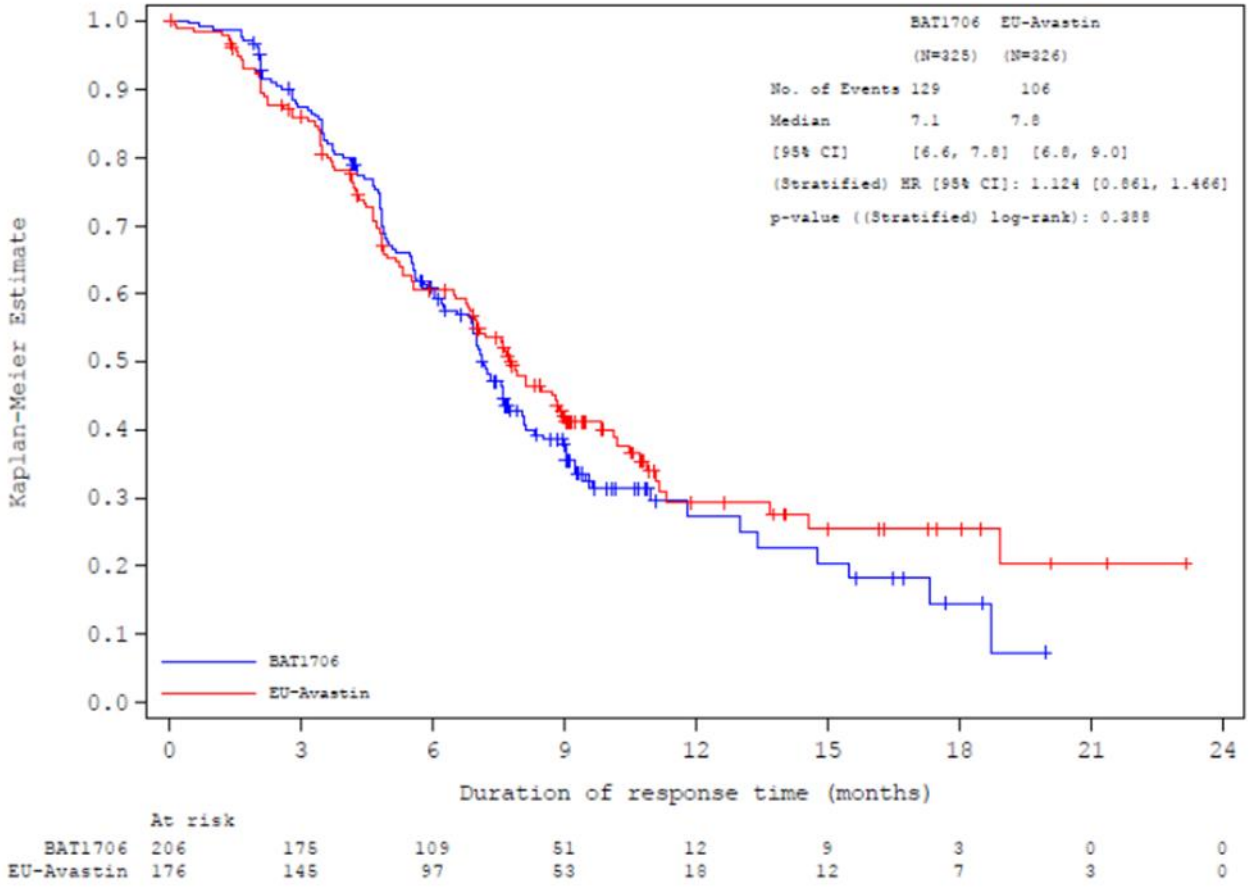
Similar results for DoR were found for the PP population (Data not shown).

Table 20. Duration of Response, Week 52 Data Set (25 June 2020) – ITT Population, BAT1706-003-CR

	BAT1706 + Carboplatin + Paclitaxel N = 325	EU-Avastin + Carboplatin + Paclitaxel N = 326
Number of Patients with a Response (CR/PR)	206	176
Number of Events, n (%)	129 (62.6)	106 (60.2)
Number of Censored, n (%)	77 (37.4)	70 (39.8)
Hazard Ratio (primary, stratified) (a)	1.124	
95% CI	[0.861, 1.466]	
P-Value (Log rank, primary, stratified) (a)	0.388	
Hazard Ratio (unstratified)	1.131	
95% CI	[0.873, 1.464]	
P-Value (Log rank, unstratified)	0.347	
Total Survival Time (b)		
Median (months)	7.129	7.819
95% CI	[6.571, 7.786]	[6.834, 8.969]
Min, Max (c)	0.03, 19.98	0.03, 23.16
Number of Patients at Risk/Failed/ Rates (%) at Follow-up Time (d) up to [95% Confidence Interval]		
12 months	12/123/27.312 [19.317; 35.900]	18/103/29.301 [20.947; 38.136]
24 months	-/129/- [-; -]	-/106/- [-; -]

CI = confidence interval; CR = complete response; Max= maximum; Min = minimum; nsNSCLC = non-squamous non-small cell lung cancer; PR = partial response. (a) Hazard Ratio BAT1706/EU-Avastin with the 95% CI were from a stratified Cox regression model with treatment as the explanatory variable and nsNSCLC stage (recurrent disease or Stage IV), gender (male or female) and ethnicity (Asian or non-Asian) as stratification factors. A less than 1 hazard ratio favoured BAT1706 arm. P-value was calculated using Log Rank test stratified by nsNSCLC stage (recurrent disease or Stage IV), gender (male or female) and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system. (b) Product-limit (Kaplan-Meier) estimates. Confidence Intervals for the median were calculated according to Brookmeyer and Crowley. (c) Minimum and maximum of all observations. (d) Based on Kaplan-Meier estimates. Notes: Percentage was based on the number of patients with a response.

Figure 5. Kaplan-Meier Curve of Duration of Response, Week 52 Data Set (25 June 2020) – ITT Population, BAT1706-003-CR



Landmark analysis ORR

Table 21. Overall Response Rates at Weeks 6 and 12 (ORR6 and ORR12)

	BAT1706 + Carboplatin + Paclitaxel (Arm A) N=325 (100%)	EU-Avastin + Carboplatin + Paclitaxel (Arm B) N=326 (100%)
Overall Response Rate at Week 6 (ORR_6)		
n (%) [a]	89 (27.4)	74 (22.7)
95% CI (exact) [b]	[22.6; 32.6]	[18.3; 27.6]
Risk Ratio [90% CI] [c]	1.19 [0.96, 1.49]	
Multivariate-Adjusted Risk Ratio [90% CI] [d]	1.20 [0.96, 1.50]	
Risk Difference [95% CI] [e]	0.04 [-0.02, 0.11]	
Multivariate-Adjusted Risk Difference [95% CI] [f]	0.04 [-0.02; 0.11]	
Overall Response Rate at Week 12 (ORR_{12})		
n (%) [a]	147 (45.2)	133 (40.8)
95% CI (exact) [b]	[39.7; 50.8]	[35.4; 46.3]
Risk Ratio [90% CI] [c]	1.10 [0.95, 1.28]	
Multivariate-Adjusted Risk Ratio [90% CI] [d]	1.10 [0.95, 1.27]	
Risk Difference [95% CI] [e]	0.04 [-0.03, 0.12]	
Multivariate-Adjusted Risk Difference [95% CI] [f]	0.04 [-0.03; 0.12]	

CI = confidential interval; CR = complete response; ITT = intention to treat; N = number of patients; n (%) = number (percent) of patients with event; ORR= overall response rate; PR = partial response

(a) The ORR_6 / ORR_{12} was calculated as the proportion of patients achieving a PR or a CR at Week 6 / Week 12.

(b) The method of Clopper and Pearson was used to calculate CIs.

(c) The risk ratio was estimated including covariates of stratification factors: nsNSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), Gender (male or female), and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system.

(d) The multivariate-adjusted risk ratio and the 90% CI were estimated by the log-binomial regression model including stratification factors. Stratification factors were from IWRS system.

e) The risk difference was estimated including covariates of stratification factors: nsNSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), gender (male or female), and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system.

(f) The multivariate-adjusted risk difference and the 95% CI were estimated by the binomial regression model including stratification factors. Stratification factors were from IWRS system.

Best Overall Response (BOR) Rate

The secondary efficacy endpoint BOR was the best result obtained among all tumour assessments from the randomisation until documented disease progression. The overall response was based on imaging, according to RECIST v1.1.

Table 22. Best Overall Response Rate, Risk ratio and Risk Difference, Week 18 Data Set (05 November 2019), ITT Population – BAT1706-003-CR

	BAT1706 + Carboplatin + Paclitaxel N=325	EU-Avastin + Carboplatin + Paclitaxel N=326
Best Overall Response		
Best Overall Response Rate, n (%) (a)	165 (50.8)	132 (40.5)
95% CI (exact) (b)	[45.2; 56.3]	[35.1; 46.0]
Risk Ratio [90% CI] (c)	1.25 [1.08, 1.44]	
Multivariate-Adjusted Risk Ratio [90% CI] (d)	1.24 [1.08, 1.43]	
Risk Difference [95% CI] (e)	0.10 [0.02, 0.18]	
Multivariate-Adjusted Risk Difference [95% CI] (f)	0.10 [0.03, 0.18]	

BOR = best overall response; CI = confidential interval; CR = complete response; ITT = intention-to-treat; IWRS = interactive web response system; nsNSCLC = non-squamous non-small cell lung cancer; ORR= overall response rate; PR = partial response.
(a) The BOR rate was calculated as the proportion of patients achieving a PR or a CR at end of study.
(b) The method of Clopper and Pearson was used to calculate Confidence Intervals.
(c) The risk ratio was estimated including covariates of stratification factors: nsNSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), Gender (male or female), and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system.
(d) The multivariate-adjusted risk ratio and the 90% CI were estimated by the log-binomial regression model including stratification factors. Stratification factors were from IWRS system.
(e) The risk difference was estimated including covariates of stratification factors: nsNSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), Gender (male or female), and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system.
(f) The multivariate-adjusted risk difference and the 95% CI were estimated by the binomial regression model including stratification factors. Stratification factors were from IWRS system.

The BOR at Month 12 results were similar to the Week 18 results and are summarised as follows. In the ITT population, the BOR rate at Month 12 was 52.3% in the BAT1706 group and 41.4% in the EU-Avastin group. The risk ratio for BOR rate (BAT1706/EU-Avastin) was 1.26 with 2-sided 90% CI of [1.09, 1.44], and the risk difference was 0.11 with 95% CI [0.03, 0.18]. The multivariate-adjusted risk ratio was 1.25 with 90% CI of [1.09, 1.44]), and the multivariate-adjusted risk difference was 0.11 with 95% CI [0.03; 0.18])

Ancillary analyses

Analysis of missing data:

According to the SAP, in the efficacy analysis of primary endpoint ORR18 as well as for all analyses of responder/survivor proportion endpoints performed on ITT and PP population, patients who do not provide data for the responder/survivor endpoint were considered non-responders.

The analyses of ORR currently based on the response achieved at week 18 includes both observed and imputed non-responder data, this is presented in the table below. The robustness of the results was evaluated by a tipping point analysis.

Table 23: Overall Response Rate at Week 18, Non-responders Imputed and Observed – ITT Population, BAT1706-003-CR, Primary data-cut of 05 November 2019

	BAT1706 + Carboplatin + Paclitaxel (Arm A) N=325	EU-Avastin + Carboplatin + Paclitaxel (Arm B) N=326
Overall Response Rate at Week 18 (ORR_{18}), n (%) (a)	156 (48.0)	145 (44.5)
Non-responders, n (%)	169 (52.0)	181 (55.5)
Non-responders observed, n (%)	102 (31.4)	89 (27.3)
Non-responders imputed (i.e., missing values), n (%)	67 (20.6)	92 (28.2)

ITT = intention-to-treat; ORR= overall response rate
(a) The ORR_{18} was calculated as the proportion of patients achieving a complete or partial response at Week 18.

In addition, a tipping point analysis was presented as a sensitivity analysis (data not shown).

Subgroup analyses of ORR18

On stratification factors: Stage (IV vs recurrent), gender and ethnicity (Asian or non-Asian) an additional subgroup analyses:

- nsNSCLC Stage (IV vs. Recurrent disease)
- Sex (male vs. female)
- Ethnicity (Asian vs. non-Asian)
- Age (<65 vs. ≥65 years),
- ECOG Performance Status (0 vs. 1)
- Planned dose of Paclitaxel (200 vs. 175 mg/m2)
- Planned dose of Carboplatin (AUC 6 vs. 5 mg/mL·minute)
- Reduced Percentage of paclitaxel dose at cycle 6 from initial dose (>80% vs. ≤80%)
- Reduced Percentage of carboplatin dose at cycle 6 from initial dose (AUC >80% vs. ≤80%)

These results are considered exploratory because of the multiplicity issue and also smaller sample sizes that cannot be pre-specified.

Table 24. Overall Response Rate at Week 18 (ORR18), Risk ratio and Multivariate-Adjusted Risk Ratio, and Risk Difference and Multivariate-Adjusted Risk Difference by Demographic nd Baseline Factors (ITT Population)

Baseline parameter	Baseline stratum	Treatment group	N	Response rate (a) n (%) [95% CI] (b)	Risk ratio [90% CI] (c)	Risk difference [95% CI] (c)	Multivariate-adjusted risk ratio [90% CI] (d)	Multivariate-adjusted risk difference [95% CI] (e)
Age, years	<65	Arm A	233	113 (48.5) [41.9, 55.1]	1.06 [0.90, 1.26]	0.03 [-0.06, 0.12]	1.04 [0.89, 1.22]	0.03 [-0.06; 0.12]
		Arm B	208	97 (46.6) [39.7, 53.7]				
	≥65	Arm A	92	43 (46.7) [36.3, 57.4]	1.13 [0.87, 1.48]	0.05 [-0.08, 0.19]	1.12 [0.86, 1.45]	0.06 [-0.07; 0.20]
		Arm B	118	48 (40.7) [31.7, 50.1]				
Baseline ECOG PS	0	Arm A	69	33 (47.8) [35.6; 60.2]	1.00 [0.75, 1.31]	0.00 [-0.15, 0.15]	1.00 [0.77, 1.30]	0.02 [-0.13; 0.17
		Arm B	103	48/103 (46.6) [36.7; 56.7]				
	1	Arm A	256	123 (48.0) [41.8; 54.4]	1.10 [0.93, 1.30]	0.04 [-0.04, 0.13]	1.06 [0.90, 1.25]	0.04 [-0.05; 0.13]
		Arm B	223	97/223 (43.5) [36.9; 50.3]				
nsNSCLC	Stage IV	Arm A	303	142/303 (46.9) [41.1; 52.7]	1.08 [0.93, 1.25]	0.04 [-0.04, 0.11]	1.08 [0.93, 1.25]	0.03 [-0.04; 0.11]
		Arm B	305	132/305 (43.3) [37.6; 49.0]				
	Recurrent disease	Arm A	22	14/22 (63.6) [40.7; 82.8]	1.03 [0.68, 1.55]	0.02 [-0.28, 0.32]	1.02 [0.68, 1.52]	0.02 [-0.27; 0.31]
		Arm B	21	13/21 (61.9) [38.4; 81.9]				
Gender	Male	Arm A	228	105 (46.1) [39.5; 52.8]	1.08 [0.91, 1.29]	0.04 [-0.05, 0.13]	1.09 [0.92, 1.29]	0.03 [-0.06; 0.12]
		Arm B	229	97 (42.4) [35.9; 49.0]				
	Female	Arm A	97	51 (52.6) [42.2; 62.8]	1.06 [0.84, 1.34]	0.03 [-0.11, 0.17]	1.03 [0.82, 1.30]	0.03 [-0.11; 0.17]
		Arm B	97	48 (49.5) [39.2; 59.8]				
Ethnicity	Asian	Arm A	141	75 (53.2) [44.6; 61.6]	1.04 [0.86, 1.25]	0.02 [-0.10, 0.14]	1.04 [0.86, 1.25]	0.02 [-0.10; 0.14]
		Arm B	141	72 (51.1) [42.5; 59.6]				
	Non-Asian	Arm A	184	81 (44.0) [36.7; 51.5]	1.11 [0.91, 1.36]	0.04 [-0.06, 0.14]	1.10 [0.90, 1.35]	0.04 [-0.06; 0.14]
		Arm B	185	73 (39.5) [32.4; 46.9]				
Paclitaxel initial dose	200 mg/m^2	Arm A	122	61 (50.0) [40.8; 59.2]	1.15 [0.91, 1.45]	0.06 [-0.06, 0.19]	0.96 [0.90, 1.02]	0.06 [-0.06; 0.19]
		Arm B	119	51 (42.9) [33.8; 52.3]				
	175 mg/m^2	Arm A	202	95 (47.0) [40.0; 54.2]	1.02 [0.85, 1.21]	0.01 [-0.09, 0.10]	0.99 [0.94, 1.05]	0.01 [-0.09; 0.10]
		Arm B	205	94 (45.9) [38.9; 52.9]				
Carboplatin initial dose	AUC 6 mg/mL min	Arm A	144	74 (51.4) [42.9; 59.8]	1.19 [0.95, 1.48]	0.08 [-0.04, 0.20]	1.17 [0.94, 1.45]	0.08 [-0.04; 0.19]
		Arm B	128	54 (42.2) [33.5; 51.2]				
	AUC 5 mg/mL min	Arm A	179	82 (45.8) [38.4; 53.4]	0.98 [0.82, 1.17]	-0.01 [-0.11, 0.09]	0.98 [0.82, 1.17]	-0.01 [-0.11; 0.09]
		Arm B	195	90 (46.2) [39.0; 53.4]				

Baseline parameter	Baseline stratum	Treatment group	N	Response rate (a) n (%) [95% CI] (b)	Risk ratio [90% CI] (c)	Risk difference [95% CI] (c)	Multivariate-adjusted risk ratio [90% CI] (d)	Multivariate-adjusted risk difference [95% CI] (e)
Reduced paclitaxel dose	>80%	Arm A	173	108 (62.4) [54.8; 69.7]	0.82 [0.72, 0.94]	-0.13 [-0.23, -0.03]	1.10 [1.03, 1.17]	0.13 [0.03; 0.23]
		Arm B	138	102 (73.9) [65.8; 81.0]				
	≤80%	Arm A	30	25 (83.3)	1.19	0.13	0.88	-0.16
		Arm B	20	13 (65.0) [40.8; 84.6]	[0.87; 1.63]	[-0.14; 0.41]	[0.75; 1.03]	[-0.41; 0.09]
Reduced carboplatin Dose	>80%	Arm A	171	107 (62.6) [54.9; 69.8]	0.84 [0.74, 0.96]	-0.12 [-0.22, -0.01]	1.09 [1.02, 1.16]	0.11 [0.01; 0.21]
		Arm B	142	103 (72.5) [64.4; 79.7]				
	≤80%	Arm A	31	26 (83.9) [66.3; 94.5]	1.07 [0.77, 1.47]	0.05 [-0.24, 0.34]	0.91 [0.76, 1.09]	-0.11 [-0.37; 0.15]
		Arm B	17	12 (70.6) [44.0; 89.7]				

Source: Table 14.2.1.1.3.1, Table 14.2.1.1.3.2, Table 14.2.1.1.3.3, Table 14.2.1.1.3.4

Abbreviations: CI = confidential interval; CR = complete response; ITT = intention-to-treat; ORR= overall response rate; PR = partial response.

Arm A represented BAT1706 plus paclitaxel and carboplatin; Arm B represented EU-Avastin plus paclitaxel and carboplatin.

(a) The ORR_{18} was calculated as the proportion of patients achieving a PR or a CR at Week 18.

(b) The method of Clopper and Pearson was used to calculate Confidence Intervals.

(c) The risk ratio and risk difference were estimated including covariates of stratification factors: nsNSCLC stage (recurrent disease after any stage at time of primary diagnosis, or Stage IV), Gender (male or female), and ethnicity (Asian or non-Asian). Stratification factors were from IWRS system.

(d) The multivariate-adjusted risk ratio and the 90% CI were estimated by the log-binomial regression model including stratification factors. Stratification factors were from IWRS system.

(e) The multivariate-adjusted risk difference and the 95% CI were estimated by the binomial regression model including stratification factors. Stratification factors were from IWRS system.

In addition, the logistic regression analyses of ORR18 based on baseline dose differences and ethnicity as well as logistic regression analyses of ORR18 based on dose reduction and ethnicity were performed in ITT and PP population (presented in Table 25 and Table 26). Overall, the results of logistic regression analyses of ORR18 in the PP population were similar to those in the ITT population.

Table 25. Logistic Regression Analysis of Overall Response Rate at Week 18 Based on Initial Dose Differences and Ethnicity - ITT Population

	Odds Ratios	95% Confidence Interval	P-Value
Treatment (BAT1706 vs EU-Avastin)	1.156	0.845, 1.582	0.363
Paclitaxel dose (200 vs 175 mg/m^2)	1.627	0.844, 3.137	0.146
Carboplatin dose (AUC 6 vs 5 mg/mL·min)	1.007	0.578, 1.754	0.982
Ethnicity (Asian vs non-Asian)	2.082	1.362, 3.184	<0.001

Source: Table 14.2.1.1.7

Abbreviations: CI = confidential interval; CR = complete response; ORR= overall response rate; PP = per-protocol; PR = partial response.

The ORR_{18} was calculated as the proportion of patients achieving a PR or a CR at Week 18.

Each of the odds ratio, 95% CI, and p-value was estimated by the logistic regression model of ORR_{18} with independent factors including paclitaxel dose (200 vs 175 mg/m^2), carboplatin dose (AUC 6 vs 5 mg/mL·min), treatment group, and ethnicity (Asian vs non-Asian).

Table 26. Logistic Regression Analysis of Overall Response Rate at Week 18 Based on Dose Reduction and Ethnicity - ITT Population

	Odds Ratios	95% Confidence Interval	P-Value
Treatment (BAT1706 vs EU-Avastin)	0.668	0.420, 1.063	0.088
Reduced Percentage of paclitaxel dose at Cycle 6 from initial dose (>80% vs. ≤80%)	2.458	0.504, 11.991	0.266
Reduced Percentage of carboplatin dose at Cycle 6 from initial dose (>80% vs. ≤80%)	0.277	0.053, 1.450	0.129
Ethnicity (Asian vs non-Asian)	1.829	1.117, 2.995	0.016

Source: Table 14.2.1.1.8

Abbreviations: CI = confidential interval; CR = complete response; ORR= overall response rate; PR = partial response.

The ORR_{18} was calculated as the proportion of patients achieving a PR or a CR at Week 18.

Each of the odds ratio, 95% CI, and p-value was estimated by the logistic regression model of ORR18 with independent factors including reduced percentage of paclitaxel dose (>80% vs ≤80% of initial dose at Cycle 6), reduced percentage of carboplatin dose (AUC >80% vs ≤80% of initial dose at Cycle 6), treatment group, and ethnicity (Asian vs non-Asian)

Summary of main efficacy results

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

Table 27. Summary of efficacy for Phase III study BAT1706-003-CR

Title: A Multicenter, Randomized 1:1, Double-blind, Phase III Study of BAT1706 versus EU-Avastin® plus Chemotherapy in Patients with Advanced Non-squamous Non-Small Cell Lung Cancer		
Study identifier	BAT1706-003-CR EUDRACT: 2017-001286-25	
Design	Multinational, double-blind, randomised, parallel-group Phase 3 clinical trial	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Combination treatment period: cycles 1-6 (21-day treatment cycle each) Monotherapy BAT1706/EU-Avastin: cycle > 7 up to 12 months from initial randomisation LTE Monotherapy with BAT1706 up to 24 months from initial randomisation-data not included
Hypothesis	Equivalence	
Treatments groups	A (N=325)	BAT1706 IV infusion, 15 mg/kg Q3W (6 cycles) with Paclitaxel 200 mg/m2(Chinese patients 175 mg/m2) and carboplatin (target area under the curve [AUC] 6 mg/mL·minute) for 6 cycles
	B (N=326)	EU-Avastin IV infusion, 15 mg/kg Q3W (6 cycles) with Paclitaxel 200 mg/m2(Chinese patients 175 mg/m2) and carboplatin (target area under the curve [AUC] 6 mg/mL·minute) for 6 cycles

Endpoints and definitions	Primary endpoint	Objective response rate (ORR9 at Week 18	Proportion of patients whose objective response rate was either CR or PR by IRC according to RECIST v1.1. criteria by 18 weeks
	Secondary endpoint	PFS	Progression free survival
	Secondary endpoint	OS	Overall survival
	Secondary endpoint	DoR	Duration of response
	Secondary endpoint	ORR6, ORR12	Objective response rate at Week 6 Objective response rate at Week 12
Database lock	05 November 2019		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT) time point: primary analysis: week 18			
Descriptive statistics and estimate variability	Treatment group		Arm A BAT1706	Arm B EU-Avastin
	Number of		N=325	N=326
	Primary endpoint	ORR18	48.0% [42.5; 53.6]	44.5% [39.0; 50.1]
		ORR Difference (ITT) (95% CI)	0.03 [-0.04, 0.11]	
	Secondary endpoint Week 52	Median PFS (months) 95%CI HR 95%CI	8.214 [7.097, 8.345] 0.932 (95% CI [0.770, 1.127]	8.115 [6.242, 8.345]

	Secondary endpoint Week 52	Mos (months) 95% CI HR (unstratified) 95% CI	16.394 [13.897, 18.957] 0.949 95% CI [0.760, 1.185]	15.507 [13.963, 19.713]
	Secondary endpoint Week 52	mDoR (months) Hazard Ratio (unstratified) 95% CI	7.13 95% CI [6.571, 7.786] 1.131 95% CI [0.799, 1.464]	7.82 [6.384, 8.98]
	Secondary endpoint	ORR6 RD [95% CI] 0RR12 RD [95% CI]	27.4% 0.04 [-0.02, 0.11] 45.2% 0.04 [-0.03, 0.12]	22.7% 40.8%

2.6.5.3. Clinical studies in special populations

No specific studies considering children, elderly patients, patients with renal or hepatic impairment were conducted.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

A single randomised, double-blind, parallel group, multicentre study (Study BAT-1706-003-CR) was conducted to compare the efficacy, safety, and immunogenicity between BAT1706 and EU- Avastin in patients with newly diagnosed advanced stage IV or recurrent non-squamous non-small cell lung cancer (nsNSCLC). Justification for extrapolation to the other approved indications for Avastin has been provided, which is further discussed in this report.

Among the 105 study centres initiated, a total of 92 study centres in 5 countries (China, Turkey, Ukraine, South Africa, and Mexico) obtained informed consent from at least 1 patient, and 86 study centres successfully randomised patients.

All studies were conducted according to the respective GCP and ICH guidelines, and all trials conducted outside the EU have been performed according to the appropriate regulatory requirements in the countries where the study was conducted.

The applicant stated that on-site inspections of the study BAT1706-003-CR sites in China, Ukraine and Australia have been performed by NMPA and FDA between January to August 2021, with no significant findings.

Design and conduct of clinical studies

The study was multicentred, randomised 1:1, double-blind, parallel-group Phase III Study comparing BAT1706 versus EU-Avastin as add-on to Chemotherapy in Patients with Advanced Non-squamous Non-Small Cell Lung Cancer. The selected study population with stage IV or recurrent disease non-squamous NSCLC with at least 6 months from previous neoadjuvant/adjuvant treatment to randomisation is considered sufficiently sensitive to identify a difference between the intended to be biosimilar BAT1706 and EU-Avastin. The efficacy and safety profile of comparator treatment regimen with EU-Avastin in combination with paclitaxel and carboplatin approved for advanced non-squamous NSCLC is well understood.

The study consists of combination period in which the investigation drug (BAT1706/EU-Avastin) was administered intravenously at 15 mg/kg in combination with paclitaxel 200 mg/m2 and carboplatin AUC 6 in a regimen according to the EU-Avastin labelling. The combination was given up to 6 cycles unless there was evidence of disease progression or intolerance of the study treatment. The first period (bevacizumab BAT1706/EU-Avastin plus chemotherapy for 6 cycles) is of relevance for the primary efficacy assessment (ORR18).

Dose modifications for both BAT1706 and EU-Avastin were not allowed during the study. Dose modifications for intolerance to chemotherapy were allowed twice, thereafter the patients could start monotherapy with BAT1706 or EU-Avastin or start another line of anticancer therapy after Investigator's judgment. The same study drug (BAT1706 or EU-Avastin) was to be continued during maintenance monotherapy period, based on the allocation at the time of randomisation. The study drug (BAT1706 or Avastin) was discontinued and the patient was permanently withdrawn from the study in the event of toxicities ≥Grade 4 or if treatment delay was > 6 weeks (> 9 weeks interval between the 2 administrations). If a subject discontinued study treatment the subject was proceeded to End-of-Treatment visit.

The protocol which allows proceeding to monotherapy after 2 dose reductions of chemotherapy may create protocol deviations as the pre-specified assessments for tumour response will be conducted after cycles 2, 4, and 6. In this aspect the landmark analysis of ORR at Week 6 and 12 besides the primary efficacy endpoint ORR18 is considered appropriate for a complete analysis of efficacy equivalence. In addition, the proportion of patients who switched to monotherapy with BAT1706 or EU-Avastin after discontinuation of combination therapy after 1-2, or 3-4, or 5-6 cycles was balanced between arms. No NAT was allowed by the study protocol and thus no data on these patients were collected.

End-of -study (EoT) was defined at week 53 from the randomisation to the patient´s last study visit, which is considered adequately long to investigate efficacy as well as immunogenicity and safety endpoints.

After the first year of therapy, regardless of the arm they were allocated to initially, patients still receiving benefit from the therapy were offered the opportunity to receive BAT1706 for up to one more year in a long-term extension (LTE) study.

The inclusion/exclusion criteria for the study BAT-1706-003-CR and the study E4599 for Avastin in the same indication (Avastin SmPC, Sandler et al 2006) are comparable.

The study design, inclusion and exclusion criteria are acceptable.

The stratification factors chosen (NSCLC stage newly diagnosed stage IV/recurrent disease, gender and ethnicity) are considered clinically relevant prognostic factors for the underlying disease.

The planned sample size was 632 (316/316); a total of 651 were randomised 1:1 325 patients in the BAT1706arm (Arm A) and 326 patients in EU-Avastin arm (Arm B).

The sample size was calculated to ensure sufficient power for both the estimation of ORR18 RD (EMA) and ORR18 RR (FDA) taking into account the estimated ORR for the reference arm (pooled ORR from meta-analysis) and the equivalence margins for RD (-12%, +15%), to preserve net effect of Avastin of 29%.

The Risk Difference is given by "BAT1706 – EU-Avastin". The asymmetric margins of the 95% CI for the RD of ORR18 with a slightly higher upper margin of 0.15 chosen, were justified as there was no medical concern that slightly higher ORR18 of BAT1706 would result in higher toxicity. However, the similarity of the safety profile is assessed separately based on the similarity in PK, safety and immunogenicity. Statistically, the Type 1 error rate is preserved, both by using post-hoc symmetric (-0.12, 0.12) or pre-specified asymmetric (-0.12, 0.15) 95%CI of RD, as the study results [-0.04, 0.11] fit within both intervals.

Taking into account the precedent with the previous approved Avastin biosimilars, an asymmetric margin for the equivalence range is not recommended. However, as the results have been shown to be robust, showing equivalence using the symmetric margins as well, besides the pre-specified asymmetric equivalence interval, conclusions on efficacy can be drawn anyway.

Demographic characteristics per study site and race shows a balanced distribution of randomised ITT population per arm. The overview of the enrolment for the main study sites (> 20 patients overall) shows a balanced distribution between the treatment arms. According to the Demographic and Baseline Data in CSR, the distribution of prior and concurrent medical history and prior and concurrent medication/procedures, specifically those related to the prophylaxis of adverse events is balanced between the arms, which is reassuring.

In overall ITT population distribution between Asian/Non-Asian population was 43.2%/ 57% and it was well balanced between arms.

Baseline disease characteristics are representative of the intended study population. The median age of study population was 61 years, balanced between arms.

Regarding the baseline disease characteristics, the majority of patients had stage IV disease as primary diagnosis (93.4% in ITT: 93.2 % in Arm A and 93.6 % in Arm B), the rest had recurrent disease (6.6% in ITT). The majority of the patients had metastases (97.1% in ITT).

According to inclusion/exclusion criteria (criterion 4), the patients with NSCLC with activating EGFR mutations or ALK translocations were excluded in regions where the targeted agents were available. Patients with unknown mutation status or known EGFR mutation or ALK receptor alteration could be included provided the corresponding targeted agent was not available. The majority of the patients in ITT had tumours with negative EGFR, ALK and ROS-1 mutation status. The proportion of the patients with positive EGFR/ALK/ROS-1 (conferring slightly higher, non-statistically significant, responsiveness) mutation status was small and balanced between the arms.

The median compliance to the study drugs and chemotherapeutics was high and balanced between arms.

Primary analyses were done on the ITT population set and in the PPS that have equal relevance in a biosimilar setting allowing a more conservative analysis (ICH E9, CPMP/ICH/363/96).

The number of patients in the ITT, PPS, SAF and PK Population sets was balanced between the treatment arms. The number of patients enrolled in the different evaluable patient populations are considered adequate. In the ITT population there were 325 in the BAT1706 (Arm A) and 326 patients in the EU-Avastin (Arm B). The patients experiencing a protocol deviation that affected their evaluation for the primary objective of the study as well as the patients without at least 1 valid post treatment evaluation were excluded from the PPS, which is endorsed.

A higher proportion of randomised subjects were excluded from PPS in EU-Avastin arm than in BAT1706 arm in accordance to PPS analysis definition (received less than 3 cycles of study drugs due to reasons other than disease progression, death, or AEs: BAT1706: 1.8% (6/325), EU-Avastin: 5.8% (19/326, OR patients without at least 1 tumour assessment and who discontinued due to other reasons than excessive toxicity, early progression or death: BAT1706: 0.9% (3/325), EU-Avastin: 4% (13/326). It is assumed that these subjects were classified as non-responders in the primary endpoint analysis in ITT.

A higher proportion of randomised subjects were excluded from PPS in BAT1706 arm than in EU-Avastin arm due to major protocol deviations. According to the applicant, 20 patients who had been incorrectly reported as NSCLC Stage IV were assigned as Major Protocol Deviations (PD) and were excluded from PP population. In addition, 3 further patients were excluded (inclusion #8: no evidence of brain lesions stability before screening); Although the database was unblinded, the PP population review and additional exclusion of these PP patients were done in a blinded manner by blinded study team members. A post-hoc sensitivity analysis based on the primary PP population showed that the differences in results between the analysis of ORR18 for the primary PP population and the Modified PP population were minor, and the equivalence margins (for risk ratio and risk difference and for multivariate-adjusted risk ratio and risk difference) were met in all scenarios.

There were several changes to the study protocol during the study, mostly initiated after discussion with the FDA. The most important changes that possibly could impact the interpretation of the study results were done in amendment 1. This amendment was implemented before any subject had reached the time for primary endpoint evaluation.

Endpoints

The primary endpoint was risk difference (RD) 95%CI of ORR in the ITT population at Week 18. The analysis of ORR in ITT is in accordance with efficacy analysis in cancer trials, however in equivalence trial analysis of ORR 18 in the per-protocol-set (PPS) population used as supportive analysis of the main analysis in ITT is considered of equal importance and should lead to similar result.

The schedule for tumour assessment was clearly defined. Patients underwent tumour assessment at Weeks 6, 12, and 18, regardless of the number of cycles actually completed, then after every 3 cycles (approximately every 9 weeks) until week 53 and at Safety Follow-up Visit (SFUV)/End of Treatment (EoT). Tumour response at different time points was determined by IRC according to RECIST v1.1.

The proposed secondary time-related efficacy endpoints: median PFS, OS, duration of response at 12 months as well as landmark analysis of ORR at Week 6 and 12 and BOR at Week 18 to support primary endpoint analysis ORR at week 18 are considered appropriate for analysis of equivalence of efficacy.

Statistical analysis

The primary analysis was performed based on both the ITT and PP population which is recommended for studies aimed to show equivalence. No specific intercurrents events are defined, but patients who did not provide data for the responder/survivor endpoint were considered non-responders.

Sensitivity analyses to assess the robustness of conclusions to missing data were to be carried out if there were more than 5% of patients missing evaluations in either treatment arm. Data for the primary endpoint of ORR18 were missing and were imputed for analysis for 67/325 (20.6%) patients in the BAT1706 group and 92/326 (28.2%) patients in the EU-Avastin group. This analysis is not what was planned since there were no results summarised based on a missing data imputation under the MAR assumption. However, a tipping point analysis was presented as a sensitivity analysis showing that the results where equivalence could not be concluded are quite implausible. Accordingly, it is considered that the provided sensitivity analysis sufficiently supports a conclusion of robust results.

The study has different primary objectives depending on regulatory region. This does not cause a multiplicity issue since only one primary objective is of interest for this application for each region.

Efficacy data and additional analyses

Primary endpoint analysis

The primary efficacy endpoint was ORR (i.e., subjects who achieved CR or PR per RECIST version 1.1 as assessed by IRC) at Week 18 (corresponding to 6 cycles of BAT1706/Avastin in combination with chemotherapy). In the ITT population observed ORR18 was 48.0% in BAT1706 arm (Arm A) and 44.5% in EU-Avastin arm (Arm B). This results in an un-adjusted risk difference (RD) of 0.03. The 2-sided 95% CI [-0.04, 0.11] was entirely contained within the pre-specified equivalence margins (-0.12, 0.15).

Importantly, the outcome in the PPS (point-estimates and confidence intervals) was consistent with that of the ITT population.

In conclusion, the 95%CI for the RD of primary endpoint ORRw18 is contained in the pre-specified equivalence margins for both ITT and PP population supporting the claim of equivalence of efficacy for BAT1706 and EU-Avastin.

According to the SAP, in the efficacy analysis of primary endpoint ORR18 as well as for all analyses of responder/survivor proportion endpoints performed on ITT and PP population, patients who do not provide data for the responder/survivor endpoint were considered non-responders.

In addition, the patients with early discontinuation and missing data were classified as non-responders. The analyses of ORR currently based on the response achieved at week 18, is accompanied with a description of the number of subjects in each arm classified as non-responders separating non-responders observed and non-responders imputed.

In the subgroup analysis for ORR18 the equivalence was shown based on the 95% CIs, which is endorsed. It is accepted that the subgroup analyses should be considered exploratory due to limitations in sample sizes. In the largest subgroups (disease stage IV newly diagnosed, male, age<65 years, baseline ECOG PS 1) and most importantly, in both ethnicity subgroups (Asian or non-Asian), the 95% CI of risk difference in ORR18 fell within the pre-specified equivalence margins (-0.12,0.15). The results for all subgroups in the PP population were similar to those in the ITT.

The logistic regression analyses of ORR18 based on baseline dose differences and ethnicity as well as logistic regression analyses of ORR18 based on dose reduction and ethnicity showed however higher rates of odds ratio of ORR18 in Asian patients compared with non-Asian patients, while similar ORR18 results were observed by baseline paclitaxel dose (200 vs 175 mg/m2) (p=0.146) or baseline carboplatin dose (AUC 6 vs 5 mg/mL·minute) (p=0.982).Ethnicity as potential modulatory factor of the ORR18 results is considered sufficiently addressed. Hence, similar ORR18 results were seen between

arms, disregarding the starting dose paclitaxel or carboplatin, dose reductions and disregarding ethnicity.

Secondary endpoints analysis

PFS: In the ITT population at primary analysis, no significant difference is noticed between the point estimate median PFS in the two arms (8.1 months in the BAT18706 group and 7.7 months in the EU-Avastin group) with stratified HR of 0.915 with 95% CI [0.741, 1.132]. PFS data in ITT population at the final analysis (Week 52, 25 June 2020) also shows comparable results between arms. Hence, the median PFS (K-M) in ITT is comparable between the two arms (8.2 months in the BAT1706 group and 8.1 months in the EU-Avastin group) with HR stratified for time to PFS of 0.932 (95% CI [0.770, 1.127], p = 0.464) and overlapping KM curves.

No significant difference in the number of patients censored for PFS is noted between the arms with the data cut-off date being the primary reason for censoring.

OS: At the date of primary analysis, the data on OS were immature with OS events 99 (30.5%) in Arm A and 102 (31.3%) in Arm B, respectively. At the final analysis at Week 52, no significant difference in the OS is noted between arms with K-M median OS (ITT population) comparable between the 2 treatment arms, with overlapping K-M curves and hazard ratio stratified for time to OS of 0.974 (95% CI [0.779, 1.218], p = 0.819).

DoR: Comparable median DoR in the patients with response were observed at the final analysis with median DoR 7.1 months in the BAT1706 group and 7.8 months in the EU-Avastin group.

Similar results for PFS, OS and DoR in the PP population at the final analysis are supporting the ITT results.

ORR6 and ORR12: Landmark analysis of the ORR at Week 6 and Week 12 in ITT and PP population showed no significant difference between arms in ORR6 (27.4% vs 22.7% in Arm A vs Arm B) and ORR12 (45.2% vs 40.8% in Arm A vs Arm B). The 95%CIs of the risk difference for ORR6 0.04 [-0.02, 0.11] and ORR120.04 [-0.03, 0.12] are entirely contained in the prespecified equivalence interval, thus supporting the clinical similarity.

BOR: BOR in ITT population at Week 18 was comparable between arms with 50.8% in the BAT1706 group and 40.5% in the EU-Avastin group with the unadjusted risk difference of 0.10 and 95% CI [0.02, 0.18] which fit in the pre-defined equivalence margins of (-0.12, 0.15), supporting equivalence shown for the primary endpoint. The results are robust, supported by multivariate-adjusted risk difference of BOR at week 18 and by BOR at week 52 risk difference (95%CI) which are in line with the primary analysis data.

2.6.7. Conclusions on the clinical efficacy

The analysis of primary endpoint ORR at Week 18 and the 95%CI for the risk difference (RD) of primary endpoint ORR18 is contained in the pre-specified equivalence margins for both ITT and PP population suggesting equivalence of efficacy for BAT1706 and EU-Avastin. Statistically, the Type 1 error rate is preserved, both by using post-hoc symmetric (-0.12, 0.12) or pre-specified asymmetric (-0.12, 0.15) 95%CI of RD, as the study results [-0.04, 0.11] fit within both intervals. Considering the precedent with the previous approved Avastin biosimilars, an asymmetric margin for the equivalence range is not recommended. However, as the results have been shown to be robust showing equivalence using the symmetric margins, a conclusion of similar efficacy can be drawn.

The robustness of similarity showed for the primary endpoint is supported by the pre-specified and post-hoc sensitivity analyses of the primary endpoint, by the landmark analysis of ORR and by the

consistency of the results between ITT and PP populations. Comparable results between arms for the secondary, time-related endpoints at the cut-off for the final analysis (Week 52, 25 June 2020), median PFS, OS and DoR with overlapping KM curves support the similarity observed for the primary point estimate. The final results on PFS, OS and DoR in the ITT are consistent with the PP population analysis.

2.6.8. Clinical safety

Data included in the safety section has been updated based on the week 52 data.

2.6.8.1. Patient exposure

BAT1706-001-CR and BAT1706-002-CR

Two Phase I studies BAT1706-001-CR and BAT1706-002-CR in healthy volunteers that were randomised, double-blind, single-dose, parallel group studies were performed.

- In study BAT1706-001-CR (conducted in New Zealand), 125 subjects were randomised and received treatment (safety analysis set): 40, 43 and 42 subjects in BAT1706, EU-Avastin and US-Avastin groups, respectively.
- In study BAT1706-002-CR (conducted in China), 80 subjects were randomised and received treatment: 39 and 41 subjects in the BAT1706 and EU-Avastin groups, respectively.

In BAT1706-001-CR 122 out of 128 randomised subjects completed the study and 6 subjects prematurely discontinued from the study. Of the 6 subjects who discontinued, 5 subjects withdrew consent, and 1 subject was discontinued because he was unable to be cannulated prior to study drug administration. In BAT1706-002-CR out of the 82 randomised subjects, 3 subjects discontinued from the BAT1706 group (1 for medical reasons and 1 for personal reasons and 1 due to loss of contact). Two subjects (both assigned to the BAT1706 group) withdrew from the study before the administration. Finally, 79 (96.3%) of the subjects completed this study.

BAT1706-003-CR (Phase III Study)

Study BAT1706-003-CR was a Phase III, randomised, double blind, multicentre, active comparator, parallel 2-arm study in patients with previously untreated advanced nsNSCLC. Bevacizumab was used together with to carboplatin and paclitaxel in the combination phase followed by monotherapy with bevacizumab. BAT1706 was compared to EU-Avastin. A total of 651 patients were randomised, 325 patients in the BAT1706 group and 326 patients in the EU-Avastin group (ITT population); and 325 and 326 patients, respectively, received treatment (safety population) (Table 28).

Table 28. Patient Disposition Week 52 Data Set (25 June 2020) by Study Period, Study BAT1706-003-CR (ITT population)

	Overall		**Combination Period**		**Monotherapy Period**	
Number (%) Patients with:	**BAT1706 + Carboplatin + Paclitaxel**	**EU-Avastin ++ Carboplatin + Paclitaxel**	**BAT1706 + Carboplatin + Paclitaxel**	**EU-Avastin ++ Carboplatin + Paclitaxel**	**BAT1706**	**EU-Avastin**
Randomised	325 (100.0)	326 (100.0)				
Received Treatment	325 (100.0)	324 (99.4)	325 (100.0)	324 (100.0)	235 (100.0)	211 (100.0)
Treatment Ongoing, n (%)	76 (23.4)	60 (18.4)	246 (75.7)	221 (68.2)	76 (32.3)	60 (28.4)

	Overall		Combination Period		Monotherapy Period	
Number (%) Patients with:	BAT1706 + Carboplatin + Paclitaxel	EU-Avastin + Carboplatin + Paclitaxel	BAT1706 + Carboplatin + Paclitaxel	EU-Avastin + Carboplatin + Paclitaxel	BAT1706	EU-Avastin
Number of Patients who Received Combination Treatment during Study, n (%)	325 (100.0)	324 (99.4)	325 (100.0)	324 (100.0)		
1 cycle	13 (4.0)	27 (8.3)	13 (4.0)	27 (8.3)		
2 cycles	23 (7.1)	24 (7.4)	23 (7.1)	24 (7.4)		
3 cycles	13 (4.0)	18 (5.5)	13 (4.0)	18 (5.6)		
4 cycles	61 (18.8)	75 (23.0)	61 (18.8)	75 (23.1)		
5 cycles	13 (4.0)	22 (6.7)	13 (4.0)	22 (6.8)		
6 cycles	202 (62.2)	158 (48.5)	202 (62.2)	158 (48.8)		
Number of Patients who Received Maintenance (Monotherapy) Treatment, n (%)	235 (72.3)	211 (64.7)			235 (100.0)	211 (100.0)
1-4 cycles	63 (19.4)	64 (19.6)			63 (26.8)	64 (30.3)
5-9 cycles	92 (28.3)	83 (25.5)			92 (39.1)	83 (39.3)
10-14 cycles	80 (24.6)	64 (19.6)			80 (34.0)	64 (30.3)
Primary Reason for End of Treatment, n (%)	249 (76.6)	264 (81.0)	90 (27.7)	113 (34.9)	159 (67.7)	151 (71.6)
Disease progression	164 (50.5)	151 (46.3)	36 (11.1)	35 (10.8)	128 (54.5)	116 (55.0)
Adverse events	32 (9.8)	34 (10.4)	21 (6.5)	25 (7.7)	11 (4.7)	9 (4.3)
Surgical procedures	0	2 (0.6)	0	2 (0.6)	0	0
Treatment delay of > 6 weeks	2 (0.6)	3 (0.9)	1 (0.3)	2 (0.6)	1 (0.4)	1 (0.5)
Lack of compliance with protocol	0	1 (0.3)	0	1 (0.3)	0	0
Death	23 (7.1)	24 (7.4)	18 (5.5)	18 (5.6)	5 (2.1)	6 (2.8)
Withdrawal by patient	17 (5.2)	30 (9.2)	9 (2.8)	19 (5.9)	8 (3.4)	11 (5.2)
Symptomatic deterioration	2 (0.6)	6 (1.8)	2 (0.6)	5 (1.5)	0	1 (0.5)
Other	9 (2.8)	13 (4.0)	3 (0.9)	6 (1.9)	6 (2.6)	7 (3.3)
Reason for End of Study /Combination Period / Monotherapy Period, n (%) [a] [b]	209 (64.3)	220 (67.5)	84 (25.8)	104 (32.1)	123 (52.3)	113 (53.6)
Complete a maximum of 24 months treatment	2 (0.6)	1 (0.3)				
Death	167 (51.4)	169 (51.8)	72 (22.2)	82 (25.3)	95 (40.4)	87 (41.2)
Lost to follow-up	7 (2.2)	9 (2.8)	2 (0.6)	2 (0.6)	5 (2.1)	7 (3.3)
Withdrawal by patient	13 (4.0)	23 (7.1)	9 (2.8)	16 (4.9)	4 (1.7)	7 (3.3)
Other	20 (6.2)	18 (5.5)	1 (0.3)	4 (1.2)	19 (8.1)	12 (5.7)
Number of Patients who Received BAT1706 in LTE, n (%)	76 (23.4)	60 (18.4)				

a. LTE = Long-term extension.

b. Note: Percentage was based on randomised patients.

c. (a) Subject 114001 and 304003 were randomised but not treated, so they were not included in the section "Reason for End of Combination Period".

d. (b) Subject 214001, 214002 and 320005 continued study at Month 12 (end of monotherapy period), so they were not included in the section "Reason for End of Monotherapy Period"

The median duration of therapy was 34.0 weeks (range: 3.0 to 62.3 weeks) for BAT1706 and 27.6 weeks (range: 3.0 to 56.4 weeks) for EU-Avastin. Patients received a median total number of 10 BAT1706 infusions and 9 EU-Avastin infusions. The large majority of the patients (97.5% in the

BAT1706 group and 97.2% in the EU-Avastin group) received the planned relative dose intensity within the range of 80% to 120%.

For the combination period, the median duration of therapy was 18.0 weeks (range: 3.0 to 25.4 weeks) for BAT1706 and 17.9 weeks (range: 3.0 to 27.6 weeks) for EU-Avastin. Patients received a median total number of 6 BAT1706 infusions and 5 EU-Avastin infusions.

During the monotherapy period, the safety population included 235 patients in the BAT1706 group and 211 patients in the EU-Avastin group. The median duration of therapy was 23.0 weeks (range: 3.0 to 42.0 weeks) for BAT1706 and 21.3 weeks (range: 3.0 to 41.4 weeks) for EU-Avastin. Patients received a median total number of 7 BAT1706 infusions and 7 EU-Avastin infusions.

Table 29. Study Drug Exposure by Study Period, Safety Population, Study BAT1706-003-CR

	Overall		**Combination Period**		**Monotherapy Period**	
Number (%) Patients with:	**BAT1706 + Carboplatin + Paclitaxel N=325**	**EU-Avastin + Carboplatin + Paclitaxel N=324**	**BAT1706 + Carboplatin + Paclitaxel N=325**	**EU-Avastin + Carboplatin + Paclitaxel N=324**	**BAT1706 N=235**	**EU-Avastin N= 211**
Duration of BAT1706/EU-Avastin Therapy (weeks) (a)						
n (%)	325 (100.0)	324 (100.0)	325 (100.0)	324 (100.0)	235 (100)	211 (100)
Mean ± SD	32.0 ± 16.39	28.8 ± 17.20	15.8 ± 5.00	14.6 ± 5.51	22.0 ± 10.66	21.4 ± 10.82
Median	34.0	27.6	18.0	17.9	23.0	21.3
Q1; Q3	18.4; 48.3	12.3; 46.2	12.3; 19.0	12.0; 18.4	12.1; 31.6	9.6; 32.7
Min; Max	3.0; 62.3	3.0; 56.4	3.0; 25.4	3.0; 27.6	3.0; 42.0	3.0; 41.4
Total Number of Infusions Received						
n (%)	325 (100.0)	324 (100.0)	325 (100.0)	324 (100.0)	235 (100)	211 (100.0)
Mean ± SD	10 ± 5.2	9 ± 5.5	5 ± 1.5	5 ± 1.7	7 ± 3.4	7 ± 3.5
Median	10	9	6	5	7	7
Q1; Q3	6; 15	4; 15	4; 6	4; 6	4; 10	3; 11
Min; Max	1; 17	1; 17	1; 6	1; 6	1; 13	1; 13
Number of Initiated Cycles						
n (%)	325 (100.0)	324 (100.0)	325 (100.0)	324 (100.0)	235 (100)	211 (100)
Mean ± SD	10 ± 5.2	9 ± 5.5	5 ± 1.5	5 ± 1.7	7 ± 3.4	7 ± 3.5
Median	10	9	6	5	7	7
Q1; Q3	6; 15	4; 15	4; 6	4; 6	4; 10	3; 11
Min; Max	1; 17	1; 17	1; 6	1; 6	1 ;13	1; 13
Cumulative Actual Treatment Dose (mg/kg)						
n (%)	325 (100.0)	324 (100.0)	325 (100.0)	324 (100.0)	235 (100)	211 (100)
Mean ± SD	152.2 ± 78.41	136.8 ± 81.43	75.2 ± 22.7	69.3 ± 25.13	106.5 ± ± 51.15	103.6 ± 51.78
Median	153.6	136.2	89.0	78.2	106.1	107.8

Number (%) Patients with:	Overall		Combination Period		Monotherapy Period	
	BAT1706 Carboplatin + Paclitaxel N=325	EU-Avastin + Carboplatin + Paclitaxel N=324	BAT1706 Carboplatin + Paclitaxel N=325	EU-Avastin + Carboplatin + Paclitaxel N=324	BAT1706 N=235	EU-Avastin N= 211
Q1; Q3	87.4; 228.8	60.5; 217.3	60.4; 90.9	59.2; 90.0	60.4; 150.4	47.9; 156.0
Min; Max	15.0; 270.4	14.9; 266.3	15.0; 94.9	14.9; 96.8	14.8; 205.7	14.6; 194.3
Dose Intensity (mg/kg/week) (b)						
n (%)	325 (100.0)	324 (100.0)	325 (100.0)	324 (100.0)	235 (100)	211 (100)
Mean ± SD	4.8 ± 0.31	4.8 ± 0.32	4.8 ± 0.33	4.8 ± 0.35	4.9 ± 0.29	4.9 ± 0.34
Median	4.8	4.9	4.9	4.9	4.9	4.9
Q1; Q3	4.7; 5.0	4.6; 5.0	4,7; 5.0	4.7; 5.0	4.8; 5.1	4.8; 5.0
Min; Max	3.2; 5.4	3.5; 5.4	3.4; 5.4	3.2; 5.4	3.1; 5.4	3.2; 5.9
Relative Dose Intensity (%) (c), n (%)						
< 60%	0	0	0	0	0	0
60% - < 80%	8 (2.5)	9 (2.8)	8 (2.5)	15 (4.6)	3 (1.3)	6 (2.8)
80% - < 90%	39 (12.0)	52 (16.0)	40 (12.3)	44 (13.6)	15 (6.4)	15 (7.1)
90% - 110%	278 (85.5)	263 (81.2)	277 (85.2)	265 (81.8)	217 (92.3)	188 (89.1)
> 110%	0	0	0	0	0	2 (0.9)
Relative Dose Intensity (%) (c), n (%)						
< 80%	8 (2.5)	9 (2.8)	8 (2.5)	15 (4.6)	3 (1.3)	6 (2.8)
80% - 120%	317 (97.5)	315 (97.2)	317 (97.5)	309 (95.4)	232 (98.7)	205 (97.2)
> 120%	0	0	0	0	0	0
Number of Patients with Delays (d), n (%)	168 (51.7)	163 (50.3)	124 (38.2)	118 (36.4)	92 (39.1)	83 (39.3)
Number of Patients without Delays (d), n (%)	144 (44.3)	134 (41.4)	188 (57.8)	179 (55.2)	143 (60.9)	128 (60.7)
Not Applicable (d), n (%)	13 (4.0)	27 (8.3)	13 (4.0)	27 (8.3)	0	0
Patients with Delays						
≤ 1 week	79 (24.3)	80 (24.7)	76 (23.4)	66 (20.4)	42 (17.9)	43 (20.4)
> 1 - 3 weeks	59 (18.2)	56 (17.3)	36 (11.1)	41 (12.7)	36 (15.3)	32 (15.2)
> 3 - 6 weeks	24 (7.4)	19 (5.9)	10 (3.1)	10 (3.1)	13 (5.5)	7 (3.3)
> 6 weeks	6 (1.8)	8 (2.5)	2 (0.6)	1 (0.3)	1 (0.4)	1 (0.5)
Days of Patients with Delays						
Mean ± SD	13 ± 14.8	12 ± 14.0	9 ± 8.9	10 ± 9.5	12 ± 13.1	11 ± 10.6
Median	8	8	5	6	9	6
Q1; Q3	4; 17	4; 15	4; 10	3; 13	4; 17	4; 15
Min; Max	1; 113	1; 80	1; 45	1; 53	1; 103	1; 54

Max = Maximum; Min = Minimum; Q = quartile; SD = Standard deviation.

(a) Duration of therapy (weeks) was calculated as: date of last BAT1706/EU-Avastin infusion minus date of first BAT1706/EU-Avastin infusion plus 21 days and divided by 7.

(b) Dose intensity was calculated as: (cumulative dose of BAT1706/EU-Avastin from first infusion) divided by duration of therapy (weeks). Actual treatment dose (used for cumulative dose) was based on the weight at the visit.

(c) Relative dose intensity was defined as dose intensity of BAT1706/EU-Avastin divided by the planned weekly dose.

(d) Delays were calculated only for patients with at least 2 administrations. Delay was defined as patients who missed the allocated day (with a maximum window of −1 up to +3 days) for trial drug infusion.

2.6.8.2. Adverse events

BAT1706-001-CR (Phase I Study)

Common Adverse Events

Table 30. Test drug related TEAEs reported for 2 or more subjects in any group, Study BAT1706-001-CR.

System Organ Class Preferred term	BAT1706 (N=40) n (%)	EU-Avastin (N=43) n (%)	US-Avastin (N=42) n (%)
Any	22 (55.0)	21 (48.8)	19 (45.2)
Blood and lymphatic system disorders	0	2 (4.7)	0
Neutropenia	0	2 (4.7)	0
Gastrointestinal disorders	3 (7.5)	2 (4.7)	2 (4.8)
Nausea	2 (5.0)	1 (2.3)	0
General disorders and administration site conditions	1 (2.5)	3 (7.0)	3 (7.1)
Vessel puncture site bruise	0	2 (4.7)	0
Infections and infestations	8 (20.0)	6 (14.0)	6 (14.3)
Upper respiratory tract infection	5 (12.5)	5 (11.6)	3 (7.1)
Injury, poisoning and procedural complications	0	2 (4.7)	1 (2.4)
Post procedural contusion	0	2 (4.7)	0
Musculoskeletal and connective tissue disorders	2 (5.0)	1 (2.3)	5 (11.9)
Back pain	0	0	2 (4.8)
Myalgia	0	0	2 (4.8)
Nervous system disorders	9 (22.5)	7 (16.3)	4 (9.5)
Headache	7 (17.5)	7 (16.3)	4 (9.5)
Respiratory, thoracic and mediastinal disorders	2 (5.0)	3 (7.0)	3 (7.1)
Nasal congestion	1 (2.5)	2 (4.7)	0
Epistaxis	1 (2.5)	0	2 (4.8)

TEAE = treatment emergent adverse event
Source: CSR BAT1706-001-CR, Table 3.1.2.3

BAT1706-002-CR (Phase I Study)

Common Adverse Events

Table 31. test drug-related TEAEs reported for 2 or more subjects in any group, Study BAT1706-002-CR.

System Organ Class Preferred term	BAT1706 (N=39) n (%)	EU-Avastin (N=41) n (%)
Any	15 (38.5)	10 (24.4)
Investigations	11 (28.2)	5 (12.2)
ALT elevation	6 (15.4)	3 (7.3)
AST elevation	3 (7.7)	1 (2.4)
GGT elevation	1 (2.6)	2 (4.9)
Blood albumin decrease	2 (5.1)	1 (2.4)
Low white blood cell count	2 (5.1)	0
Metabolic and Nutritional Diseases	2 (5.1)	4 (9.8)
Hypertriglyceridemia	0	2 (4.9)
Hyperglycemia	2 (5.1)	0
Kidney and Urinary Tract Disorders	2 (5.1)	1 (2.4)
Hematuria	2 (5.1)	0

TEAE = treatment emergent adverse event

BAT1706-003-CR (Phase III Study)

Table 32. Overview of TEAEs, Safety Population, Study BAT1706-003-CR

	Overall		Combination Period		Monotherapy Period	
Number (%) Patients with:	BAT1706 ++ Carboplatin + Paclitaxel N=325	EU-Avastin ++ Carboplatin + Paclitaxel N=324	BAT1706 ++ Carboplatin + Paclitaxel N=325	EU-Avastin ++ Carboplatin + Paclitaxel N=324	BAT1706 N=235	EU-Avastin N=211
Any TEAE	316 (97.2)	319 (98.5)	315 (96.9)	317 (97.8)	210 (89.4)	184 (87.2)
Any test drug related TEAE (a)	198 (60.9)	191 (59.0)	162 (49.8)	161 (49.7)	125 (53.2)	101 (47.9)
Any BAT1706 related TEAE	198 (60.9)	0	162 (49.8)	0	125 (53.2)	0
Any EU-Avastin related TEAE	0	191 (59.0)	0	161 (49.7)	0	101 (47.9)
Any Carboplatin related TEAE	300 (92.3)	301 (92.9)	300 (92.3)	301 (92.9)	96 (40.9)	81 (38.4)
Any Paclitaxel related TEAE	307 (94.5)	303 (93.5)	307 (94.5)	303 (93.5)	105 (44.7)	84 (39.8)
Any serious TEAE	100 (30.8)	108 (33.3)	81 (24.9)	92 (28.4)	24 (10.2)	21 (10.0)
Any test drug related serious TEAE (a)	33 (10.2)	31 (9.6)	23 (7.1)	28 (8.6)	11 (4.7)	3 (1.4)
Any BAT1706 related serious TEAE	33 (10.2)	0	23 (7.1)	0	11 (4.7)	0
Any EU-Avastin related serious TEAE	0	31 (9.6)	0	28 (8.6)	0	3 (1.4)
Any Carboplatin related serious TEAE	57 (17.5)	62 (19.1)	55 (16.9)	61 (18.8)	2 (0.9)	2 (0.9)
Any Paclitaxel related serious TEAE	57 (17.5)	62 (19.1)	55 (16.9)	61 (18.8)	2 (0.9)	2 (0.9)

Number (%) Patients with:	Overall		Combination Period		Monotherapy Period	
	BAT1706 ++ Carboplatin + Paclitaxel N=325	EU-Avastin ++ Carboplatin + Paclitaxel N=324	BAT1706 ++ Carboplatin + Paclitaxel N=325	EU-Avastin ++ Carboplatin + Paclitaxel N=324	BAT1706 N=235	EU-Avastin N=211
Any Grade ≥3 TEAE	222 (68.3)	239 (73.8)	200 (61.5)	222 (68.5)	72 (30.6)	52 (24.6)
Any Grade ≥4 TEAE	93(28.6)	95 (29.3)	88 (27.1)	88 (27.2)	9 (3.8)	10 (4.7)
Any test drug related Grade ≥3 TEAE (a)	80 (24.6)	74 (22.8)	58 (17.8)	58 (17.9)	34 (14.5)	21 (10.0)
Any test drug related Grade ≥4 TEAE (a)	24 (7.4)	21 (6.5)	23 (7.1)	19 (5.9)	1 (0.4)	2 (0.9)
Any BAT1706 related Grade ≥3 TEAE	80 (24.6)	0	58 (17.8)	0	34 (14.5)	0
Any BAT1706 related Grade ≥4 TEAE	24 (7.4)	0	23 (7.1)	0	1 (0.4)	0
Any EU-Avastin related Grade ≥3 TEAE	0	74 (22.8)	0	58 (17.9)	0	21 (10.0)
Any EU-Avastin related Grade ≥4 TEAE	0	21 (6.5)	0	19 (5.9)	0	2 (0.9)
Any Carboplatin related Grade ≥3 TEAE	181 (55.7)	193 (59.6)	179 (55.1)	189 (58.3)	6 (2.6)	7 (3.3)
Any Carboplatin related Grade ≥4 TEAE	77 (23.7)	78 (24.1)	77 (23.7)	77 (23.8)	1 (0.4)	1 (0.5)
Any Paclitaxel related Grade ≥3 TEAE	186 (57.2)	195 (60.2)	184 (56.6)	191 (59.0)	6 (2.6)	7 (3.3)
Any Paclitaxel related Grade ≥4 TEAE	78 (24.0)	78 (24.1)	78 (24.0)	77 (23.8)	1 (0.4)	1 (0.5)
Any TEAE leading to death	18 (5.5)	19 (5.9)	15 (4.6)	13 (4.0)	3 (1.3)	6 (2.8)
Any test drug related TEAE leading to death (a)	8 (2.5)	4 (1.2)	7 (2.2)	3 (0.9)	1 (0.4)	1 (0.5)
Any BAT1706 related TEAE leading to death	8 (2.5)	0	7 (2.2)	0	1 (0.4)	0
Any EU-Avastin related TEAE leading to death	0	4 (1.2)	0	3 (0.9)	0	1 (0.5)
Any Carboplatin related TEAE leading to death	7 (2.2)	5 (1.5)	7 (2.2)	5 (1.5)	0	0
Any Paclitaxel related TEAE leading to death	7 (2.2)	5 (1.5)	7 (2.2)	5 (1.5)	0	0

TEAE = treatment emergent adverse event (a) Test drug included only BAT1706 or EU-Avastin. NCI-CTCAE version 4.03 was used to grade the severity of adverse events.Related TEAEs are events with relationship missing, unknown, possibly related or definitely related.TEAEs which start during LTE were not included.

Table 33. TEAEs Reported for 10% or More of patients in either Treatment Group, Safety Population, Study BAT1706-003-CR

MedDRA Primary System Organ Class Preferred Term	Overall		Combination Period		Monotherapy Period	
	BAT1706 ++ Carboplatin + Paclitaxel N=325	EU-Avastin ++ Carboplatin + Paclitaxel N=324	BAT1706 ++ Carboplatin + Paclitaxel N=325	EU-Avastin ++ Carboplatin + Paclitaxel N=324	BAT1706 N=235	EU-Avastin N=211
Patients with at least one TEAE	316 (97.2)	319 (98.5)	315 (96.9)	317 (97.8)	210 (89.4)	184 (87.2)
Blood and lymphatic system disorders	262 (80.6)	263 (81.2)	260 (80.0)	259 (79.9)	89 (37.9)	72 (34.1)

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	Overall EU-Avastin ++ Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	Combination Period EU-Avastin ++ Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	Monotherapy Period EU-Avastin N=211
Neutropenia	187 (57.5)	187 (57.7)	186 (57.2)	187 (57.7)	24 (10.2)	13 (6.2)
Anaemia	186 (57.2)	168 (51.9)	182 (56.0)	165 (50.9)	56 (23.8)	41 (19.4)
Leukopenia	171 (52.6)	178 (54.9)	169 (52.0)	178 (54.9)	27 (11.5)	14 (6.6)
Thrombocytopenia	142 (43.7)	149 (46.0)	140 (43.1)	148 (45.7)	20 (8.5)	22 (10.4)
Lymphopenia	34 (10.5)	25 (7.7)	30 (9.2)	25 (7.7)	9 (3.8)	2 (0.9)
Gastrointestinal disorders	197 (60.6)	189 (58.3)	185 (56.9)	178 (54.9)	59 (25.1)	47 (22.3)
Nausea	78 (24.0)	79 (24.4)	74 (22.8)	74 (22.8)	12 (5.1)	8 (3.8)
Constipation	60 (18.5)	64 (19.8)	58 (17.8)	56 (17.3)	8 (3.4)	15 (7.1)
Diarrhoea	56 (17.2)	60 (18.5)	49 (51.1)	57 (17.6)	13 (5.5)	7 (3.3)
Vomiting	52 (16.0)	49 (15.1)	47 (14.5)	42 (13.0)	5 (2.1)	9 (4.3)
Skin and subcutaneous tissue disorders	198 (60.9)	169 (52.2)	190 (58.6)	164 (50.6)	17 (7.2)	22 (10.4)
Alopecia	171 (52.6)	148 (45.7)	169 (52.0)	147 (45.4)	6 (2.6)	7 (3.3)
General disorders and administration site conditions	170 (52.3)	168 (51.9)	153 (47.1)	148 (45.7)	53 (22.6)	40 (19.0)
Asthenia	57 (17.5)	59 (18.2)	49 (15.1)	50 (15.4)	12 (5.1)	15 (7.1)
Fatigue	52 (16.0)	45 (13.9)	46 (14.2)	44 (13.6)	11 (4.7)	3 (1.4)
Pyrexia	39 (12.0)	29 (9.0)	29 (8.9)	26 (8.0)	12 (5.1)	3 (1.4)
Malaise	31 (9.5)	33 (10.2)	29 (8.9)	32 (9.9)	2 (0.9)	3 (1.4)
Nervous system disorders	163 (50.2)	165 (50.9)	150 (46.2)	150 (46.3)	48 (20.4)	44 (20.9)
Hypoesthesia	46 (14.2)	53 (16.4)	45 (13.8)	49 (15.1)	11 (4.7)	8 (3.8)
Neuropathy peripheral	37 (11.4)	36 (11.1)	28 (8.6)	32 (9.9)	12 (5.1)	9 (4.3)
Dizziness	33 (10.2)	28 (8.6)	22 (6.8)	25 (7.7)	12 (5.1)	5 (2.4)
Metabolism and nutrition disorders	168 (51.7)	157 (48.5)	143 (44.0)	143 (44.1)	86 (36.6)	64 (30.3)
Decreased appetite	90 (27.7)	79 (24.4)	83 (25.5)	72 (22.2)	16 (6.8)	14 (6.6)
Hypercholesterolaemia	30 (9.2)	35 (10.8)	19 (5.8)	25 (7.7)	20 (8.5)	21 (10.0)
Investigations	153 (47.1)	149 (46.0)	112 (34.5)	120 (37.0)	84 (35.7)	76 (36.0)
Alanine aminotransferase increased	44 (13.5)	56 (17.3)	35 (10.8)	43 (13.3)	19 (8.1)	26 (12.3)
Aspartate aminotransferase increased	47 (14.5)	49 (15.1)	36 (11.1)	34 (10.5)	16 (6.8)	24 (11.4)
Gamma-glutamyl transferase increased	48 (14.8)	48 (14.8)	30 (9.2)	32 (9.9)	24 (10.2)	26 (12.3)
Weight decreased	43 (13.2)	42 (13.0)	29 (8.9)	35 (10.8)	17 (7.2)	14 (6.6)
Musculoskeletal and connective tissue disorders	141 (43.4)	138 (42.6)	132 (40.6)	125 (38.6)	49 (20.9)	33 (15.6)

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	Overall EU-Avastin + Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	Combination Period EU-Avastin + Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	Monotherapy Period EU-Avastin N=211
Arthralgia	64 (19.7)	54 (16.7)	55 (16.9)	47 (14.5)	19 (8.1)	11 (5.2)
Pain in extremity	58 (17.8)	45 (13.9)	51 (15.7)	43 (13.3)	12 (5.1)	3 (1.4)
Back pain	44 (13.5)	33 (10.2)	34 (10.5)	24 (7.4)	20 (8.5)	12 (5.7)
Myalgia	31 (9.5)	35 (10.8)	30 (9.2)	34 (10.5)	3 (1.3)	2 (0.9)
Respiratory, thoracic and mediastinal disorders	141 (43.4)	136 (42.0)	121 (37.2)	116 (35.8)	51 (21.7)	49 (23.2)
Epistaxis	42 (12.9)	40 (12.3)	39 (12.0)	36 (11.1)	5 (2.1)	5 (2.4)
Cough	40 (12.3)	36 (11.1)	24 (7.4)	28 (8.6)	21 (8.9)	14 (6.6)
Infections and infestations	127 (39.1)	115 (35.5)	101 (31.1)	90 (27.8)	51 (21.7)	47 (22.3)
Upper respiratory tract infection	38 (11.7)	30 (9.3)	23 (7.1)	25 (7.7)	22 (9.4)	8 (3.8)
Pneumonia	37 (11.4)	29 (9.0)	31 (9.5)	19 (5.9)	7 (3.0)	12 (5.7)
Renal and urinary disorders	113 (34.8)	109 (33.6)	63 (19.4)	59 (18.2)	66 (28.1)	66 (31.3)
Proteinuria	99 (30.5)	87 (26.9)	50 (15.4)	39 (12.0)	61 (26.0)	62 (29.4)
Vascular disorders	77 (23.7)	76 (23.5)	51 (15.7)	59 (18.2)	39 (16.6)	31 (14.7)
Hypertension	60 (18.5)	54 (16.7)	34 (10.5)	38 (11.7)	36 (15.3)	27 (12.8)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = Treatment-emergent adverse event.

Medical Dictionary for Regulatory Activities version 23.1.

Table 34. Test drug related TEAEs reported for 1% or more of patients in either treatment group, Safety Population, Study BAT1706-003-CR

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	Overall EU-Avastin + Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	Combination Period EU-Avastin + Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	Monotherapy Period EU-Avastin N=211
Patients with at least one trial drug related TEAE	198 (60.9)	191 (59.0)	162 (49.8)	161 (49.7)	125 (53.2)	101 (47.9)
Renal and urinary disorders	81 (24.9)	71 (21.9)	39 (12.0)	30 (9.3)	53 (22.6)	53 (25.1)
Proteinuria	73 (22.5)	64 (19.8)	33 (10.2)	26 (8.0)	50 (21.3)	50 (23.7)
Haematuria	7 (2.2)	9 (2.8)	5 (1.5)	5 (1.5)	2 (0.9)	5 (2.4)
Gastrointestinal disorders	76 (23.4)	58 (17.9)	60 (18.5)	52 (16.0)	25 (10.6)	13 (6.2)
Vomiting	14 (4.3)	15 (4.6)	12 (3.7)	11 (3.4)	0	0
Diarrhoea	16 (4.9)	12 (3.7)	14 (4.3)	12 (3.7)	0	0
Nausea	16 (4.9)	12 (3.7)	15 (4.6)	11 (3.4)	0	0
Constipation	14 (4.3)	12 (3.7)	13 (4.0)	11 (3.4)	3 (1.3)	1 (0.5)
Gingival bleeding	17 (5.2)	7 (2.2)	10 (3.1)	5 (1.5)	8 (3.4)	3 (1.4)
Abdominal pain	6 (1.8)	4 (1.2)	6 (1.8)	3 (0.9)	1 (0.4)	1 (0.5)
Abdominal distension	4 (1.2)	5 (1.5)	4 (1.2)	5 (1.5)	0	0
Toothache	6 (1.8)	3 (0.9)	4 (1.2)	3 (0.9)	3 (1.3)	0

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	Overall EU-Avastin + Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	Combination Period EU-Avastin + Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	Monotherapy Period EU-Avastin N=211
Abdominal discomfort	6 (1.8)	2 (0.6)	5 (1.5)	1 (0.3)	1 (0.4)	1 (0.5)
Haematochezia	3 (0.9)	5 (1.5)	3 (0.9)	5 (1.5)	0	0
Abdominal pain upper	2 (0.6)	4 (1.2)	2 (0.6)	4 (1.2)	0	0
Blood and lymphatic system disorders	71 (21.8)	61 (18.8)	63 (19.4)	52 (16.0)	25 (10.6)	20 (9.5)
Neutropenia	42 (12.9)	35 (10.8)	37 (11.4)	34 (10.5)	10 (4.3)	4 (1.9)
Leukopenia	43 (13.2)	30 (9.3)	38 (11.7)	30 (9.3)	12 (5.1)	5 (2.4)
Thrombocytopenia	40 (12.3)	32 (9.9)	38 (11.7)	26 (8.0)	8 (3.4)	12 (5.7)
Anaemia	39 (12.0)	27 (8.3)	37 (11.4)	25 (7.7)	12 (5.1)	8 (3.8)
Lymphopenia	8 (2.5)	3 (0.9)	6 (1.8)	3 (0.9)	3 (1.3)	0
Respiratory, thoracic and mediastinal disorders	64 (19.7)	54 (16.7)	56 (17.2)	48 (14.8)	18 (7.7)	9 (4.3)
Epistaxis	32 (9.8)	31 (9.6)	29 (8.9)	28 (8.6)	5 (2.1)	4 (1.9)
Haemoptysis	18 (5.5)	13 (4.0)	11 (3.4)	13 (4.0)	7 (3.0)	1 (0.5)
Cough	7 (2.2)	4 (1.2)	6 (1.8)	4 (1.2)	2 (0.9)	0
Dyspnoea	6 (1.8)	1 (0.3)	3 (0.9)	0	3 (1.3)	1 (0.5)
Dysphonia	2 (0.6)	4 (1.2)	2 (0.6)	3 (0.9)	0	1 (0.5)
Productive cough	4 (1.2)	2 (0.6)	4 (1.2)	2 (0.6)	1 (0.4)	0
Vascular disorders	56 (17.2)	50 (15.4)	32 (9.8)	36 (11.1)	35 (14.9)	24 (11.4)
Hypertension	53 (16.3)	45 (13.9)	28 (8.6)	30 (9.3)	33 (14.0)	23 (10.9)
Investigations	57 (17.5)	45 (13.9)	38 (11.7)	32 (9.9)	31 (13.2)	24 (11.4)
Alanine aminotransferase increased	17 (5.2)	20 (6.2)	10 (3.1)	14 (4.3)	9 (3.8)	12 (5.7)
Aspartate aminotransferase increased	18 (5.5)	20 (6.2)	9 (2.8)	12 (3.7)	10 (4.3)	12 (5.7)
Gamma-glutamyltransferase increased	10 (3.1)	8 (2.5)	8 (2.5)	4 (1.2)	3 (1.3)	6 (2.8)
Weight decreased	11 (3.4)	3 (0.9)	8 (2.5)	1 (0.3)	4 (1.7)	2 (0.9)
Blood bilirubin increased	6 (1.8)	3 (0.9)	4 (1.2)	2 (0.6)	4 (1.7)	3 (1.4)
Blood pressure increased	5 (1.5)	4 (1.2)	4 (1.2)	2 (0.6)	2 (0.9)	2 (0.9)
General disorders and administration site conditions	50 (15.4)	39 (12.0)	36 (11.1)	35 (10.8)	18 (7.7)	7 (3.3)
Fatigue	13 (4.0)	14 (4.3)	11 (3.4)	14 (4.3)	3 (1.3)	0
Malaise	12 (3.7)	11 (3.4)	12 (3.7)	10 (3.1)	1 (0.4)	2 (0.9)
Asthenia	10 (3.1)	8 (2.5)	8 (2.5)	7 (2.2)	2 (0.9)	2 (0.9)
Pyrexia	6 (1.8)	7 (2.2)	4 (1.2)	7 (2.2)	2 (0.9)	0
Pain	5 (1.5)	3 (0.9)	3 (0.9)	2 (0.6)	2 (0.9)	1 (0.5)
Chest discomfort	4 (1.2)	2 (0.6)	0	2 (0.6)	4 (1.7)	0
Noncardiac chest pain	4 (1.2)	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.9)	0
Metabolism and nutrition disorders	47 (14.5)	36 (11.1)	41 (12.6)	28 (8.6)	21 (8.9)	15 (7.1)
Decreased appetite	26 (8.0)	20 (6.2)	25 (7.7)	17 (5.2)	2 (0.9)	4 (1.9)

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	 EU-Avastin + Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	 EU-Avastin + + Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	 EU-Avastin N=211
Hypercholesterolaemia	10 (3.1)	8 (2.5)	7 (2.2)	5 (1.5)	5 (2.1)	5 (2.4)
Hypertriglyceridaemia	7 (2.2)	9 (2.8)	4 (1.2)	6 (1.9)	5 (2.1)	5 (2.4)
Hyperuricaemia	9 (2.8)	5 (1.5)	7 (2.2)	4 (1.2)	4 (1.7)	3 (1.4)
Hypoalbuminaemia	5 (1.5)	8 (2.5)	4 (1.2)	7 (2.2)	2 (0.9)	3 (1.4)
Hyperlipidaemia	9 (2.8)	2 (0.6)	9 (2.8)	2 (0.6)	4 (1.7)	0
Hypokalaemia	6 (1.8)	3 (0.9)	6 (1.8)	2 (0.6)	1 (0.4)	1 (0.5)
Nervous system disorders	45 (13.8)	34 (10.5)	33 (10.2)	28 (8.6)	14 (6.0)	11 (5.2)
Headache	14 (4.3)	10 (3.1)	10 (3.1)	7 (2.2)	5 (2.1)	4 (1.9)
Hypoaesthesia	10 (3.1)	9 (2.8)	8 (2.5)	8 (2.5)	3 (1.3)	3 (1.4)
Dizziness	12 (3.7)	6 (1.9)	10 (3.1)	4 (1.2)	2 (0.9)	3 (1.4)
Neuropathy peripheral	3 (0.9)	4 (1.2)	1 (0.3)	3 (0.9)	2 (0.9)	1 (0.5)
Skin and subcutaneous tissue disorders	36 (11.1)	32 (9.9)	31 (9.5)	29 (9.0)	6 (2.6)	5 (2.4)
Rash	19 (5.8)	9 (2.8)	14 (4.3)	9 (2.8)	5 (2.1)	0
Pruritus	12 (3.7)	10 (3.1)	12 (3.7)	9 (2.8)	0	3 (1.4)
Alopecia	11 (3.4)	9 (2.8)	11 (3.4)	9 (2.8)	0	0
Musculoskeletal and connective tissue disorders	37 (11.4)	29 (9.0)	29 (8.9)	26 (8.0)	13 (5.5)	5 (2.4)
Arthralgia	16 (4.9)	12 (3.7)	11 (3.4)	12 (3.7)	6 (2.6)	1 (0.5)
Pain in extremity	14 (4.3)	10 (3.1)	11 (3.4)	10 (3.1)	4 (1.7)	1 (0.5)
Muscular weakness	8 (2.5)	9 (2.8)	7 (2.2)	7 (2.2)	1 (0.4)	2 (0.9)
Back pain	6 (1.8)	4 (1.2)	4 (1.2)	2 (0.6)	2 (0.9)	2 (0.9)
Myalgia	5 (1.5)	5 (1.5)	3 (0.9)	5 (1.5)	2 (0.9)	0
Cardiac disorders	21 (6.5)	11 (3.4)	10 (3.1)	7 (2.2)	13 (5.5)	5 (2.4)
Sinus tachycardia	3 (0.9)	4 (1.2)	2 (0.6)	3 (0.9)	1 (0.4)	2 (0.9)
Tachycardia	5 (1.5)	0	1 (0.3)	1 (0.3)	2 (0.9)	0
Cardiac ventricular disorder	4 (1.2)	0	1 (0.3)	0	4 (1.7)	0
Infections and infestations	18 (5.5)	14 (4.3)	13 (4.0)	12 (3.7)	8 (3.4)	5 (2.4)
Upper respiratory tract infection	6 (1.8)	2 (0.6)	3 (0.9)	1 (0.3)	3 (1.3)	1 (0.5)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = Treatment-emergent adverse event.

MedDRA version 23.1.

"Trial drug" only included BAT1706 or EU-Avastin in this table.

Related TEAEs were events with relationship missing, unknown, possibly related or definitely related.

The TEAEs which started during LTE were not included.

2.6.8.3. Serious adverse event/deaths

BAT1706-001-CR (Phase I Study)

One subject (Subject 001147) in the BAT1706 group had a TE-SAE of fibula fracture considered to be severe intensity but unrelated to the study drug.

BAT1706-002-CR (Phase I Study)

No death or other SAE was reported during in study BAT1706-002-CR.

BAT1706-003-CR (Phase III Study)

Deaths

Through Week 52 of the study, 167 (51.4%) patients in the BAT1706 group and 169 (52.2%) patients in the EU-Avastin group died. The primary cause of death was disease progression for 114 (35.1%) patients in the BAT1706 group and 129 (39.8%) patients in the EU-Avastin group.

Incidence of TEAEs with a Fatal Outcome by SOC and PT (Safety Population), Study BAT1706 003-CR is described below.

Table 35. Incidence of TEAEs with a Fatal Outcome by SOC and PT (Safety Population), Study BAT1706 003-CR

Primary cause of death, MedDRA SOC Preferred term	BAT1706 + Carboplatin + Paclitaxel N=325	EU-Avastin + Carboplatin + Paclitaxel N=324	Total (N=649)
Any death	167 (51.4)[‡]	169 (52.2)	336 (51.8)
General disorders and administration site conditions	136 (41.8)	142 (43.8)	278 (42.8)
Disease progression	114 (35.1)	129 (39.8)	243 (37.4)
Death	21 (6.5)	12 (3.7)	33 (5.1)
Cardiac death	1 (0.3)	0	1 (0.2)
Multiple organ dysfunction syndrome	0	1 (0.3)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	12 (3.7)	8 (2.5)	20 (3.1)
Respiratory failure	4 (1.2)	3 (0.9)	7 (1.1)
Pulmonary haemorrhage	2 (0.6)	2 (0.6)	4 (0.6)
Chronic obstructive pulmonary disease	1 (0.3)	1 (0.3)	2 (0.3)
Haemoptysis	2 (0.6)	0	2 (0.3)
Dyspnoea	0	1 (0.3)	1 (0.2)
Pneumonia aspiration	1 (0.3)	0	1 (0.2)
Pneumothorox	1 (0.3)	0	1 (0.2)
Pulmonary embolism	0	1 (0.3)	1 (0.2)
Respiratory distress	1 (0.3)	0	1 (0.2)
Infections and infestations	7 (2.2)	5 (1.5)	12 (1.8)
Pneumonia	4 (1.2)	4 (1.2)	8 (1.2)
Infection	1 (0.3)	0	1 (0.2)
Post procedural pneumonia	1 (0.3)	0	1 (0.2)
Sepsis	0	1 (0.3)	1 (0.2)
Septic shock	1 (0.3)	0	1 (0.2)
Cardiac disorders	5 (1.5)	5 (1.5)	10 (1.5)
Cardiac arrest	3 (0.9)	3 (0.9)	6 (0.9)
Myocardial infarction	1 (0.3)	1 (0.3)	2 (0.3)
Cardio-respiratory arrest	0	1 (0.3)	1 (0.2)
Cardiopulmonary failure	1 (0.3)	0	1 (0.2)
Nervous system disorders	2 (0.6)	4 (1.2)	6 (0.9)
Cerebrovascular accident	2 (0.6)	1 (0.3)	3 (0.5)
Cerebral haemorrhage	0	1 (0.3)	1 (0.2)
Haemorrhagic stroke	0	1 (0.3)	1 (0.2)

Primary cause of death, MedDRA SOC Preferred term	BAT1706 + Carboplatin + Paclitaxel N=325	EU-Avastin + Carboplatin + Paclitaxel N=324	Total (N=649)
Ischaemic stroke	0	1 (0.3)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	2 (0.6)	3 (0.5)
Malignant melanoma	0	1 (0.3)	1 (0.2)
Metastases to central nervous system	0	1 (0.3)	1 (0.2)
Neoplasm malignant	1 (0.3)	0	1 (0.2)
Gastrointestinal disorders	2 (0.6)	0	2 (0.3)
Haematemesis	1 (0.3)	0	1 (0.2)
Pancreatitis necrotising	1 (0.3)	0	1 (0.2)
Blood and lymphatic system disorders	0	1 (0.3)	1 (0.2)
Myelosuppression	0	1 (0.3)	1 (0.2)
Metabolism and nutrition disorders	0	1 (0.3)	1 (0.2)
Cachexia	0	1 (0.3)	1 (0.2)
Uncoded	2 (0.6)	1 (0.3)	3 (0.5)
Uncoded	2 (0.6)	1 (0.3)	3 (0.5)

‡ One additional patient had died which had not been captured at the time of the Month 12 analyses of primary cause of death but has been added to this table.

TEAEs with a fatal outcome that were considered by the Investigator to be test drug related were reported for 8 (2.5%) patients in the BAT1706 group and 3 (0.9%) patients in the EU-Avastin group (Table 36).

Table 36. Incidence of Study Drug Related TEAEs Leading to Death by SOC, PR and study period (Safety Population)

	Overall		Combination Period		Monotherapy Period	
MedDRA Primary System Organ Class Preferred Term	BAT1706 + Carboplatin + Paclitaxel N=325	EU-Avastin + Carboplatin + Paclitaxel N=324	BAT1706 + Carboplatin + Paclitaxel N=325	EU-Avastin + Carboplatin + Paclitaxel N=324	BAT1706 N=235	EU-Avastin N= 211
Patients with at least one trial drug (BAT1706 or EU-Avastin) related TEAE leading to death	8 (2.5)	4 (1.2)	7 (2.2)	3 (0.9)	1 (0.4)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	5 (1.5)	2 (0.6)	4 (1.2)	1 (0.3)	1 (0.4)	1 (0.5)
Pulmonary haemorrhage	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)	0	0
Haemoptysis	2 (0.6)	0	1 (0.3)	0	1 (0.4)	0
Dyspnoea	0	1 (0.3)	0	0	0	1 (0.5)
Pneumothorax	1 (0.3)	0	1 (0.3)	0	0	0
Nervous system disorders	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	0	0
Depressed level of consciousness	1 (0.3)	0	1 (0.3)	0	0	0
Haemorrhage intracranial	0	1 (0.3)	0	1 (0.3)	0	0
Ischaemic stroke	0	1 (0.3)	0	1 (0.3)	0	0
Gastrointestinal disorders	2 (0.6)	0	2 (0.6)	0	0	0
Haematemesis	1 (0.3)	0	1 (0.3)	0	0	0

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	Overall EU-Avastin + Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	Combination Period EU-Avastin + Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	Monotherapy Period EU-Avastin N= 211
Intestinal perforation	1 (0.3)	0	1 (0.3)	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = Treatment-emergent adverse event.
Medical Dictionary for Regulatory Activities version 23.1.
"Trial drug" only included BAT1706 or EU-Avastin in this table.
Related TEAEs were events with relationship missing, unknown, possibly related or definitely related.
The TEAEs which started during LTE were not included.

Other Serious Adverse Events

At least 1 TE-SAE was reported for 100 (30.8%) patients in the BAT1706 group and 108 (33.3%) patients in the EU-Avastin group (Table 37). The most common TE-SAEs comprised pneumonia (21 [6.5%] patients in the BAT1706 group and 14 [4.3%] patients in in the EU-Avastin group), neutropenia (10 [3.1%] and 12 [3.7%] patients, respectively), and thrombocytopenia (7 [2.2%] and 12 [3.7%] patients, respectively), febrile neutropenia (9 [2.8%] and 8 [2.5%] patients, respectively), and anaemia (6 [1.8%] and 10 [3.1%] patients, respectively).

Table 37. Incidence of Treatment-Emergent Serious Adverse Events Occurring in ≥ 2 Patients in Either Group by SOC, PT and study period (Safety Population), Study BAT1706-003-CR

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	Overall EU-Avastin + Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	Combination Period EU-Avastin + Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	Monotherapy Period EU-Avastin N=211
Patients with at least one treatment emergent SAE	100 (30.8)	108 (33.3)	81 (24.9)	92 (28.4)	24 (10.2)	21 (10.0)
Blood and lymphatic system disorders	31 (9.5)	47 (14.5)	31 (9.5)	45 (13.9)	0	2 (0.9)
Neutropenia	10 (3.1)	12 (3.7)	10 (3.1)	12 (3.7)	0	0
Thrombocytopenia	7 (2.2)	12 (3.7)	7 (2.2)	12 (3.7)	0	0
Febrile neutropenia	9 (2.8)	8 (2.5)	9 (2.8)	7 (2.2)	0	1 (0.5)
Anaemia	6 (1.8)	10 (3.1)	6 (1.8)	9 (2.8)	0	1 (0.5)
Myelosuppression	3 (0.9)	10 (3.1)	3 (0.9)	10 (3.1)	0	0
Leukopenia	3 (0.9)	3 (0.9)	3 (0.9)	3 (0.9)	0	1 (0.5)
Infections and infestations	28 (8.6)	22 (6.8)	23 (7.1)	17 (5.2)	6 (2.6)	5 (2.4)
Pneumonia	21 (6.5)	14 (4.3)	18 (5.5)	10 (3.1)	3 (1.3)	4 (1.9)
Bacteraemia	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)	0	0
Respiratory, thoracic and mediastinal disorders	22 (6.8)	19 (5.9)	17 (5.2)	14 (4.3)	5 (2.1)	6 (2.8)
Pneumothorax	8 (2.5)	1 (0.3)	6 (1.8)	1 (0.3)	2 (0.9)	0
Pleural effusion	4 (1.2)	4 (1.2)	4 (1.2)	2 (0.6)	0	2 (0.9)
Pulmonary embolism	2 (0.6)	3 (0.9)	2 (0.6)	2 (0.6)	0	1 (0.5)
Pulmonary haemorrhage	3 (0.9)	2 (0.6)	3 (0.9)	2 (0.6)	0	0
Haemoptysis	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.5)
Dyspnoea	0	2 (0.6)	0	1 (0.3)	0	1 (0.5)
Epistaxis	0	2 (0.6)	0	2 (0.6)	0	0

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	Overall EU-Avastin + Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	Combination Period EU-Avastin + Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	Monotherapy Period EU-Avastin N=211
Pneumonitis	2 (0.6)	0	2 (0.6)	0	0	0
Gastrointestinal disorders	12 (3.7)	12 (3.7)	9 (2.8)	12 (3.7)	3 (1.3)	0
Diarrhoea	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	0	0
Haematochezia	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	0	0
Oesophageal perforation	0	2 (0.6)	0	2 (0.6)	0	0
Pancreatitis acute	2 (0.6)	0	2 (0.6)	0	0	0
Cardiac disorders	10 (3.1)	4 (1.2)	5 (1.5)	1 (0.3)	5 (2.1)	3 (1.4)
Atrial fibrillation	3 (0.9)	0	2 (0.6)	0	1 (0.4)	0
Sinus tachycardia	2 (0.6)	0	1 (0.3)	0	1 (0.4)	0
Vascular disorders	5 (1.5)	8 (2.5)	4 (1.2)	6 (1.9)	1 (0.4)	2 (0.9)
Hypertension	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	0	0
Venous thrombosis limb	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.4)	0
Deep vein thrombosis	0	2 (0.6)	0	2 (0.6)	0	0
General disorders and administration site conditions	8 (2.5)	4 (1.2)	7 (2.2)	4 (1.2)	1 (0.4)	0
Malaise	2 (0.6)	0	2 (0.6)	0	0	0
Metabolism and nutrition disorders	4 (1.2)	4 (1.2)	3 (0.9)	2 (0.6)	1 (0.4)	2 (0.9)
Decreased appetite	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)	0	1 (0.5)
Hyponatraemia	2 (0.6)	0	1 (0.3)	0	1 (0.4)	0
Malnutrition	2 (0.6)	0	2 (0.6)	0	0	0
Renal and urinary disorders	3 (0.9)	2 (0.6)	2 (0.6)	2 (0.6)	1 (0.4)	0
Acute kidney injury	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = Treatment-emergent adverse event.
MedDRA version 23.1.
"Trial drug" only included BAT1706 or EU-Avastin in this table.
Related TEAEs were events with relationship missing, unknown, possibly related or definitely related.
The TEAEs which started during LTE were not included.

TE-SAEs related to BAT1706 were reported for a total of 33 (10.2%) patients and TE-SAEs related to EU-Avastin were reported for 31 (9.6%) patients.

Table 38. Incidence of test drug related serious adverse events occurring in ≥2 patients by SOC, PT and study period (Safety population), Study BAT1706-003-CR.

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	Overall EU-Avastin + Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	Combination Period EU-Avastin + Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	Monotherapy Period EU-Avastin N=211
Patients with at least one trial drug (BAT1706 or EU-Avastin) related treatment emergent SAE	33 (10.2)	31 (9.6)	23 (7.1)	28 (8.6)	11 (4.7)	3 (1.4)
Respiratory, thoracic and mediastinal disorders	9 (2.8)	7 (2.2)	7 (2.2)	5 (1.5)	2 (0.9)	2 (0.9)
Haemoptysis	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.4)	0
Pneumothorax	3 (0.9)	0	3 (0.9)	0	0	0
Pulmonary haemorrhage	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)	0	0
Epistaxis	0	2 (0.6)	0	2 (0.6)	0	0

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	Overall EU-Avastin + Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	Combination Period EU-Avastin + Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	Monotherapy Period EU-Avastin N=211
Pulmonary embolism	1 (0.3)	1 (0.3)	1 (0.3)	0	0	1 (0.5)
Blood and lymphatic system disorders	6 (1.8)	8 (2.5)	6 (1.8)	8 (2.5)	0	0
Thrombocytopenia	3 (0.9)	3 (0.9)	3 (0.9)	3 (0.9)	0	0
Neutropenia	1 (0.3)	3 (0.9)	1 (0.3)	3 (0.9)	0	0
Febrile neutropenia	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)	0	0
Gastrointestinal disorders	8 (2.5)	6 (1.9)	6 (1.8)	6 (1.9)	2 (0.9)	0
Haematochezia	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)	0	0
Oesophageal perforation	0	2 (0.6)	0	2 (0.6)	0	0
Infections and infestations	2 (0.6)	3 (0.9)	1 (0.3)	3 (0.9)	1 (0.4)	0
Pneumonia	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.4)	0

MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event MedDRA version 23.1
Related TEAEs were events with relationship missing, unknown, possibly related or definitely related.
The TEAEs which started during LTE were not included.

Adverse Events that Led to Discontinuation

TEAE leading to discontinuation of treatment was reported for 26 (8.0%) of patients in the BAT1706 group and 28 (8.6%) patients in the EU-Avastin group, the SOC and PT by study period are presented in Table 39.

Table 39. TEAEs Leading to Discontinuation of Any Study Treatment by SOC, PT and study period(Safety Population), Study BAT1706-003-CR

MedDRA Primary System Organ Class Preferred Term	Overall BAT1706 + Carboplatin + Paclitaxel N=325	Overall EU-Avastin + Carboplatin + Paclitaxel N=324	Combination Period BAT1706 + Carboplatin + Paclitaxel N=325	Combination Period EU-Avastin + Carboplatin + Paclitaxel N=324	Monotherapy Period BAT1706 N=235	Monotherapy Period EU-Avastin N= 211
Patients with at least one TEAE leading to discontinuation of treatment	26 (8.0)	28 (8.6)	20 (6.2)	19 (5.9)	6 (2.6)	9 (4.3)
Respiratory, thoracic and mediastinal disorders	8 (2.5)	4 (1.2)	8 (2.5)	4 (1.2)	0	0
Haemoptysis	0	3 (0.9)	0	3 (0.9)	0	0
Pneumothorax	3 (0.9)	0	3 (0.9)	0	0	0
Pulmonary embolism	2 (0.6)	1 (0.3)	2 (0.6)	1 (0.3)	0	0
Gastrointestinal disorders	7 (2.2)	4 (1.2)	6 (1.8)	4 (1.2)	1 (0.4)	0
Haematochezia	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0	0
Oesophageal perforation	0	2 (0.6)	0	2 (0.6)	0	0
Pancreatitis acute	2 (0.6)	0	2 (0.6)	0	0	0
Renal and urinary disorders	1 (0.3)	9 (2.8)	1 (0.3)	2 (0.6)	0	7 (3.3)
Proteinuria	0	8 (2.5)	0	2 (0.6)	0	6 (2.8)
Vascular disorders	3 (0.9)	6 (1.9)	2 (0.6)	4 (1.2)	1 (0.4)	2 (0.9)
Embolism	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)	0	1 (0.5)
Cardiac disorders	3 (0.9)	0	2 (0.6)	0	1 (0.4)	0
Cardiac failure	2 (0.6)	0	1 (0.3)	0	1 (0.4)	0

MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event

MedDRA version 23.1.

Related TEAEs were events with relationship missing, unknown, possibly related or definitely related.

The TEAEs which started during LTE were not included.

Adverse Events of Special Interest

The following are considered AESIs in the Phase III study BAT1706-003-CR:

- Hypertension ≥ Grade 3.
- Proteinuria ≥ Grade 3.
- Gastrointestinal perforation, gastrointestinal abscesses and gastrointestinal fistulae (any grade)
- Wound healing complications ≥ Grade 3.
- Haemorrhage ≥ grade 3 (any grade central nervous system [CNS] bleeding; ≥ Grade 2 haemoptysis).
- Arterial thromboembolic events (any grade).
- Venous thromboembolic events ≥ Grade 3.
- Posterior Reversible Encephalopathy Syndrome (any grade).
- Chronic heart failure ≥ Grade 3.
- Non-gastrointestinal fistula or abscess ≥ Grade 2.

By the data cut-off date, the targeted AESIs of wound healing complication ≥ Grade 3 and chronic heart failure ≥ Grade 3 were not detected during the study. AESIs reported in study BAT1706-003-CR are reported in Table 40.

Table 40. AESIs by Worst NCI-CTCAE Toxicity Grade by Study Population, Safety Population, Study BAT1706-003-CR

	Overall		**Combination Period**		**Monotherapy Period**	
Number (%) Patients with:	**BAT1706 ++ Carboplatin + Paclitaxel N=325**	**EU-Avastin ++ Carboplatin + Paclitaxel N=324**	**BAT1706 ++ Carboplatin + Paclitaxel N=325**	**EU-Avastin ++ Carboplatin + Paclitaxel N=324**	**BAT1706 N=235**	**EU-Avastin N= 211**
Arterial thromboembolic events (any grade)	4 (1.2)	9 (2.8)	4 (1.2)	7 (2.2)	0	3 (1.4)
Gastrointestinal perforation, gastrointestinal abscesses and gastrointestinal fistulae (any grade)	2 (0.6)	3 (0.9)	2 (0.6)	3 (0.9)	0	0
Haemorrhage Grade ≥3 (any Grade CNS bleeding; ≥ Grade 2 haemoptysis)	10 (3.1)	9 (2.8)	7 (2.2)	8 (2.5)	3 (1.3)	1 (0.5)
Hypertension Grade ≥3	24 (7.4)	23 (7.1)	13 (4.0)	15 (4.6)	15 (6.4)	8 (3.8)
Non-gastrointestinal fistula or abscess ≥ Grade 2	0	4 (1.2)	0	4 (1.2)	0	0
Posterior reversible encephalopathy syndrome (any grade)	0	1 (0.3)	0	0	0	1 (0.5)
Proteinuria Grade ≥3	5 (1.5)	8 (2.5)	0	1 (0.3)	5 (2.1)	7 (3.3)
Venous thromboembolic events Grade ≥3	1 (0.3)	3 (0.9)	0	2 (0.6)	1 (0.4)	1 (0.5)

CNS = central nervous system

NCI-CTCAE version 4.03 was used to grade the severity of adverse events.

TEAEs are defined as events that emerge during treatment having been absent pre-treatment, or worsen relative to the pre-treatment state and with onset dates occurring within the first dosing day of study treatment (BAT1706, EU-Avastin, Carboplatin, or Paclitaxel) until 28 days after the last dose of study treatment (BAT1706, EU-Avastin, Carboplatin, or Paclitaxel).

TEAEs which start during LTE were not included.

Most AESIs were ≥ Grade 3 in severity. Twelve patients experienced AESIs leading to death. Ten (1.5%) patients died of haemorrhage (6 [1.8%] patients in Arm A and 4 [1.2%] patients in Arm B); 1 (0.3%) patient died of gastrointestinal perforation in Arm A; and 1 (0.3%) patient died of arterial thromboembolic event in Arm B (Data not shown).

The time to first occurrence of most AESIs was ≥ 49 days and most AESIs resolved during treatment. This is driven mostly by the most common AESI events of hypertension which mostly occurred after ≥ 49 days and proteinuria which only occurred after ≥ 49 days. The time to resolution is driven by hypertension which often was resolved during treatment. For the other AESIs time to occurrence and time to resolution varies.

Hypersensitivity and Infusion-related TEAEs

An anaphylactic reaction was reported in 7 (1.1%) patients, and hypersensitivity/drug hypersensitivity/infusion-related reactions was reported in 13 (2.0%) patients. The incidence of anaphylactic reactions was higher in the EU-Avastin arm compared with the BAT1706 arm (1.9% versus 0.3%) with one patient in the EU-Avastin arm and one patient in the BAT1706 arm having hypersensitivity and anaphylactic reaction of severity Grade ≥ 3, respectively. There was no BAT1706 related hypersensitivity/infusion-related reaction and only 3 (0.9%) cases were reported as EU-Avastin related (hypersensitivity and infusion-related reaction were reported for 1 (0.3%) and 2 (0.6%) patients, respectively). None of these events led to treatment discontinuation. Due to low numbers adjudging a difference between the products is not possible.

2.6.8.4. Laboratory findings

Haematology

BAT1706-001-CR (Phase I Study)
For haematology parameters, post-baseline decreases in mean WBC counts and absolute neutrophil counts were observed at all post dose time points for each of the treatment groups. These decreases were small and mean values remained within the study reference ranges. Some individual shifts in haematology parameters were observed but the rates of the shifts were similar among treatment groups.

BAT1706-002-CR (Phase I Study)
Seven (17.9%) abnormal WBC count, 5 (12.8%) abnormal neutrophil absolute value, and 1 (2.6%) abnormal lymphocyte count were reported in the BAT1706 injection group. In the EU-Avastin group, abnormal WBC count of clinical significance was reported for 2 (4.9%) subjects.

BAT1706-003-CR (Phase III Study)
Decreases in the mean values of platelet counts, WBC counts, neutrophil counts, and haemoglobin were observed in both treatment arms. Overall, the proportion of patients with Grade 3/4 haematological toxicity was less than 15% except for ≥ Grade 3 neutropenia (low neutrophil count) (134 [41.2%] patients in the BAT1706 group and 142 [43.8%] patients in the EU-Avastin group) and ≥ Grade 3 leukopenia (low WBC count) (61 [18.9%] patients in the BAT1706 group and 68 [21.0%] patients in the EU-Avastin group).

Blood Chemistry

BAT1706-001-CR (Phase I Study)
Small mean decreases from baseline were observed in lactate dehydrogenase and triglyceride values in all 3 treatment groups but were within the study reference ranges. Mean creatine kinase values for all treatment groups were above the study reference range (60 to 220 IU/L) at a number of time points for the BAT1706 group (Day 15, 43, 71, and 99 (242.6, 440.2, 240.9, and 249.0 IU/L, respectively) and the EU-Avastin group (Day 43 and Day 71 (306.3 and 461.7 IU/L, respectively).

Individual shifts from baseline for ≥5 subjects were observed for ALT, creatine kinase, lactate dehydrogenase, total protein, and triglyceride values at various timepoints; the rates of the shifts were similar among the treatment groups.

BAT1706-002-CR (Phase I Study)
All mean blood biochemistry parameters (creatine kinase, lactate dehydrogenase, ALT, AST, γ-glutamyl transpeptidase, alkaline phosphatase, total protein, albumin, total bilirubin, direct bilirubin, blood urea nitrogen, creatinine, uric acid, cholesterol, triglyceride, fasting glucose, potassium, sodium and calcium) were within the reference range.

In the BAT1706 injection group, the most common abnormal blood biochemistry laboratory tests with clinical significance were ALT (9 [23.1%]), followed by AST (6 [15.4%]), fasting blood glucose (3 [7.7%]), γ-glutamyl transpeptidase (2 [5.1%]), albumin (2 [5.1%]), creatine kinase (1 [2.6%]), total bilirubin (1 [2.6%]), and triglyceride (1 [2.6%]). In the EU-Avastin group, the most common abnormal laboratory results with clinical significance were triglyceride (6 [14.6%]) after treatment, followed by ALT (5 [12.2%]), creatine kinase (2 [4.9%]), AST (2 [4.9%]), γ-glutamyl transpeptidase (2 [4.9%]), albumin (2 [4.9%]), fasting blood glucose (2 [4.9%]), and potassium (1 [2.4%]).

There were no clinically significant coagulation parameter findings.

BAT1706-003-CR (Phase III Study)

Grade 3/4 toxicities were observed in ≤5% of the patients in each arm except for gamma-glutamyl transpeptidase (24 [7.6%] patients in the BAT1706 group and 37 [11.9%] patients in the EU-Avastin group) and the respective frequency of grade 4 was 1 (0.3%) and 3 (1.0%) and sodium low (21 [6.6%] patients in the BAT1706 group and 17 [5.4%] patients in the EU-Avastin group.

Grade 4 toxicities were observed in ≤1% of the patients in either treatment arm for AST, ALT, glucose (low), total cholesterol, sodium (high and low), potassium (high and low), and calcium (high and low).

Urinalysis

BAT1706-001-CR (Phase I Study)
No abnormalities with clinical significance for urinalysis were reported.

BAT1706-002-CR (Phase I Study)
In BAT1706 injection group, the most common abnormal laboratory result with clinical significance included red blood cell [5 (12.8%)], followed by protein [1 (2.6%)] and white blood cell [1 (2.6%)]. In Bevacizumab group, the most common abnormal laboratory result with clinical significance included red blood cell [3 (7.3%)], followed by protein [1 (2.4%)] and white blood cell [1 (2.4%)].

BAT1706-003-CR (Phase III Study)

At baseline, 13 (2.0%) patients (7 [2.2%] patients in Arm A and 6 [1.9%] patients in Arm B) had abnormal clinically significant (ACS) protein level in urine. At the end of treatment, 43 (22.5%) of patients in the BAT1706 arm and 34 (19.1%) of patients in the EU-Avastin arm had ACS protein level in urine.

From baseline to EoT, less than 5% of patients had ACS glucose in urine at each visit. Less than 5% of patients had ACS blood in urine at each visit. No abnormal level of choriogonadotropin beta in urine was observed in any patient.

Vital signs and physical findings

BAT1706-001-CR (Phase I Study)
There were no clinically relevant differences in mean values and mean changes from baseline for vital sign measurements between the treatment groups.

BAT1706-002-CR (Phase I Study)
Descriptive statistics for changes from baseline in vital sign parameters (temperature, SBP, DBP and pulse) were highly similar between the BAT1706 and EU-Avastin treatment groups, with no clinically meaningful changes over time.

BAT1706-003-CR (Phase III Study)
The median values of vital signs parameters (SBP, DBP, pulse rate, body temperature, and weight) showed minimal changes at all visits from baseline to EoT in both the treatment arms. The median changes from baseline to EoT were minimal in the 2 treatment arms.

Electrocardiograms
BAT1706-001-CR (Phase I Study)
There were no clinically significant abnormal ECG data reported during the study. Abnormal ECG evaluations were recorded; however, none of these was considered to be clinically significant. There were no clinically significant shifts from baseline for overall ECG evaluations during the study.

There were no subjects with a QTcB of >500 milliseconds (ms) for any of the study treatments. QTcB increases from baseline that were >480 ms and ≤500 ms were observed for 1 subject each in the BAT1706 and US-Avastin groups.

BAT1706-002-CR (Phase I Study)
Abnormal ECG results of clinical significance after administration were reported for 4 (10.3%) subjects in BAT1706 group and 2 (4.9%) subjects in EU-Avastin group.

The change trends of 12-lead ECG parameters were similar and comparable between the 2 groups.

BAT1706-003-CR (Phase III Study)
Results from ECG assessments at baseline were similar between treatment groups (safety population).

Mean changes from baseline to EoT were minimal for most ECG parameters. Overall, similar results were observed in both arms in the change from baseline to EoT for ECG parameters.

Rates of abnormal ECG values were similar between treatment groups:

- Abnormal clinically significant (ACS) ECG results were observed for 8 (2.5%) patients in the BAT1706 group and 14 (4.3%) patients in the EU-Avastin group at baseline; and 16 (4.9%) and 10 (3.1%) patients, respectively, had ACS ECG results at EoT.
- Abnormal not clinically significant (ANCS) ECG results were observed for 152 (46.8%) patients in the BAT1706 group and 167 (51.5%) patients in the EU-Avastin group; and 94 (28.9%) and 100 (30.9%) patients, respectively, had ANCS ECG results at EoT.

ECG shifts from normal at baseline to ACS value were observed in 16 (9.2%) patients in the BAT1706 group and in 8 (5.1%) patients in the EU-Avastin group. Shifts from normal at baseline to ANCS value were observed in 75 (43.4%) patients in the BAT1706 group and in 82 (52.2%) patients in the EU-Avastin group.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

The applicant has not conducted specific safety studies in special populations. This is acceptable for this biosimilar application.

2.6.8.7. Immunological events

To assess the similarity of immunogenicity between BAT1706 and Avastin, the BAT1706 development programme included assessments of ADA as well as NADA in all 3 clinical studies for all subjects.

In studies BAT1706-001-CR and BAT1706-002-CR, healthy male subjects were tested for ADA, and ADA-positive samples were to be analysed for NADA.

In BAT1706-001-CR, all subjects in all 3 treatment groups (BAT1706 [N = 39]; EU-Avastin [N = 43]; US-Avastin [N = 42]) were negative for ADA (specific for BAT1706 / EU-Avastin / US-Avastin) at all study visits including the baseline visit. Similarly, all subjects in both treatment groups of study BAT1706-002-CR (BAT1706 [N = 41]; EU-Avastin [N = 41]) were negative for ADA (specific for BAT1706 / EU-Avastin) at all study visits including the baseline visit.

In BAT1706-003-CR Phase III study, blood samples for ADA determination were done at baseline (pre-infusion at Cycle 1), Day 15 of Cycle 1, Cycle 3 pre-infusion, Cycle 5 pre-infusion, Cycle 7 pre-infusion, and afterwards every 9 weeks up to Week 52.

In total, 13 and 15 patients were positive for ADA at baseline in BAT1706 and EU-Avastin group, respectively. The overall ADA incidence was low and the rates of ADA positive results comparable between arms. There were 4 and 5 ADA-positive patients at end of treatment in BAT1706 and EU-Avastin group, respectively. Neutralizing antibodies were not detected in any patient during the study.

Altogether, the assessment of immunogenicity results did not raise any clinically significant safety concerns.

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

Formal studies to assess the potential drug-drug interaction studies with BAT1706 have not been carried out. This is acceptable for a biosimilar application.

2.6.8.9. Discontinuation due to adverse events

There are numerical differences for TEAEs, grade ≥3 TEAEs, SAEs and TEAEs that led to discontinuation reported for the different bevacizumab treatment arms, however no specific trend can be identified. Overall BAT1706 and EU-Avastin appears similar and the TEAEs presented are the expected considering the treatments used and the underlying disease.

2.6.8.10. Post marketing experience

BAT1706 is not marketed in any country.

2.6.9. Discussion on clinical safety

The main safety data to support comparability between BAT1706 and the EU-Avastin was derived from the phase III study BAT1706-003-CR. In addition, two phase I single dose, parallel group studies, BAT1706-001-CR and BAT1706-002-CR were performed in healthy volunteers.

BAT1706-003-CR is a Phase III, randomised, double blind, multicentre, active comparator, parallel 2-arm study in patients without driver mutations with previously untreated advanced nsNSCLC. Bevacizumab was used together with carboplatin and paclitaxel in the combination phase followed by monotherapy with bevacizumab. BAT1706 was compared to EU-Avastin. All TEAEs, regardless of relationship to the study medication/study procedures, from the start of the first study medication administration until 28 days after discontinuation/completion of the study medication or up to Week 53 after randomisation were collected.

In the BAT1706-001-CR Study, there was reported one serious TEAE of fibula fracture in BAT1706 group. The event was considered unrelated to the study drug and resolved. The subject's medical history included osteochondrosis. Another subject from the US-Avastin group experienced the event of increase in muscle enzyme which was considered serious and unrelated to the study drug as well. The event resolved. There were no deaths or other significant TEAEs in this study.

In the BAT1706-002-CR Study, one subject from the BAT1706 group had hypertriglyceridemia of grade 3 which was assessed as unrelated to the study drug. In the EU-Avastin group, there were 7 subjects who experienced any TEAE of grade 3 or 4; five of them had hypertriglyceridemia of grade 3, one subject had hypertriglyceridemia of grade 4 and one subject had hypokalaemia of grade 4. In this study, no reports of any fatalities were reported. The Phase I studies only included single doses, i.e. they don't contribute to the long term safety profile and only included healthy subjects introducing heterogeneity versus the intended population of cancer patients. Furthermore, the number of patients included was limited. Overall, the safety profile in the Phase I studies was similar for BAT1706 and EU-Avastin.

A total of 649 patients received treatment, 325 patients in the BAT1706 group and 324 patients in the EU-Avastin group. Overall, the number of patients exposed to bevacizumab is considered adequate for evaluation of the safety of BAT1706 in comparison to EU-Avastin. Overall data as well as separate data for the combination treatment period and monotherapy period up till 52 weeks have been provided.

The most common primary reason for end of treatment was disease progression (50.5% BAT1706 and 46.3% EU-Avastin) followed by adverse events (9.8% BAT1706 and 10.4% EU-Avastin), death ((7.1% BAT1706 and 7.4% EU-Avastin) and withdrawal by patient (5.2% BAT1706 and 9.2% EU-Avastin).

Study drug exposure in the BAT1706 and EU-Avastin groups displayed a median duration of 34.0 weeks and 27.6 weeks, respectively. There was a median of 10 and 9 infusions for BAT1706 and EU-Avastin with a median cumulative actual dose of 153.6 and 136.2 mg/kg, respectively. Drug exposure, including, number of infusions received, dose intensity, relative dose intensity and dose delays in the safety population was similar for both BAT1706 and EU-Avastin. The median therapy duration and median cumulative actual dose was higher in the BAT1706 arm and the difference stems from the combination treatment phase for the cumulative dose. However, considering the similarity for the other exposure and safety parameters, this raises no concern.

Slightly fewer patients, 235 compared to 211 for BAT1706 and EU-Avastin respectively continued in the monotherapy phase of the study. No significant differences between the treatment groups could be detected. The overall incidence of TEAEs at Week 52 was balanced between the treatment groups, as well as the rate of discontinuations of treatment due to disease progression, concretely in 164 (50.5%) patients from the BAT1706 group and in 151 (46.3%) patients in the EU-Avastin group. Similarly, AEs

which led to discontinuation occurred in a similar proportion of patients; in 32 (9.8%) patients and 34 (10.4%) patients, respectively.

One or more TEAEs were reported for almost all patients in the study, 316/325 (97.2% and 319/324 (98.5%) in the BAT1706 group and Avastin group respectively. TEAEs with NCI-CTCAE severity Grade ≥3 was experienced by 222 (68.3%) subjects in the BAT1706 group and 239 (73.8%) subjects in the EU-Avastin group. TE-SAE were experienced by 100 (30.8%) of patients treated with BAT1706 and 108 (33.3%) of patients treated with EU-Avastin. A fatal TEAE was experienced by 18 (5.5%) and 19 (5.9%) patients in the BAT1706 arm and EU-Avastin arm respectively. TEAE leading to discontinuation of treatment was experienced by 26 patients (8.0%) in the BAT1706 arm and 28 (8.6%) in the EU-Avastin arm.

The frequency of TEAEs reported, the most common PT TEAE reported, test drug related TEAE of grade ≥3 and AESIs was overall similar between the treatment arms in the BAT1706-003 study. Slight numerical differences in reported PT terms were recorded, however no specific trend can be identified. Also, the frequency of TE-SAE and TEAE leading to treatment discontinuation was similar between the treatment arms. Overall, the number of deaths were balanced between the treatment arms and the majority of deaths are related to progression of the underlaying disease. There were 8 (2.5%) deaths considered related/possibly related by the investigator to BAT1706 and 4 (1.2%) deaths related to EU-Avastin. One death in each group occurred during the monotherapy period. However, considering that the overall number of deaths were similar, the small numbers of deaths considered related to bevacizumab, no specific trend for cause of death and that the causes reported can be considered known AEs attributed to bevacizumab and/or the studied disease, this raises no concern.

An extensive analysis of cardiac data from ECG and blood pressure measurements and from AE reporting for the Week 52 data-cut was provided. The mean changes from baseline to EoT were minimal for most ECG parameters for the 12-month study period. The rates of clinically significant abnormal ECG findings and changes from baseline in SBP and DBP during the study were comparable between treatment groups throughout the study. Similarly, the targeted analysis of recorded cardiac disorder TEAEs, SAEs, fatal events or TEAEs leading to treatment discontinuation did not raise any significant concerns related to cardiac disorders which would be associated with administration of BAT1706 product.

The provided analysis of TEAE, treatment related TEAE, SAE and treatment-related SAE and AESI per age groups (overall / <65 years / 65 to <75 years / ≥75 years) was provided. The slight disproportion of patients in individual age subgroups between treatment arms was recognised but no significant difference in the safety profile were observed between BAT1706 and EU-Avastin groups in view of the individual age groups. In the age group of 65 to <75 years, frequently reported TEAEs with a ≥10% greater incidence rate in the BAT1706 group than in the EU-Avastin group were anaemia, alopecia, epistaxis and proteinuria. In case of the TEAEs related to study treatment, in the age group of <65 years, 138 (59.2%) patients in the BAT1706 group and 135 (65.9%) patients in the EU-Avastin group experienced any drug-related TEAE. In age group of 65 to <75 years, any TEAE occurred in 53 (67.1%) and 49 (46.2%) patients, in this order, and in age group of ≥75 years it occurred in 7 (53.8%) patients from each group. In view of the characteristics of the reported TEAEs as per specific PTs (proteinuria and epistaxis as more frequently reported TEAEs in the BAT1706 group compared to EU-Avastin group), no significant differences were detected. No pattern could be identified.

The treatment arms appear similar with regards to haematology and blood chemistry parameters.

The frequency of hypersensitivity and infusion related reactions were low and none of the reactions that were considered related to bevacizumab led to treatment discontinuation. Overall, adjudging a

difference between the products is not possible due to low numbers and the products appear reasonably similar.

2.6.10. Conclusions on the clinical safety

The applicant has provided comprehensive safety and immunogenicity data including follow-up for 52 weeks of the pivotal phase 3 study. The totality of the safety results supports biosimilarity of BAT1706 and Avastin.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 41. Summary of Safety Concerns

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

2.7.2. Pharmacovigilance plan

The proposed pharmacovigilance plan is in line with that of the reference product and is considered acceptable. No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection were identified. Furthermore, no additional pharmacovigilance activities were identified.

The PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.3. Risk minimisation measures

Since there are no safety concerns identified in Module SVIII, neither routine nor additional risk minimisations measures are considered applicable.

The PRAC having considered the data submitted agrees that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7.4. Conclusion

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

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. 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.

2.9. Product information

2.9.1. User consultation

A user consultation with target patient groups on the package information leaflet (PL) has been performed based on a bridging report making reference to Oyavas 25 mg/mL concentrate for solution for infusion (EMEA/H/C/005556/0000) regarding content and Alunbrig 30 mg film-coated tablets Alunbrig 90 mg film-coated tablets/Alunbrig 180 mg film-coated tablets (EMEA/H/C/004248/0000) regarding layout. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Avzivi (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

BAT1706 has been developed as a biosimilar to Avastin (bevacizumab), a recombinant humanised monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor (VEGF).

The applicant claims the same therapeutic indications for BAT1706 as granted for Avastin in the EU. For all proposed indications for BAT1706, the recommended posology and method of administration correspond to those of Avastin.

The claimed indications are:

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

Avzivi 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.

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

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

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

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

Avzivi, 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.

Avzivi, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

Avzivi 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.

Avzivi, 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.

Quality

The applicant has performed an extensive biosimilarity exercise, evaluating relevant quality attributes by a panel of state-of-the-art analytical methods. The analytical similarity assessment has been performed with a combination of methods assessing the primary and higher order structures, particles and aggregates, purity and product-related substances, process-related impurities, post-translational modifications including charge variants and glycosylation profile. In addition, biological activities including Fab and Fc-related functions have been evaluated and comparative stability testing has been performed.

Overall, the provided data indicates a high degree of similarity between BAT1706 and EU approved Avastin. Some minor differences are noted, for instance, in the N-glycans profile, charged forms and total purity. The applicant justified the differences and provided arguments related to bevacizumab

mode of action, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful.

Clinical

Clinical development programme included two Phase I studies in healthy male subjects to compare PK with EU-Avastin and US-Avastin (BAT1706-001-CR conducted in New Zealand) and with EU-Avastin conducted in China (BAT1706-002-CR). In addition, a single Phase III clinical study BAT1706-003-CR to compare the efficacy, safety, PK and immunogenicity of BAT1706 plus paclitaxel and carboplatin vs. EU-Avastin plus paclitaxel and carboplatin in patients with advanced nsNSCLC was conducted in 5 countries (China, Turkey, Ukraine, South Africa, and Mexico).

According to the applicant the studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines ICH E6(R2) and the applicable drug and data protection laws and regulations of the countries where the clinical study was conducted.

There were no formal scientific advice(s) given by EMA or Member State(s) for this medicinal product. A summary of the MAA has been presented for the Rapporteur's.

3.2. Results supporting biosimilarity

Quality

Overall, the provided data indicated a high degree of similarity between BAT1706 and EU approved Avastin. Some minor differences are noted, for instance, in the N-glycans profile, charged forms and total purity. The applicant justified the differences and provided arguments related to bevacizumab mode of action, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful.

The presented data show that batches of BAT1706 and EU approved Avastin have similar potencies with respect to both Fab-related biological activity and Fc-related functions. The comparison of degradation profiles also supports the claim for biosimilarity.

Pharmacokinetics

PK similarity between BAT1706 and the reference product EU-Avastin was demonstrated in the two Phase I studies (BAT-1706-001-CR and BAT-1706-002-CR), as the 90% CI for the geometric means ratios of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} parameters were fully contained within the predefined bioequivalence limits of 0.80 to 1.25.

Supportive PK data from a subgroup of patients in the Phase III study showed that exposures based on bevacizumab concentration and PK parameter comparisons were similar between the BAT1706 and EU-Avastin groups in patients with advanced non-squamous non-small cell lung cancer (nsNSCLC).

Similarity in immunogenicity was demonstrated in both Phase I studies and in the Phase III study.

Pharmacokinetic similarity is considered sufficiently demonstrated between BAT1706 and the reference product EU-Avastin.

Clinical Efficacy:

A single randomised 1:1, double-blind, parallel group, multicentre study (Study BAT-1706-003-CR) was conducted to compare the efficacy, safety, and immunogenicity between BAT1706 and EU- Avastin in patients with newly diagnosed advanced stage IV or recurrent non-squamous non-small cell lung cancer (nsNSCLC).

The outcome of the analysis of primary endpoint ORR (i.e., subjects who achieved CR or PR per RECIST version 1.1 as assessed by IRC) at Week 18 (corresponding to 6 cycles of BAT1706/Avastin in combination with chemotherapy) in the ITT population was 48.0% in BAT1706 arm (Arm A) and 44.5% in EU-Avastin arm (Arm B). This results in an un-adjusted risk difference (RD) of ORR18 of 0.03. The 2-sided 95% CI [-0.04, 0.11] was entirely contained within the pre-specified equivalence margins (-0.12, 0.15).

Importantly, the outcome in the PP population (point-estimates and confidence intervals) was consistent with that of the ITT population.

In conclusion, the 95%CI for the RD of primary endpoint ORRw18 is contained in the pre-specified equivalence margins for both ITT and PP population suggesting equivalence of efficacy for BAT1706 and EU-Avastin.

The results of the primary endpoint analysis were also supported by the subgroup analysis for ORR18 in pre-specified stratification subgroups ((NSCLC stage newly diagnosed stage IV/recurrent disease, gender and ethnicity) and in subgroups determined based on other clinically relevant prognostic factors (i.e. age, ECOG PS, etc). It is agreed that the subgroup analyses should be considered exploratory due to limitations in sample sizes. In the largest subgroups (disease stage IV newly diagnosed, male, age<65 years, baseline ECOG PS 1) and most importantly, in both ethnicity subgroups (Asian or non-Asian), the 95% CI of risk difference in ORR18 fell within the pre-specified equivalence margins (-0.12,0.15). The results for all subgroups in the PP population were similar to those in the ITT.

In addition, landmark analysis of the ORR at Week 6 and Week 12 in ITT and PP population shows no significant difference between arms in ORR6 (27.4% vs 22.7% in Arm A vs Arm B) and ORR12 (45.2% vs 40.8% in Arm A vs Arm B). The 95%CIs of the risk difference for ORR6 0.04 [-0.02, 0.11] and ORR12 0.04 [-0.03, 0.12] are entirely contained in the prespecified equivalence interval, thus supporting the clinical similarity.

Analysis of BOR at week 18 and repeated at Week 52 supports the equivalence observed for the primary endpoint.

The secondary endpoint median PFS, OS, DoR deemed similar at the primary analysis at Week 18 and importantly, at the final analysis at Week 52 for the 2 compounds in both ITT and PP populations.

Clinical Safety:

The main safety data to support comparability between BAT1706 and the EU-Avastin was derived from the phase III study BAT1706-003-CR. Overall, the number of patients exposed to bevacizumab is considered adequate for evaluation of the safety of BAT1706 in comparison to EU-Avastin and the follow-up time including up to the final analysis at week 52 is considered acceptable.

Drug exposure, including number of infusions received, dose intensity, relative dose intensity and dose delays in the safety population was overall similar for both BAT1706 and EU-Avastin.

The frequency of TEAEs reported, the most common PT TEAE reported, test drug related TEAE of grade ≥3 and AESIs was similar between the treatment arms in the BAT1706-003 study. Also, the frequency of TE-SAE and TEAE leading to treatment discontinuation was similar between the treatment arms for the presented follow-up time. Overall, the number of deaths were balanced between the treatment arms.

3.3. Uncertainties

3.4. and limitations about biosimilarity

Quality

The applicant presented an extensive biosimilarity exercise, evaluating relevant quality attributes by a panel of state-of-the-art analytical methods. The provided data indicate a high degree of similarity between BAT1706 and EU approved Avastin. The concerns initially raised on the first submissions are now considered solved and there are no remaining uncertainties and limitations.

Pharmacokinetics

No uncertainties and limitations remain.

Clinical Efficacy:

The asymmetric margins of the 95% CI for the RD of ORR18 with a slightly higher upper margin of 0.15 chosen, were justified as there was no medical concern that slightly higher ORR18 of BAT1706 would result in higher toxicity. The similarity of the safety profile is assessed separately based on the totality of data on, safety and immunogenicity. Statistically, the Type 1 error rate is preserved, both by using post-hoc symmetric (-0.12, 0.12) or pre-specified asymmetric (-0.12, 0.15) 95%CI of RD, as the study results [-0.04, 0.11] fit within both intervals.

Preferably, taking in account the precedent with the previous approved Avastin biosimilars, an asymmetric margin for the equivalence range should not be applied. However, the results are considered robust, with the primary endpoint 95%CI falling in the equivalence interval either by using post-hoc defined symmetric margins or the prespecified asymmetric margins.

In addition, a tipping point analysis was presented as a sensitivity analysis. This analysis is not what was planned since there are no results summarised based on a missing data imputation under the MAR assumption. However, the tipping point analysis shows that the results where equivalence could not be concluded are quite implausible. Accordingly, it is considered that the provided sensitivity analysis sufficiently supports a conclusion of robust results.

During the review of the statistical outputs, it was observed that some patients had major protocol deviations so far unrecognised. Consequently, a total of 24 additional patients were excluded from the PP population after database lock. The differences in results between the analysis of ORR18 for the primary PP population and the Modified PP population were minor, and the equivalence margins (for risk ratio and risk difference and for multivariate-adjusted risk ratio and risk difference) were met in all scenarios.

Clinical Safety:

The median treatment duration (BAT1706: 34.0 weeks; EU-Avastin: 27.6 weeks) and median cumulative actual dose (BAT1706: 153.6 mg/kg; EU-Avastin: 136.2 mg/kg) was higher in the BAT1706 arm and the difference stems from the combination treatment phase for the median cumulative dose (BAT1706: 89.0 mg/kg; EU-Avastin: 78.2 mg/kg). However, considering the similarity for the other exposure and safety parameters, this raises no concern.

Slightly fewer patients, 235 compared to 211 for BAT1706 and EU-Avastin respectively continued in the monotherapy phase of the study. No significant differences between the treatment groups could be detected. The overall incidence of TEAEs at Week 52 was balanced between the treatment groups, as well as the rate of discontinuations of treatment due to disease progression, concretely in 164 (50.5%) patients from the BAT1706 group and in 151 (46.3%) patients in the EU-Avastin group. Similarly, AEs

which led to discontinuation occurred in a similar proportion of patients; in 32 (9.8%) patients and 34 (10.4%) patients, respectively.

Slight numerical difference in reported PT terms were recorded, however no specific trend can be identified.

A slight difference between treatment arms was noted with regards to 8 vs. 3 deaths due to TEAE attributed to be related to BAT1706 and EU-Avastin respectively. There were 8 (2.5%) deaths considered related/possibly related by the investigator to BAT1706 and 4 (1.2% deaths related to EU-Avastin. One death in each group occurred during the monotherapy period. However, considering that the overall number of deaths were similar, the small numbers of deaths considered related to bevacizumab, no specific trend for cause of death and that the causes reported can be considered known AEs attributed to bevacizumab and/or the studied disease, this raises no concern.

3.5. Discussion on biosimilarity

Quality

From a quality perspective, the applicant presented an extensive biosimilarity exercise, evaluating relevant quality attributes by a panel of state-of-the-art analytical methods. Overall, the provided data indicated a high degree of similarity between BAT1706 and EU approved Avastin. Some minor differences are noted, for instance, in the N-glycans profile, charged forms and total purity. The applicant justified the differences and provided arguments related to bevacizumab mode of action, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful.

No issues on biosimilarity remain. From a quality perspective, BAT1706 is approvable as biosimilar to EU-Avastin.

Pharmacokinetics

Pharmacokinetic similarity is considered sufficiently demonstrated between BAT1706 and the reference product EU-Avastin.

Immunogenicity similarity has been demonstrated in both Phase I studies and in the Phase III study.

Clinical efficacy

The analysis of primary endpoint ORR at Week 18 and the 95%CI for the RD of primary endpoint ORR18 is contained in the pre-specified equivalence margins for both ITT and PP population suggesting equivalence of efficacy for BAT1706 and EU-Avastin. Statistically, the Type 1 error rate is preserved, both by using post-hoc symmetric (-0.12, 0.12) or pre-specified asymmetric (-0.12, 0.15) 95%CI of RD, as the study results [-0.04, 0.11] fit within both intervals.

The similarity showed by the analysis of equivalence for the primary endpoint is supported by the pre-specified and post-hoc sensitivity analyses of the primary endpoint, by the landmark analysis of ORR and by the consistency of the results between ITT and PP populations. Comparable results between arms for the secondary, time-related endpoints at the cut-off for the final analysis (Week 52, 25 June 2020), median PFS, OS and DoR with overlapping KM curves support the similarity observed for the primary point estimate. The final analysis results of PFS, OS and DoR are consistent between the ITT and PP population, which is reassuring.

Clinical safety

The presented safety data is overall comparable, and similarity is considered sufficiently demonstrated between BAT1706 and the reference product Avastin.

3.6. Extrapolation of safety and efficacy

Overall, literature data support a consistent mechanism of action for bevacizumab across indications, targeting VEGF and angiogenesis in various tumour types. The relevance of bevacizumab's anti-angiogenesis activity for clinical efficacy and the important role that vascularisation of the tumours plays in tumour development and growth for each indication is well documented. Anti-angiogenesis via the VEGF pathway has been shown to be a key therapeutic strategy in the treatment of mCRC (Seeber et al 2018), NSCLC (Kurzrock and Steward 2017, Coelho et al 2017), mRCC (Sun et al 2018), OC (Moghaddam et al 2012) and cervical cancer (Minion and Tewari 2018). The safety risks for Avastin are well known and common across indications and dosing regimens.

Therefore, extrapolation to all other indications labelled for the reference product bevacizumab is considered acceptable.

3.7. Additional considerations

Not applicable.

3.8. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Avzivi's similarity to the reference product Avastin is considered demonstrated. 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 Avzivi 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 Avzivi is favourable in the following indication(s):

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

Avzivi 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.

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

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

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

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

Avzivi, 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).

Avzivi, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

Avzivi 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).

Avzivi, 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.