25 June 2020
EMA/380645/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aybintio

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/005106/0000

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
AE	Adverse event
AESI	Adverse events of special interest
ALK	Anaplastic lymphoma kinase
ALP	Aspartate aminotransferase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve from time zero to infinity
AUC_{last}	Area under the concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0-τ,ss}$	Area under the concentration-time profile for a dosing interval (τ) at steady state
$\%AUC_{extrap}$	Area under the concentration-time curve from time t to infinity as a percentage of total AUC
BALB	Baseline albumin
BL	Baseline
BMI	Body mass index
BSA	Body surface area
C1q	Complement component 1, q subcomponent, a chain
CR	Complete response
CCr	Creatinine clearance
CRCL	Creatinine clearance calculated using cockcroft-gault equation
CD	Circular dichroism
CD	Cluster of differentiation
CDC	Complement-dependent cytotoxicity
CE-SDS	Capillary electrophoresis-sodium dodecyl sulphate
CEX	Cation-exchange chromatography
CHF	Congestive heart failure
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed concentration at t_{max}
$C_{max,ss}$	Steady state maximum concentration
C_{min}	Minimum observed concentration at t_{max}
$C_{min,ss}$	Steady state minimum concentration
CoA	Certificate of analysis

CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
C_{trough}	Serum concentration at baseline and prior to dosing
CV	Coefficient of variation
DOR	Duration of response
DP	Drug product
DS	Drug substance
ECL	Electrochemiluminescence
ECOG	Eastern cooperative oncology group
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ENR	Enrolled set
EOS	End of study
EOT	End of treatment
EPAR	European public assessment report
EU	European union
FAS	Full analysis set
FDA	Food and Drug Administration
FcRn	Neonatal Fc receptor
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
FIGO	International federation of gynecology and obstetrics
FTIR	Fourier transform infrared spectroscopy
GMP	Good manufacturing practice
HCP	Host cell protein
HILIC	Hydrophilic interaction liquid chromatography
HPLC	High performance liquid chromatography
HUVEC	Human umbilical vein endothelial cells
ICH	The international council for harmonization of technical requirements for pharmaceuticals for human use
icIEF	Imaged capillary isoelectric focusing
IFN	Interferon
IgG	Immunoglobulin G
IP	Investigational product

i.v. or IV	Intravenous
λ_z	Terminal rate constant
LC	Liquid chromatography
LSMean	Least squares mean
MAA	Marketing authorisation application
MALLS	Multi-angle laser light scattering
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
MFI	Micro-flow imaging
MHC	Major histocompatibility complex
Min	Minimum
MoA	Mechanism of action
MRI	Magnetic resonance imaging
MS	Mass spectrometry
N/A	Not available or not applicable
NAb	Neutralizing antibody
NGHC	Non-glycosylated heavy chains
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PC	Paclitaxel/carboplatin
PD	Pharmacodynamics
PD	Progressive disease
PFS	Progression-free survival
PI	Prediction interval
PK	Pharmacokinetics
PPS	Per-protocol set
PR	Partial response
PT	Preferred term
QC	Quality control
RECIST	Response evaluation criteria in solid tumors version 1.1
RAN	Randomized set
RMP	Risk management plan
SA	Scientific advice
SAE	Serious adverse event
SAF	Safety set
SD	Standard deviation
SD	Stable disease
SEC	Size-exclusion chromatography
SmPC	Summary of product characteristics
SOC	System organ class

$t_{½}$	Terminal half life
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach maximum (peak) plasma concentration (C_{max})
TMB	Tetramethylbenzidine
TNM	Tumor, nodes, metastasis
ULN	Upper limit of normal
US(A)	United States (of America)
UPLC	Ultra performance liquid chromatography
VEGF	Vascular endothelial growth factor
Vc	Central volume of distribution
Vz	Volume of distribution during the terminal phase

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Samsung Bioepis NL B.V. submitted on 26 June 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Aybintio, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

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

Aybintio 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 SmPC section 5.1.

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

Aybintio, 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.

Aybintio, 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 SmPC section 5.1).

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

Aybintio, 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 SmPC section 5.1).

Aybintio, 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.

Aybintio, in combination with 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 SmPC section 5.1).

Aybintio, 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 SmPC Section 5.1).

The legal basis for this application refers to:

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

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

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Avastin 25 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 01/12/2005
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/04/300/001-002

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

- Product name, strength, pharmaceutical form: Avastin 25 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 01/12/2005
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/04/300/001-002

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

- Product name, strength, pharmaceutical form: Avastin 25 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 01/12/2005
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation numbers: EU/1/04/300/001-002

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant received Scientific Advice on 22 May 2014 (EMEA/H/SA/2783/1/2014/III), 26 February 2015 (EMEA/H/SA/2783/1/FU/1/2015/II), 22 June 2017 (EMEA/H/SA/2783/1/FU/2/2017/III) and 26 July 2018 (EMEA/H/SA/2783/1/FU/3/2018/I) for the development programme supporting the indication granted by CHMP. The Scientific Advice pertained to the following quality, preclinical and clinical aspects of the dossier:

Quality: Analytical Methods Panel to use in support of the demonstration of analytical similarity. Appropriateness of the VEGF neutralisation assay proposed. Characterization studies used for both strengths developed, 100 mg and 400 mg vials. Appropriateness of the stability studies.

Preclinical: *In vitro* study plan to provide non-clinical evidence of similarity. Waiver of in vivo studies.

The main clinical aspects under consideration were:

- The design of the PK study in Healthy volunteer to demonstrate similarity in PK profiles of SB8, EU Avastin, and US Avastin with emphasis on the dose to use.
- The design of the PK study in Healthy volunteer to demonstrate similarity between DP pre and post manufacturing changes.
- The design of the efficacy and safety trial in patients with metastatic or recurrent non-squamous non-small cell lung cancer and supportive PK assessment, including population selected and the primary endpoint, proposed margins and statistical assumptions, duration and safety database.
- Extrapolation of the clinical results in non-small cell lung cancer to support registration in the other indications approved for the Reference Medicinal Product.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Andrea Laslop Co-Rapporteur: Agnes Gyurasics

The application was received by the EMA on	26 June 2019
The procedure started on	18 July 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 October 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	9 October 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	21 October 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 January 2020
The following GCP inspections were requested by the CHMP and their	

outcome taken into consideration as part of the Efficacy assessment of the product:	
- A GCP inspection at two investigator sites (located in Hungary and Russia) and at the sponsor site located in South Korea between 07 January and 07 February 2020. The outcome of the inspections carried out was issued on	10 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	02 March 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 March 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	26 March 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 May 2020
The CHMP agreed on a second list of outstanding issues in writing to be sent to the applicant on	28 May 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	01 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP members on	10 June 2020
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 Aybintio on	25 June 2020

2. Scientific discussion

2.1. Problem statement

About the product

Aybintio (Company code SB8) has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Avastin having bevacizumab as the active substance.
Aybintio (bevacizumab) belongs to the pharmacotherapeutic group "monoclonal antibodies" (ATC code: L01XC07).

Bevacizumab selectively binds to human VEGF and inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralizing the biologic activity of VEGF reduces the vascularization of tumours, thereby inhibiting tumour growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was also inhibited, and microvascular permeability was reduced.

The Applicant claims the same therapeutic indications for Aybintio as granted for Avastin in the EU, except for the treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel. Aybintio is intended for the treatment of the carcinoma of the colon or rectum, breast cancer, non-small cell lung cancer, renal cell cancer, epithelial ovarian, fallopian tube or primary peritoneal cancer, and carcinoma of the cervix (see section 1). The recommended posology and method of administration correspond to those of Avastin.

Aybintio must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

2.2. Quality aspects

2.2.1. Introduction

Aybintio is a biosimilar medicinal product (reference product Avastin). It is presented as a sterile concentrate for solution for infusion containing 100 mg of bevacizumab in a 4 mL vial or 400 mg bevacizumab in a 16 mL vial (strength 25 mg/mL). The active substance bevacizumab is formulated with commonly used excipients: trehalose dihydrate, sodium acetate trihydrate, acetic acid, polysorbate 20 and water for injections.

Aybintio is provided in a single use Type I glass vial with a butyl rubber stopper and an aluminium crimping cap. Aybintio is supplied in packs of 1 vial of 4 mL or 16 mL.

The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/mL (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4 mg/mL to 16.5 mg/mL.

2.2.2. Active Substance

General Information

Bevacizumab, also referred to as SB8, is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster Ovary (CHO) cells. It selectively binds to human vascular endothelial growth factor (VEGF).

Bevacizumab is composed of two heavy chains (453 amino acid residues) and two light chains (214 amino acid residues) with a total molecular weight of 149 kDa. One N-linked glycosylation site is located at Asn303.

Manufacture, process controls and characterisation

Manufacture

The SB8 active substance for commercial supply is manufactured at the Biogen large-scale manufacturing facility in Hillerod in Denmark. All sites involved in manufacture and testing of the active substance have been listed. The exact responsibility of each listed site is described. Confirmation of the GMP status of the different sites was provided.

The manufacturing process of the SB8 active substance is a process typical for monoclonal antibodies. The manufacturing process begins with thawing of a vial of the working cell bank (WCB), which is a CHO cell line transfected with SB8 expression vector. After thawing of the WCB vial, the culture is serially expanded in cell mass and volume for inoculation into the production bioreactor. The cell culture fluid is subsequently purified through a series of chromatographic steps, virus inactivation and filtration steps.

Batch and scale as well as the batch numbering system have been appropriately defined.

Different categories of process parameters have been defined:

- Process input parameters:

Critical controlled parameters (CCPs) are input parameters that impact product quality within a unit operation and may also affect process performance. Key controlled parameters (KCPs) are unlikely to affect a critical quality attribute (CQA), but they do impact process consistency.

- Process output parameters:

In-process controls (IPCs) and in-process tests (IPTs) are process 'outputs'. Critical in-process controls (CIPCs) and critical in-process tests (CIPTs) are a subset that assess product quality attributes.

Control of materials

Materials used in the manufacture of the active substance have been listed identifying where each material is used in the process. Information on the quality and control of these materials has been provided. For non-compendial raw materials appropriate in-house specifications are in place. The composition of the media and solutions used in the cell culture as well as the composition of buffers and solutions for the purification steps are given. In addition, the chromatographic resins and filters are listed and the test performed on these items are mentioned.

Information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop a research bank is given. A two-tiered cell bank system consisting of a master cell bank (MCB) and WCB has been established from the research cell bank. The cell banks have been appropriately characterised and genetic stability of the cell substrate been tested. Criteria for the generation of future cell banks are defined.

Control of critical steps and intermediates

Appropriate limits for process parameters have been established. The parameters are considered appropriate to ensure that the manufacturing process is sufficiently under control. Of note, a revision of certain in- and output parameters have taken place after the process validation taking process knowledge gained from the validation campaign, manufacturing experience, additional process characterisation results, risk assessments, and overall process capabilities into account. To address the potential impact of the extended H-chain C-terminal sequence variant (detected at low levels in SB8, but not in Avastin) on product safety, the initially proposed control strategy has been strengthened.

The qualification data including specificity, linearity, accuracy, precision (repeatability and intermediate precision), and range demonstrate the analytical method is suitable for its use.

Process validation

Validation of the active substance manufacturing process consisted of consecutive process verification batches. All investigated parameters successfully met the criteria; a few deviations could be sufficiently justified to have no impact on the validity of the conducted process validation. Further studies addressing impurity and viral clearance, process intermediate hold time, chromatographic resin lifetime, and shipping have been conducted. These studies confirm that the active substance manufacturing process performs effectively and reproducibly to deliver an active substance meeting its predetermined specifications and quality attributes.

Manufacturing process development

Different levels of risk assessment have been conducted to a) identify CQAs, b) guide the level of process evaluation and c) to determine the appropriate risk mitigation and control strategy for the process validation campaign.

The development of the active substance manufacturing process from the pilot to the clinical and further to the process performance validation phase has been described.

Of importance, the clinical studies have been supplied with clinical material derived from the site located in the US whereas the process verification was done at the commercial Biogen site in Hillerod, DK. A comprehensive comparability exercise demonstrated that the clinical material from the US site has a comparable quality profile with material from the Biogen site in Hillerod. Therefore, it is confirmed that the used clinical material is representative for the intended commercial material. This issue was also discussed in a scientific advice where the CHMP principally agreed with the strategy for the process transfer to a different site. Some recommendations concerning the conduct of the comparability exercise were not fully taken on board in the initial submission. Nevertheless, the issues raised during the procedure could be solved.

Characterisation

An extensive characterisation of the active substance has been performed. Standard and state-of-the art methods for primary, secondary, and higher-order structures, glycosylation, charge variants, purity/impurities, cellular potency, and binding activity have been used for the elucidation of structure and other characteristics of SB8. For most tests, active substance and finished product derived from the process verification campaigns have been included. Certain quality attributes have been characterised at the level of finished product only. The Applicant's argumentation that characterisation data with the finished product are considered to be equivalent to those that would have been obtained with the active substance since the active substance and finished product have identical active ingredients, can be agreed. As requested, potentially immunogenic carbohydrate structures and the presence of terminal alpha-1,3 galactose structures have been addressed. It should be noted that although Fc effector functions of bevacizumab may play only a very limited role in the claimed indications (the primary mode of action is the binding of soluble VEGF-A isoforms and thus inhibition of binding of this ligand to its receptor) a full characterisation of the Fc effector functions has been performed. Of note, no ADCC or CDC activity could be detected, which supports the Applicant's conclusion that the Fc-effector functions are not relevant.

The Applicant has discussed potential process-related as well as product related impurities. Process-related impurities which include HCP, host cell DNA were monitored.

Detailed control strategy of product-related impurities for commercial batches was provided.

Specification

The specification for routine release control of active substance include tests for identity, purity and impurities, biological activity and other general tests.

The Applicant provided justifications for quality attributes that are not included in the SB8 specifications. In addition, adequate justification was provided for the proposed methods.

Analytical procedures

Overall, the analytical procedures were sufficiently described and the analytical methods are considered adequate for their intended use. The validation of non-compendial analytical procedures was performed satisfactory according to the corresponding guideline ICH Q2(R1). For the majority of the analytical methods, active substance and finished product batches were included in the validation studies. Anyway, it is agreed that the method validation using active substance batches is also valid for finished product batches, since both active substance and finished product batches have the same formulation. Some uncertainties regarding the samples used for the validation of the analytical procedures have been solved.

The transfer of the analytical methods was adequately performed. The information provided in relation to analytical method transfers is considered acceptable.

Compendial methods were verified, which is in line with ICH Q2(R1).

Batch analyses

The batches were tested and fulfilled the acceptance criteria valid at the time of testing. These data indicate that the active substance manufacturing process consistently delivers material meeting its predetermined specifications and quality attributes.

Reference standard

No international standard for bevacizumab is available. Thus, internal reference standards have been established during the SB8 development. A protocol for qualification for future reference standards for commercial batches has been provided.

Container closure

A description of the container closure system has been provided, including the identity of materials of construction of each primary packaging component.

Furthermore, an extractable study was conducted: no metals attributable to the test article were observed whereas the detected organic compounds were generally present at levels which would not be expected to pose any risk of adverse effects.

Stability

The proposed shelf-life of commercial active substance is based on the long-term stability results and is acceptable. Representativeness of the batches for the commercial active substance was discussed and appropriately addressed.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

SB8 finished product is a clear to slightly opalescent, colourless to pale brown, sterile and preservative-free solution and presented as a single-use vial containing 100 mg and 400 mg of bevacizumab as concentrate for solution for intravenous infusion.

One single-use vial contains bevacizumab as the active substance, and the following excipients: trehalose dihydrate, sodium acetate trihydrate, acetic acid, and polysorbate 20. All excipients comply with the Ph. Eur.

The primary packaging material for SB8 100 mg and 400 mg finished product consists of a Type I glass vial, a sterilised bromobutyl rubber stopper and a cap. The components of the container closure system are Ph. Eur. grade.

Pharmaceutical development

The formulation development was based on the reference medicinal product Avastin. Studies were performed to confirm the effects of pH, buffer, excipient, and protein concentration on the stability of SB8 finished product. The differences in buffering agents between Aybintio and Avastin were justified and are considered acceptable.

Manufacturing process development

Before initiating process verification of SB8 100 mg finished product, an engineering batch each from SB8 100 mg and 400 mg. The SB8 100 mg and 400 mg finished product engineering runs were successfully completed. Each of the studies within the batch record was executed and satisfactory results were obtained. The parameters and conditions verified during the studies would be applied to process verification runs.

Container Closure System [100 mg/ 400 mg]

In order to assess the suitability of the finished product container closure system, extractables of the extractable compounds were set and leachables studies were conducted. Container closure integrity has been studied during development of SB8 finished product and this test is included in the ongoing stability studies.

Elemental impurities in the finished product were evaluated in a leachables study. The study results demonstrated that no metallic impurity was identified permitted daily exposure (PDE) levels listed in ICH Q3D. Therefore, it is agreed that potential risks associated to the elemental impurities are low and that there is no need to include control of elemental impurities in the finished product specification.

Manufacture of the product and process controls

Manufacture

All sites involved in manufacture and testing of the active substance have been listed. The exact responsibility of each listed site is described. Confirmation of the GMP status of the different sites was provided.

The manufacture of SB8 finished product includes thawing and pooling of the active substance, bulk formulation, mixing, reduction filtration and sterile filtration and aseptic filling, visual inspection, bulk packaging, labelling and secondary packaging.

The same principles for input and output definitions applied for active substance are also applied for finished product process controls. For the input parameters, critical-, key- and non-key control parameters have been defined for each step in the process as well as the outputs; critical and process consistency in-process controls and in-process tests. The criticality is associated with impact on the defined CQAs of the SB8 finished product. The definitions for the limits have been described.

Process validation

The manufacturing process validation presented for SB8 finished product 100 mg and 400 mg involves the following studies: manufacturing process verification, sterile filter validation, media fill qualification, shipping qualification.

The manufacturing process has been validated on commercial batches of SB8 finished product 100 mg and 400 mg at the commercial product manufacturing site according to an approved protocol and with predefined acceptance criteria. The overall results confirm that the process is considered well under control to reproducibly manufacture SB8 finished product complying with the established specifications.

The validation of the filters used for bioburden reduction and sterilisation of the SB8 solution is conducted. All results complied with the predetermined acceptance criteria and verify that the filters are appropriate for filtering SB8 finished product volumes.

Media fill qualification is conducted at the SB8 finished product manufacturing site. The Applicant confirmed that the overall duration of the conducted media fill runs is reflective of the filling time of the commercial process.

Product specification

The specification for routine release control of finished product include tests for identity, purity and impurities, biological activity and other general tests.

Detailed justifications of the specifications were provided.

Analytical procedures

The analytical procedures used for release and shelf life testing of both SB8 active substance and finished product are provided in the respective active substance section of the dossier. Concerning the establishment of acceptance criteria reference is made to the respective active substance section of the dossier. Non-compendial methods are adequately validated.

Batch analysis

Data have been presented for 100 mg and 400 mg finished product batches manufactured during development.

All results in the batch analysis section of tested parameters were within the defined limits.

No new product-related impurities are seen in the SB8 finished product. Specific impurity data that is presented for the finished product refers to extended controls on particulate matter. In addition to the release and stability testing using the compendial Ph. Eur. 2.9.19 method, particulates have been assessed in characterisation studies. These studies were performed on the process verification batches and show that the particle content is similar in magnitude for these batches of 100 mg and 400 mg.

Reference standard

The reference standards used in the release and stability testing of SB8 finished product are the same as those used for the release and stability testing of SB8 active substance.

Stability of the product

The proposed shelf life of 100 mg/4 mL and 400 mg/16 mL finished product is 36 months when stored at the recommended temperature of 2-8°C.

SB8 stability studies are complete and were conducted with accordance with ICH and CHMP guidelines in the proposed commercial primary packaging. All quality attributes met acceptance criteria and showed no significant changes for 36 months at long-term and accelerated conditions.

At the long-term storage condition, the up-to-date results met the acceptance criteria and there is no significant change for any parameter.

Furthermore, stability profiles were compared between the 100 and 400 mg finished product in terms of purity/impurity and biological activity at long-term, accelerated, and stress conditions. The results are considered comparable.

A photostability study was provided and data showed that SB8 finished product is photosensitive. The outer commercial packaging protects the finished product from light.

A shelf life of 36 months (2°C-8°C, protected from light) for the finished product is acceptable.

In-use stability studies were carried out to evaluate the stability of SB8 finished product after dilution. Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 30°C in sodium chloride 9 mg/ml (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Adventitious agents

The strategy used to ensure that the SB8 active substance and the resulting finished product are free of adventitious agents has been provided. The strategy is in compliance with the requirements in the ICH Guideline Q5A and includes: a) testing of the MCB and WCB, as well as the end of production cell bank b) control of raw materials of human or animal origin, c) in-process testing of unprocessed bulk harvest for adventitious agents, d) virus clearance validation studies to establish a retroviral safety factor for the SB8 purification process, e) procedural and facility controls.

Certificates of Suitability and / or Certificates of Origin have been provided for all raw materials of human or animal origin. Mycoplasma testing for qualification of the MCB, WCB and end of production cell bank was performed in accordance with ICH guidelines (Q5D). Furthermore, during active substance manufacture, the unprocessed bulk is analysed for mycoplasma, which is also based on Ph. Eur. 2.6.7. No mycoplasma has been detected in the unprocessed bulks.

Virus safety testing on the MCB and WCB were performed in accordance with ICH guidelines Q5A and Q5D.

Viral clearance capacity of the SB8 purification process was validated in accordance with the ICH Guideline Q5A (R1). Specific steps, which were considered as effective steps for viral clearance, were selected and their viral clearance capacity was validated. Two virus inactivation steps, virus filtration, and chromatography steps were selected for validation. The validation was performed using fresh resin and aged resin. Viral clearance study using aged resin was performed to demonstrate that the viral clearance capacity is maintained throughout the resin life cycle. All purification processes mentioned above have orthogonal purification mechanisms.

Overall, adventitious agents safety is considered sufficiently assured.

Biosimilarity

The Applicant has conducted a comprehensive and well-established biosimilarity exercise (Table 1), which is line with the relevant EMA guidelines.

Table 1– Key findings from the analytical biosimilarity exercise

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
Primary structure	Amino acid sequence	Reducing peptide mapping (MS)	Identical primary sequence
	Molecular mass	Mass spectroscopy	No difference recorded
	Carbohydrate side chains	HILIC-UPLC	Predominant glycoform G0F for both SB8 and the reference medicinal product, markedly higher amount of high-mannose in SB8, Lower amount of afucose for SB8
Heterogeneity	Charge related variants	CEX-chromatography	Lower amount of main, higher amount of acidic and basic components
		icIEF	Lower amount of main, higher amount of acidic component
		Hydrophobic interaction chromatography	Markedly higher amount of “post-main” fractions
Higher order structure	Secondary and tertiary structure	CD spectroscopy FTIR Intrinsic and extrinsic fluorescence	Comparable higher order structure
	Molecular size in solution	SEC-MALLS	Slightly higher estimated MW for the HMW component
		Analytical ultracentrifuge	Closely similar sedimentation coefficient figures, differences in f/fo indicated but data not shown
	Subvisible particles	Micro flow imaging	Higher count of subvisible particles except for the ≥25 µm ones
Biological activity	Antigen (VEGF-A) binding	ELISA	Similar relative binding activity
…	VEGF-A neutralisation	Reporter gene bioassay	Similar relative neutralisation activity

Molecular parameter	Attribute	Methods for control and characterisation	Key findings
	VEGFR phosphorylation inhibition	Tyr1175 phosphorylation assessment by time-resolved fluorescence energy transfer	Similar relative inhibiting activity
	Inhibition of HUVEC proliferation	Proliferation assay using fluorescent dye activation	Similar relative inhibiting activity
	FcγRn binding	SPR	Similar binding constants
	FcγRI, FcγRγIIa, FcγRIIb, FcγRIIIa, FcγRIIIb binding	SPR	Similar binding constants

The outcome of the product quality risk assessment leading to a risk ranking and classification of quality attributes into critical and non-critical quality attributes has been presented. The biosimilarity programme started with an extensive characterisation of the EU-sourced reference medicinal product Avastin. A total of 46 EU-sourced Avastin lots have been purchased from the market and have been used for the similarity range establishment. A list including the exact lot number, strength and the expiry data of each single Avastin lot is provided. The expiry dates of the Avastin lots cover the period from February 2014 until September 2018, and the selection of the reference medicinal product has been appropriately justified following the guideline EMA/CHMP/BWP/247713/2012.

The characterisation of the reference medicinal product and the subsequent side-by-side comparison, using 18 SB8 lots and 9 Avastin lots, included a broad panel of standard and state-of-the-art methods which covered relevant physicochemical as well as biological quality attributes.

In particular, quantity, primary structure (molecular weight, amino acid sequence, N- and C-terminal sequence, peptide mapping, methionine oxidation, deamidation, glycation), purity and impurities (SE-HPLC, reducing and non-reducing CE-SDS), charged variants (CEX-HPLC, icIEF), hydrophobic variants (HI-HPLC), carbohydrate structure (identification of the N-glycan site, N-glycan identification, N-glycan profile), and higher order structure (CD-, intrinsic, extrinsic, and Fourier Transform Infrared spectroscopy, Hydrogen/Deuterium exchange, differential scanning calorimetry, SE-HPLC/MALLS, analytical ultracentrifugation, dynamic light scattering, and micro-flow imaging) have been addressed.

Regarding the biological characteristics cell-based potency assays, binding assays, and Fc related activities, and additional assays have been used.

In summary, the used panel of methods for characterisation and comparison of SB8 with its reference medicinal product is considered sufficient and no additional tests have been requested. As requested, the qualification status of the methods has been provided. In summary, the provided qualification results confirm that the methods are suitable for the intended use. Further details of certain biological assays have been provided. This is acceptable.

Based on the data derived from extensive characterisation of the reference medicinal product, similarity ranges for the biosimilarity development have been established by statistical means. The statistical analysis involved tolerance intervals. The Applicant neither justified why this specific statistical tool was chosen nor discussed potential limitations and shortcomings of the tolerance interval approach. For certain quality attributes (e.g. glycovariants %G1F and %G2F) the established similarity ranges seem to be relatively wide which increases the risk of false positive conclusions on biosimilarity. In the case of the above-mentioned glycovariants differences between SB8 and Avastin seem to be obvious, even though the data for SB8 were still within the similarity ranges. However, it should be noted that a tabulated overview of all raw data has been included. Thus, an assessment on biosimilarity was possible independently from the used statistical method and its potential limitations. As a consequence, no specific need to question the acceptability of the tolerance interval approach was identified. It should also be mentioned that for most of the quality attributes, only a subset of the purchased reference medicinal product lots, not the total of 46 reference medicinal product lots, have been characterised.

Following the characterisation of the reference medicinal product and establishment of similarity ranges, a side-by side comparison of SB8 with Avastin has been performed. This side-by-side comparison included pilot, clinical and process performance qualification active substance batches as well as clinical and process performance qualification batches of the finished product (for both presentations) and Avastin. For all studies, EU Avastin was used as the reference medicinal product. For certain quality attributes (in particular in cases where only a qualitative comparison was possible and for methods which were considered as orthogonal to another method) the number of batches included in the side-by-side comparison was reduced. The inclusion of the clinical and process performance batches of SB8 active substance and finished product is endorsed. Biosimilarity could be demonstrated for most quality attributes. In particular, the various assays addressing the biological functions of bevacizumab showed a highly similar profile of SB8 with its reference medicinal product. At the physicochemical level, some differences have been observed:

Of importance, the presence of additional C- and N-terminal sequence variants was observed in SB8, but not in EU Avastin. It was highlighted that the presence of sequence variants at low levels may have unanticipated safety consequences that were not apparent in the clinical studies. Consequently, potential safety risks from these sequence variants have been discussed by the Applicant. Thus, these sequence variants are considered as product-related impurities which need to be strictly controlled by an appropriate control system, and the recommendations regarding the control strategy were given.

A slightly higher purity profile has been measured for SB8 (lower %Total Aggregate and %Non-Glycosylated Heavy Chain – NGHC). It is agreed with the Applicant that this slightly improved purity profile does not preclude the biosimilarity claim.

Differences have been observed for hydrophobic variants by HI-HPLC and the charged variant profile by CEX-HPLC and icIEF. Additional in-depth characterisation including structure-activity relationship studies have been conducted to elucidate the root cause for these altered hydrophobic and charged variant profiles and to rule out that these differences may jeopardise the biosimilarity claim. Taking into account the additional characterisation work as well as the demonstrated biosimilarity with respect to the biological quality attributes, it is agreed that these differences have been sufficiently justified. Nevertheless, to further substantiate the claim that the different hydrophobic variant profile does not impact the biological activity, the Applicant has compared VEGF neutralisation (with the VEGF neutralisation assay) and the FcRn binding of the isolated fractions.

Differences have been detected for the glycovariants %High Mannose and %Afucose. The Applicant justified these differences by the non-relevance of the Fc effector functions for the mode of action of bevacizumab. Taking into consideration the comparable binding characteristics of SB8 and Avastin to the Fcγ receptors and the absence of ADCC and CDC for both SB8 and Avastin, the conclusion of the Applicant can be agreed. However, high mannose glycovariants may be relevant for the clearance of bevacizumab via the mannose receptor. As a consequence, an appropriate control for high mannose is agreed.

Finally, the graphical presentation regarding the content of glycovariants %G1F and %G2F indicate slight differences between SB8 and Avastin although the data for SB8 are within the pre-established biosimilarity ranges. The Applicant has sufficiently justified that these differences have no impact on the biosimilarity claim.

To complement the biosimilarity exercise a number of comparative short-term stability studies under stress conditions to investigate and compare degradation pathways of SB8 with Avastin have been performed. These stress conditions included heat stress, basis and acidic stress, oxidative and photo stress. The data derived from these studies support the biosimilarity claim; a few concerns related to these comparative studies have been resolved.

In summary, biosimilarity at quality level has been demonstrated. Although for some physicochemical quality attributes differences have been detected, these differences have been sufficiently justified to have no impact on the clinical performance of Aybintio and its biosimilarity to the reference medicinal product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, a sufficient and comprehensive Module 3 has been provided. The active substance as well as the finished product manufacturing process have been appropriately described. In principle, an effective process control strategy based on appropriate controls of material attributes, in process controls and process parameters, and active substance and finished product specifications is in place to ensure that the process consistently delivers material meetings its predefined specifications and quality attributes.

The performed consecutive process validation and the provided batch release data support this conclusion.

Comparability of clinical material and process performance qualification/intended commercial material after process transfer to a different site has been demonstrated.

A comprehensive and robust biosimilarity exercise demonstrates similarity of the biosimilar candidate with its reference medicinal product. Certain differences regarding hydrophobic, charged and N-glycan variants could be in most parts sufficiently justified: additional in-depth characterisation including structure-activity relationship studies of the fractioned samples have been conducted to elucidate the root cause for these altered hydrophobic and charged variant profiles and to rule out these differences may jeopardise the biosimilarity claim. In addition, a broad pattern of used bio- and binding assays could demonstrate biosimilarity for the biological characteristics.

However, the presence of additional C- and N-terminal sequence variants at low levels, observed in SB8 but not in EU Avastin, was a matter of discussion during the procedure. The question emerged whether biosimilarity between two recombinant proteins, in this case between two IgG monoclonal antibodies, can be considered demonstrated despite certain differences in the amino acid sequence, since the concept of biosimilarity of recombinant proteins requires sequence identity. However, it should be highlighted that these sequence variants are extensions at the ends of the amino acid chain, and not amino acid insertions within the protein. The above-mentioned identity refers to the main component of the active substances and minor variants are conceived as product-related substances. The heavy chain C-terminal lysine heterogeneity is well known, and additional N-terminal residues from the signal peptides are not uncommon either. In summary, these sequence variants are considered as product-related impurities which need to be strictly controlled by an appropriate control system.

Since a potential impact of these sequence variants on safety/immunogenicity – although not observed in the clinical efficacy and safety comparability study – could not be completely ruled out, the Applicant strengthened the control strategy initially proposed. In addition, the Applicant is recommended to a) consider a further tightening of the limit when a number of batch results sufficient for statistical analysis is available, and b) to implement a more direct control dedicated to control C-terminal sequence variants present in Aybintio post-marketing.

In addition, the non-clinical and clinical data provided by the Applicant during the procedure support the demonstration of no clinically relevant difference in immunogenicity risk between SB8 and EU Avastin and do not preclude demonstration of biosimilarity (see clinical part of the assessment report).

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The fermentation and purification of the active substance are adequately described, controlled and validated. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

The chemical, pharmaceutical and biological documentation comply with existing guidelines.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

From a quality point of view, biosimilarity with the reference product Avastin is considered demonstrated.

The overall quality of Aybintio is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.6. 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 two points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

The Applicant conducted a comprehensive panel of *in vitro* studies with the aim of demonstrating biosimilarity between the reference product EU Avastin and SB8.

Table 2: **Summary of *In Vitro* PD Study Results**

Type of Study	Results	
Potency assays	HUVEC anti-proliferation	The potency of SB8 on anti-proliferation in HUVEC was similar to that of EU Avastin®.
	VEGF neutralization (VEGF-A 165)	The potency of SB8 on VEGF neutralization was similar to that of EU Avastin®.
Binding assays	VEGF-A 165 binding (ELISA)	The binding activity of SB8 to VEGF-A 165 measured by ELISA was similar to that of EU Avastin®.
	FcRn binding	The binding affinity of SB8 to FcRn was similar to that of EU Avastin®.
Additional assays	VEGF-A 165 binding (SPR)	The binding activity of SB8 to VEGF-A 165 measured by SPR was similar to that of EU Avastin®.
	VEGF-A 121 binding	The binding activity of SB8 to VEGF-A 121 was similar to that of EU Avastin®.
	VEGF-A 189 binding	The binding activity of SB8 to VEGF-A 189 was similar to that of EU Avastin®.
	VEGF-A specificity (VEGF-B, C, D, and PIGF-1,2)	The specificity of SB8 to VEGF-A was similar to that of EU Avastin®.
	FcRγIa binding	The binding activity of SB8 to FcRγIa was similar to that of EU Avastin®.
	FcRγIIa binding	The binding affinity of SB8 to FcRγIIa was similar to that of EU Avastin®.
	FcRγIIb binding	The binding affinity of SB8 to FcRγIIb was similar to that of EU Avastin®.
	FcRγIIIa binding	The binding affinity of SB8 to FcRγIIIa was similar to that of EU Avastin®.
	FcRγIIIb binding	The binding affinity of SB8 to FcRγIIIb was similar to that of EU Avastin®.
	C1q binding	The binding activity of SB8 to C1q was similar to that of EU Avastin®.
	VEGFR phosphorylation inhibition	The inhibition potency of SB8 on VEGFR phosphorylation was similar to that of EU Avastin®.
	HUVEC anti-migration	The anti-migration potency of SB8 was similar to that of EU Avastin®.
	HUVEC anti-survival	The anti-survival potency of SB8 was similar to that of EU Avastin®.
	ADCC	No ADCC activity was also observed in SB8 as expected in EU Avastin®.
	CDC	No CDC activity was also observed in SB8 as expected in EU Avastin®.

ADCC: antibody-dependent cellular cytotoxicity; CDC: complement-dependent cytotoxicity; FcRn: binding to neonatal Fc receptor; HUVEC: human umbilical vein endothelial cells; VEGF: vascular endothelial growth factor

In summary, the biological functions of SB8 and EU-sourced Avastin, i.e. VEGF-A binding, VEGF-A neutralization, inhibition of HUVEC proliferation and migration as well as Fc-related activities, have been demonstrated to be similar.

Two *in vivo* xenograft mouse studies were submitted, one in which biosimilarity was aimed to be demonstrated in a non-small cell lung cancer (NSCLC) xenograft model, and one in which a colorectal carcinoma xenograft model was used.

Study No. E0303-U1501: Evaluation of the Efficacy of Test Article SB8 in the Treatment of Subcutaneous NCI-H358 Human Non-small Cell Lung Cancer Xenograft Model

In line with the evaluation of the therapeutic equivalence of SB8 and EU Avastin in NSCLC patients a non-clinical *in vivo* study was performed in mice bearing human lung cancer cell line-derived tumours. Mice were inoculated with NCI-H358 subcutaneously and treated three times weekly for a total of three weeks with doses of 0.7 mg/kg or 5 mg/kg of SB8, EU Avastin or US Avastin (and vehicle) when tumours had reached a predefined size (Study No. E0303-U1501). The endpoints for the comparative assessment of efficacy were tumour size and tumour volume. In the 0.7 mg/kg dose group US and EU Avastin showed similar efficacy in terms of tumour growth reduction whereas SB8 can be considered less effective and even comparable to the vehicle group.

In contrast, the 5 mg/kg dosing groups showed statistically significantly higher therapeutic efficacy as compared to the vehicle group with comparable values for tumour weight and volume irrespective of the compound administered.

Table 3: **Comparable Anti-tumour Activity on tumour Volume and tumour Weight across the SB8, US Avastin, and EU Avastin Treated Groups**

Article	SB8 formulation buffer	0.7 mg/kg			5 mg/kg		
		SB8	US Avastin®	EU Avastin®	SB8	US Avastin®	EU Avastin®
TGI by tumor volume (%)	N/A	–15	27	24	80	79	80
Tumor volume on Day 28 (mean ± SEM)	1150 ± 98	1319 ± 227	834 ± 123	869 ± 138	235 ± 24***	245 ± 26***	231 ± 27***
p-value	N/A	0.093[a]			0.923[a]		
TGI by tumor weight (%)	N/A	–23	29	30	75	74	77
Tumor weight on Day 28 (mean ± SD)	966.2 ± 269.5	1191.4 ± 678.0	683.7 ± 382.6*	671.8 ± 262.3*	245.7 ± 68.6***	250.5 ± 106.1***	221.9 ± 79.0***
p-value	N/A	0.077[b]			0.687[a]		

TGI: tumor growth inhibition; SEM: standard error of the mean; N/A: not available; SD: standard deviation
[a] Result by one-way ANOVA using Minitab statistical software (normal distribution)
[b] Result by Kruskal-Wallis test using Minitab statistical software (non-normal distribution)
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$: Results from Student's t-test using SPSS 18.0 software in comparison to the tumor volume and weight of SB8 formulation buffer treated group on Day 28

Study No. E0303-U1502: Evaluation of the Efficacy of Test Articles in the Treatment of Subcutaneous COLO 205 Human Colorectal Carcinoma Xenograft Model

In the colorectal carcinoma xenograft mouse study (Study No. E0303-U1502), the biosimilarity exercise has only been conducted with US Avastin as reference product.

SB8 was capable of significantly reducing both the gain of tumour volume and tumour weight relative to the vehicle group. However, when comparing the antitumouric efficacy of SB8 with the one of US Avastin, only the decreases in tumour volumes (as determined by the caliper method) did not significantly differ among the groups, whereas SB8 was significantly less efficient in decreasing tumour weight gain compared to US Avastin at all three tested doses (see discussion on non-clinical aspects).

Table 4: **Anti-tumour activity of SB8 TOX DP, SB8 Clinical DP, and US Avastin on tumour growth inhibition by tumour weight in the COLO 205 colorectal carcinoma xenograft mice model (Study No. E0303-U1502)**

Group No.	Treatment	Tumor Weight (mg)[a] on Day 35	TGI[b] (%) on Day 35	*P*-value[c] on Day 35
G1	Human IgG_1 Isotype Control (Vehicle)	1668.6 ± 138.5	N/A	N/A
G2	SB8 TOX DP (0.5 mg/kg)	1000.0 ± 72.0	40	<0.001
G3	SB8 TOX DP (1.5 mg/kg)	997.7 ± 72.8	40	<0.001
G4	SB8 TOX DP (5 mg/kg)	1113.1 ± 69.2	33	0.002
G5	SB8 Clinical DP (0.5 mg/kg)	1032.0 ± 66.1	38	<0.001
G6	SB8 Clinical DP(1.5 mg/kg)	1083.3 ± 84.3	35	0.001
G7	SB8 Clinical DP (5 mg/kg)	1038.8 ± 73.2	38	0.001
G8	US Avastin® (0.5 mg/kg)	738.4 ± 53.3	56	<0.001
G9	US Avastin® (1.5 mg/kg)	651.9 ± 46.6	61	<0.001
G10	US Avastin® (5 mg/kg)	821.6 ± 96.8	51	<0.001

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been conducted (see discussion on non-clinical aspects).

Safety pharmacology programme

No safety pharmacology studies have been conducted (see discussion on non-clinical aspects).

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

No dedicated pharmacokinetic studies have been conducted (see discussion on non-clinical aspects).

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity study was submitted.

Repeat dose toxicity

A four-week repeat dose toxicity study (Study Report – 000080642) conducted in cynomolgus monkeys was submitted. This study also contained toxicokinetic investigations (serum levels and ADA formation). Study No. SBL327- 001 has been conducted with US Avastin as reference product.

Table 5: **Repeated dose toxicity study design:**

Group No.	No. of Animals		Treatment Article	Dose Level (mg/kg)	Dosing Route	Dosing Schedule
	Male	Female				
1	3	3	SB8 vehicle	0	Intravenous infusion	Twice a week for 4 weeks (total 8 times: Day 1, 4, 8, 11, 15, 18, 22, and 25)
2	3	3	SB8	50		
3	3	3	US Avastin®	50		

The Applicant demonstrated that SB8 and US Avastin were well tolerated by cynomolgus monkeys, even at considerably higher doses than the intended therapeutic ones. Furthermore, the toxicological and toxicokinetic profiles of SB8 and US Avastin groups were well comparable.

There were no toxicologically significant changes considered to be SB8 or US Avastin related in clinical signs, injection site observation, body weight, food consumption, ophthalmology, electrocardiography, urinalysis, haematology, blood chemistry, necropsy, or organ weights in any group. However, thickening of the epiphyseal cartilage has been observed in SB8 and US Avastin groups. Moreover, the formation of germinal centres was observed in white pulp or secondary follicles in the spleen and mesenteric lymph nodes in both the SB8 and US Avastin groups, suggesting anti-drug antibody formation towards the administered SB8 and US Avastin. However, no SB8 and US Avastin–specific ADAs were identified in the toxicokinetic investigations that were included in this study.

2.3.5. Ecotoxicity/environmental risk assessment

Bevacizumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), bevacizumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

A comprehensive panel of *in vitro* studies was conducted in support of demonstrating biosimilarity between EU Avastin and SB8. In summary, the biological functions of SB8 and EU-sourced Avastin, i.e. VEGF-A binding, VEGF-A neutralization, inhibition of HUVEC proliferation and migration as well as Fc-related activities, have been demonstrated to be similar.

In support of the *in vitro* comparability exercise, two *in vivo* pharmacology studies in murine xenograft models as well as one repeated dose toxicity study in cynomolgus monkeys were submitted. From the regulatory perspective, these studies were not required to support a MAA for SB8, which was communicated to the Applicant within an EMA scientific advice procedure (EMA/CHMP/SAWP/290133/2014, May 22, 2014), and which is in line with relevant EMA/CHMP guidelines on biosimilar products (EMEA/CHMP/BMWP/42832/2005 Rev1; EMA/CHMP/BMWP/403543/2010). Nevertheless, it is acknowledged that the Applicant submitted these *in vivo* studies, as they were required for fulfilling the regulatory needs for the globally harmonized development of SB8 and are only provided as supportive information.

Biosimilarity between SB8 and US Avastin has been tested in all three submitted *in vivo* studies, however, EU Avastin as reference product was only included in one of these studies (a study using a non-small cell lung cancer xenograft mouse model). As no dedicated studies were submitted in which the comparability between US and EU Avastin was investigated, the studies that were exclusively conducted with US Avastin are not considered relevant for the evaluation of biosimilarity between SB8 and EU Avastin.

In the non-small cell lung cancer xenograft model study, biosimilarity between SB8 and EU Avastin in terms of decreasing tumour volume and weight was generally shown at therapeutically sufficiently high doses (5 mg/kg). The low dose of 0.7 mg/kg appeared to be sub-therapeutic in the mouse model, which is reflected by the extremely high standard deviations in this dosing group. Thus, the observed differences between test and reference groups are regarded to be of low significance. However, in the colorectal carcinoma xenograft mouse study (Study No. E0303-U1502), biosimilarity between SB8 and US Avastin in the efficacy of decreasing tumour weight gain has not been shown, in fact SB8 performed significantly worse in decreasing tumour weight gain relative to US Avastin. This observation points towards non-biosimilarity. However, the non-biosimilarity observed in the colorectal xenograft mouse study constitutes an isolated finding that was not reproduced in clinical trials, and that in vivo xenograft models are – in general – characterised by an inherently large variability so that their study results are not necessarily reliable for biosimilarity exercises. The results of this study do not contradict overall biosimilarity. Furthermore, as no dedicated studies were submitted in which the comparability between US and EU Avastin was investigated, this study is not unambiguously representative for demonstrating biosimilarity or absence of biosimilarity between SB8 and EU Avastin.

No dedicated pharmacokinetic studies have been conducted, which is acceptable according to the EMA/CHMP guidelines on biosimilar products (EMEA/CHMP/BMWP/42832/2005 Rev1, EMA/CHMP/BMWP/403543/2010).

The toxicological and toxicokinetic profiles of SB8 and US Avastin in the four weeks repeated dose toxicity study in cynomolgus monkeys (Study No. SBL327-001) were comparable (however, this study was exclusively conducted with US Avastin as comparator). Regarding the mismatch in this study between germinal centre reaction observed in white pulp or secondary follicles in the spleen and mesenteric lymph nodes and the lacking ADAs in both the SB8 and US Avastin groups, it was clarified that the ADA serum analyses were not a likely cause of the observed mismatch. Furthermore, the Applicant stated that the extent of germinal reactions in lymph nodes and the spleen was very limited, suggesting that potential ADA levels created out of these germinal reactions were low or even BLD. Additionally, the Applicant elaborated that potential SB8-ADA immune complexes may have been cleared by an FcγR-mediated mechanism, which may have further decreased ADA levels (potentially BLD). No other toxicity studies were submitted, which is acceptable and in line with relevant EMA guidelines (e.g. EMEA/CHMP/BMWP/42832/2005 Rev1).

In accordance with the EMA "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" EMEA/CHMP/BMWP/42832/2005 Rev1, specific studies on genotoxicity, carcinogenicity, reproductive and developmental toxicity, and local tolerance have not been submitted.

2.3.7. Conclusion on the non-clinical aspects

The submitted non-clinical data are considered adequate to support biosimilarity of SB8 and the reference product.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 6: Overview of the Clinical Development Plan for Evaluation of Pharmacokinetic Similarity/ Comparability

Study ID (Country)	**Study Objectives**	**Subjects**	**Study Design/ Duration**	**Treatments**	**PK/Immunogenicity Endpoints**
SB8-G11-NHV Phase I (Belgium) Study Period: April 25th 2015 – September 21st 2015	Comparative pharmacokinetic (PK), safety, tolerability, immunogenicity Primary Objective: To investigate and compare the PK profiles of SB8 and EU Avastin in healthy male subjects	119 healthy male subjects: SB8: 40 EU Avastin: 40 US-Avastin: 39	A randomized, double-blind, three-arm, parallel group, single-dose study. A maximum of 16 weeks (including 4 weeks of screening period)	Single-dose i.v. infusion for 90 minutes: 3 mg/kg of either SB8, EU Avastin or US Avastin	**PK** Primary: • AUC_{inf} Secondary: • AUC_{last}, C_{max} • T_{max}, V_z, λz, $t_{½}$, CL, $\%AUC_{extrap}$ **Immunogenicity** • Incidence ADAs and NABs to bevacizumab
SB8-G31-NSCLC Phase III (Belarus, Georgia, Germany, Hungary, Republic of Korea, Poland, Romania, Russia, Serbia, Spain, Taiwan, Thailand, Ukraine) Study period: Jul 05th 2016 to Aug 09th 2018	Comparative efficacy, safety, immunogenicity, and PK Primary objective: To demonstrate equivalence of SB8 to EU Avastin in terms of the best overall response rate (ORR) by 24 weeks of chemotherapy	Patients with metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC) Randomized: 763 patients (SB8:379; EU-Avastin:384) **PK population**: 341 patients: - SB8:161 - EU Avastin:180	A randomized, double-blind, parallel-group, multicenter study. 24 weeks of the induction treatment period followed by maintenance monotherapy until disease progression, unacceptable toxicity, death, or 12 months from the randomization of the last patient (end of study [EOS]); Follow-up for survival status until the withdrawal of consent or death or 12 months from randomization of the last patient (EOS).	15 mg/kg of SB8 or EU-Avastin by IV infusion every 3 weeks a) with paclitaxel/ carboplatin chemotherapy for 4 to 6 cycles of the induction treatment period b) then as monotherapy during the maintenance phase	**PK** - C_{trough} - C_{max} at Cycles 1,3,5,7 **Immunogenicity** - Incidence of ADAs and NABs to bevacizumab

2.4.2. Pharmacokinetics

A **pivotal PK study SB8-G11-NHV** in healthy subjects (SB8 versus EU-Avastin, SB8 versus US sourced Avastin [hereafter referred to as, 'US Avastin'], EU Avastin versus US Avastin) assessing similarity in PK profiles between SB and EU Avastin was submitted.

Additional PK evaluation was performed in a **subset of patients**, comparing SB8 versus EU Avastin as part of the **clinical efficacy/safety study SB8-G31-NSCLC**.

PK Assays

A quantitative Enzyme linked Immunosorbent Assay (ELISA) has been developed for the determination of SB8 and Avastin in human serum. The same assay was used in both studies (Phase I and Phase III study). This method utilized an indirect ELISA format to measure the concentration of SB8 and Bevacizumab in human serum.

Clinical Phase I Study SB8-G11-NHV – Pivotal Pharmacokinetics

Study Phase I SB8-G11-NHV was a randomized, double-blind, three arm, parallel-group, single dose study conducted in healthy male volunteers aged 18-55 years.

The study was performed at one trial site in the EU (Belgium). The study duration was from April 25th to September 21st 2015.

A total of 187 healthy male subjects were screened, of which 119 subjects were randomised in a 1:1:1 ratio to receive a single-dose of 3mg/kg of either SB8 (40 subjects), EU sourced Avastin (40 subjects), or US sourced Avastin (39 subjects) via IV infusion for 90 minutes.

A total of 5 (4.2%) subjects (2 subjects in the SB8 treatment group, 2 subjects in the EU Avastin treatment group, and 1 subject in the US Avastin treatment group) had major protocol deviations (i.e. not meeting inclusion/exclusion criteria after dosing, one subject received an incorrect dose of the IP, one subject was administered disallowed therapy), leading to exclusion of the PK population and leaving 38 subjects in each treatment group.

Test product was SB8, and reference products were EU-sourced Avastin and US-sourced Avastin.

Blood samples for PK analysis were collected at 0 (pre-dose), 0.75, 1.5 (end of infusion), 3, 6, 12, 24, 48 and 96 hours, then at Day 8 (168 h), 15 (336 h), 22 (504 h), 29 (672 h), 43 (1008 h) 57 (1344 h), 71 (1680 h), and 85 (2016 h) after start of infusion.

The <u>primary objective</u> was to investigate and compare the PK profiles between SB8 and EU sourced Avastin in healthy male subjects.

The <u>secondary objective</u> was to investigate and compare the safety, tolerability, and immunogenicity between SB8 and EU sourced Avastin in healthy male subjects.

Additionally, SB8 was compared with US-Avastin in order to comply with the FDA requirements.

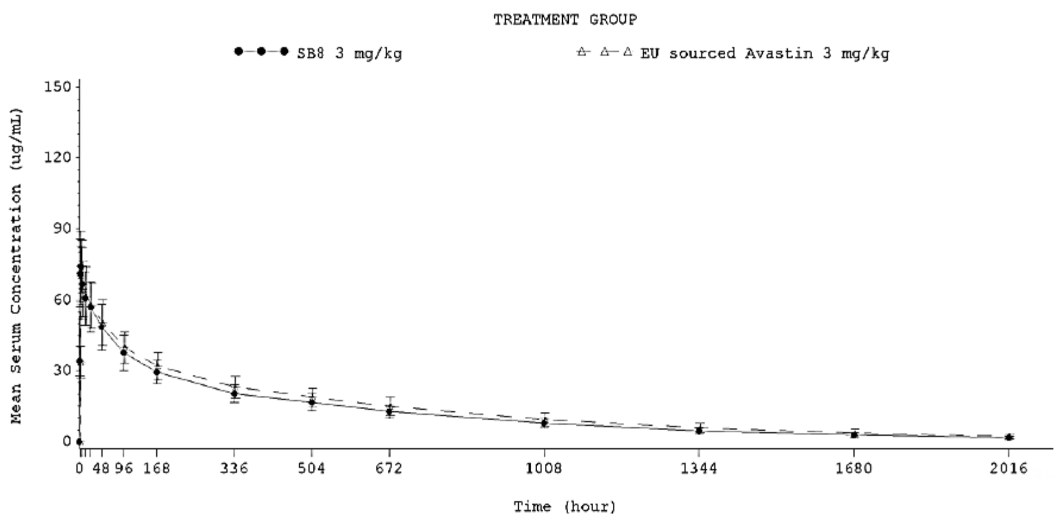
Primary Pharmacokinetic Endpoints: AUC_{inf}

Secondary Pharmacokinetic Endpoints: AUC_{last}, C_{max}, T_{max}, V_z, λ_z, $t_{½}$, CL, $\%AUC_{extrap}$

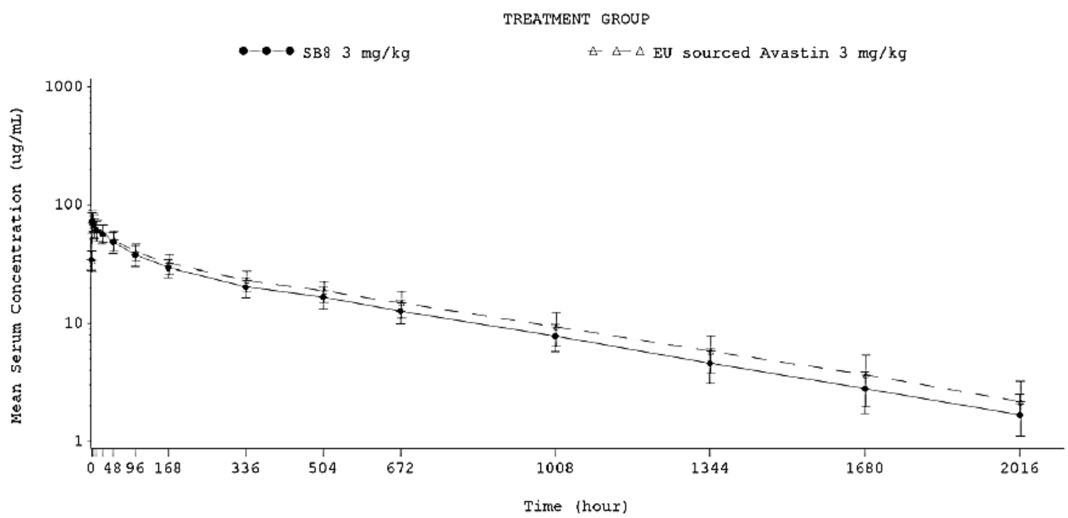
Equivalence of the primary (AUC_{inf}) and key secondary endpoints (AUC_{last}, C_{max}) was determined if the 90% CI for the ratio of geometric means of test-to-reference was within the predefined acceptance interval of 0.8 to 1.25.

<u>Pharmacokinetic Results</u>

The mean serum concentrations versus nominal times curves on linear and semi-logarithmic scale for the PK population are presented for pairwise comparison of SB8 and EU-sourced Avastin in Figure 1.



Linear Scale



Log-linear Scale

Figure 1: Mean Serum Concentrations Versus Nominal Times on Linear (Top Graph) and Semi-logarithmic Scale (Bottom Graph) of SB8 and EU Sourced Avastin

<u>Summary statistics of PK parameters</u>

Summary statistics of PK parameters are presented for the PK population in the table below.

Table 7: Summary of PK Parameters (PK population)

PK Parameter	Statistics	SB8 N=38	EU Avastin® N=38	US Avastin® N=38
AUC_{inf} (µg·h/mL)	n	38	38	38
	Mean	25354.4	28896.8	28684.8
	SD	4833.10	6221.62	5425.14
	Median	24755.3	28010.4	29813.7
	Min	16262	19790	16978
	Max	34102	45595	41345
AUC_{last} (µg·h/mL)	n	38	38	38
	Mean	24199.2	27342.2	27177.9
	SD	4367.53	5374.53	4770.93
	Median	23532.9	26611.5	28243.0
	Min	16010	18995	16354
	Max	32329	41834	38149
C_{max} (µg/mL)	n	38	38	38
	Mean	76.259	76.059	76.485
	SD	14.6999	11.7053	16.9916
	Median	73.865	75.615	76.755
	Min	55.94	56.90	19.61
	Max	106.03	110.19	113.04
T_{max} (h)	n	38	38	38
	Mean	3.639	3.638	5.646
	SD	2.1885	2.4261	15.6665
	Median	3.000	3.000	3.000
	Min	1.52	1.52	1.52
	Max	12.00	12.00	97.12
V_z (mL)	n	38	38	38
	Mean	6118.6	5566.4	5654.1
	SD	960.98	833.62	999.97
	Median	6000.5	5442.7	5634.9
	Min	4740	4335	3738
	Max	8868	7760	8124
CL (mL/h)	n	38	38	38
	Mean	9.721	8.517	8.659
	SD	1.7803	1.6570	1.8600
	Median	9.786	8.735	8.263
	Min	6.58	5.00	6.07
	Max	15.98	11.28	14.03
$t_{½}$ (h)	n	38	38	38
	Mean	444.4	464.2	462.8
	SD	79.46	81.06	86.98
	Median	434.6	435.5	438.1
	Min	316	299	345
	Max	660	629	651

N = number of subjects in the PK population; n = number of subjects with an available assessment
Source: Section 5.3.3.1 CSR SB8-G11-NHV Table 11-3, Table 14.2-1.2

<u>Statistical comparison of the PK parameters</u>

For assessment of PK similarity, AUC_{inf}, AUC_{last}, and C_{max} between SB8 and EU-Avastin, between SB8 and US-Avastin and between EU-Avastin and US-Avastin in the PK population were compared.

Table 8: Statistical Comparison of Primary PK Parameters between SB8 and EU Sourced Avastin (PK population)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (µg·h/mL)	SB8	38	38	24901.3	0.880	0.8154; 0.9498
	EU Avastin®	38	38	28294.9		
AUC_{last} (µg·h/mL)	SB8	38	38	23812.9	0.886	0.8258; 0.9516
	EU Avastin®	38	38	26862.9		
C_{max} (µg/mL)	SB8	38	38	74.927	0.996	0.9333; 1.0628
	EU Avastin®	38	38	75.232		

A: SB8, B: EU Avastin®.
CI = confidence interval; LSMean = least squares mean; N = number of subjects in PK population; n = number of subjects with an available assessment
Source: Section 5.3.3.1 CSR SB8-G11-NHV, Table 11-4, Table 14.2-2.1, Table 14.2-2.2, and Table 14.2-2.3

Table 9: Statistical Comparison of Primary PK Parameters between SB8 and US Sourced Avastin (PK population)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (µg·h/mL)	SB8	38	38	24901.3	0.885	0.8201;0.9546
	US Avastin®	38	38	28143.3		
AUC_{last} (µg·h/mL)	SB8	38	38	23812.9	0.891	0.8296;0.9565
	US Avastin®	38	38	26732.5		
C_{max} (µg/mL)	SB8	38	38	74.927	1.012	0.9223;1.1093
	US Avastin®	38	38	74.074		

A: SB8, B: US Avastin®.
LSMean = least squares mean; CI = confidence interval; N = number of subjects in PK population; n = number of subjects with an available assessment
Source: Section 5.3.3.1 CSR SB8-G11-NHV, Table 11-5, Table 14.2-2.1, Table 14.2-2.2, and Table 14.2-2.3

Table 10: Statistical Comparison of Primary PK Parameters between EU Sourced Avastin and US Sourced Avastin (PK population)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (µg·h/mL)	EU Avastin®	38	38	28294.9	1.005	0.9299;1.0870
	US Avastin®	38	38	28143.3		
AUC_{last} (µg·h/mL)	EU Avastin®	38	38	26862.9	1.005	0.9349;1.0801
	US Avastin®	38	38	26732.5		
C_{max} (µg/mL)	EU Avastin®	38	38	75.232	1.016	0.9313;1.1076
	US Avastin®	38	38	74.074		

A: EU Avastin®, B: US Avastin®.
LSMean = least squares mean; CI = confidence interval; N = number of subjects in PK population; n = number of subjects with an available assessment
Source: Section 5.3.3.1 CSR SB8-G11-NHV, Table 11-6, Table 14.2-2.1, Table 14.2-2.2, and Table 14.2-2.3

Clinical Phase III Study SB8-G31-NSCLC – Supportive Pharmacokinetics

This was a Phase III, randomized, double-blind, multicenter study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB8 and Avastin in patients with metastatic or recurrent NSCLC. 763 patients were randomized 1:1 to receive either SB8 or EU-Avastin at a dose of 15mg/kg i.v. every 3 weeks, for 4 and up to a maximum of 6 cycles in the induction treatment phase together with PC chemotherapy, and then as a maintenance monotherapy as per randomization until disease progression, unacceptable toxicity, death or end of study (12 months from randomization of the last patient), whichever occurred first.

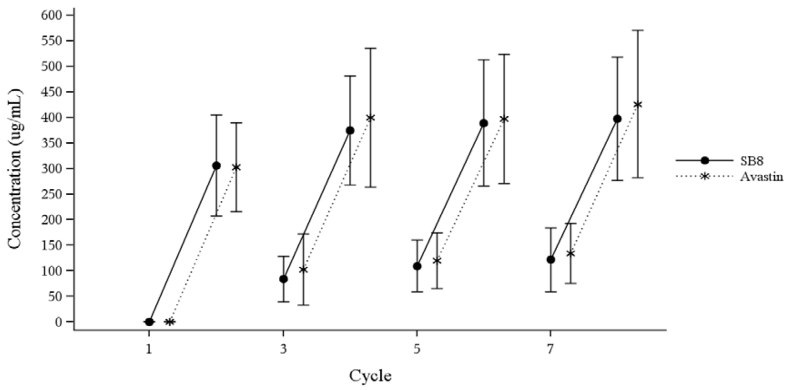
In a subset of these patients, the steady state PK of bevacizumab was assessed. Hence, the PK population comprised a total of 341/763 patients (44.7%) of whom 161/379 patients (42.5%) received SB8 and 180/384 (46.9%) received EU-Avastin, respectively.

The PK study objective was to measure the study serum trough (C_{trough}) and maximum (C_{max}) concentration profiles of bevacizumab from Cycle 1 up to Cycle 7 and to compare them between the SB8 and EU Avastin treatment groups.

Blood sampling for PK analysis was performed at pre-dose (C_{trough}) and post-dose (C_{max}) of IP (within 15 minutes after the end of infusion) of Cycles 1, 3, 5, and 7.

Pharmacokinetic results:

The mean values of pre-dose (C_{trough}) and post-dose (C_{max}) serum concentration profiles up to Cycle 7 are depicted in Figure 2, suggesting that steady state was reached at Cycle 3.



Error bar = standard deviation

Figure 2: Mean (±Standard Deviation) Serum Concentration Profiles from Cycle 1 to Cycle 7 (Pharmacokinetics Population)

Table 11 displays the summary of serum trough (C_{trough}) and maximum (C_{max}) concentration (µg/mL) of the PK population.

Table 11: Summary of Serum Trough (C_{trough}) and Maximum (C_{max}) Concentration (µg/mL) (Pharmacokinetics Population)

Timepoint	PK Parameter	Statistics	SB8 N = 161	Avastin® N = 180	Total N = 341
Cycle 1	C_{trough}	n	142	166	308
		Mean (SD)	0.0000 (0.00000)	0.0000 (0.00000)	0.0000 (0.00000)
		Min Max	0.000 0.000	0.000 0.000	0.000 0.000
		CV%	N/A	N/A	N/A
	C_{max}	n	155	170	325
		Mean (SD)	306.0352 (98.71872)	302.6362 (87.10467)	304.2573 (92.69569)
		Min Max	3.874 793.989	63.090 647.127	3.874 793.989
		CV%	32.257	28.782	30.466
Cycle 3	C_{trough}	n	137	152	289
		Mean (SD)	83.7568 (44.49701)	102.3939 (69.36822)	93.5590 (59.53844)
		Min Max	0.000 383.413	0.181 529.695	0.000 529.695
		CV%	53.126	67.746	63.637
	C_{max}	n	133	146	279
		Mean (SD)	374.9657 (106.54366)	399.4598 (136.27431)	387.7834 (123.39489)
		Min Max	95.476 963.943	52.495 1411.699	52.495 1411.699
		CV%	28.414	34.115	31.821
Cycle 5	C_{trough}	n	118	141	259
		Mean (SD)	109.0906 (50.65915)	119.9343 (54.65786)	114.9939 (53.04905)
		Min Max	19.406 428.824	23.253 435.126	19.406 435.126
		CV%	46.438	45.573	46.132
	C_{max}	n	114	140	254
		Mean (SD)	389.3132 (123.07791)	397.6183 (125.84175)	393.8908 (124.43233)
		Min Max	71.920 928.535	0.345 847.097	0.345 928.535
		CV%	31.614	31.649	31.591
Cycle 7	C_{trough}	n	100	121	221
		Mean (SD)	121.7382 (62.62150)	133.7669 (58.84136)	128.3241 (60.73872)
		Min Max	13.537 538.977	0.000 436.760	0.000 538.977
		CV%	51.439	43.988	47.332
	C_{max}	n	98	119	217
		Mean (SD)	397.5435 (120.74092)	426.1350 (144.24538)	413.2227 (134.59866)
		Min Max	36.279 864.711	35.824 1039.151	35.824 1039.151
		CV%	30.372	33.850	32.573

CV% = coefficient variation; C_{max} = maximum concentration; C_{trough} = trough concentration; Max = maximum; Min = minimum; N/A = not applicable; PK = pharmacokinetic; SD = standard deviation. N = number of subjects in the PK Population; n = number of subjects with non-missing values or without protocol deviation for PK blood sampling at the cycle.
Below the lower limit of quantitation concentrations at pre-dose were set to zero. The lower limit of quantitation was 0.100 µg/ml or 0.200 µg/ml.
Source: Table 14.2-6.1

SB8-POPPK-01– Supportive Pharmacokinetics

A PK modelling approach was used to assess PK similarity between SB8 and Avastin in healthy subjects and patients with NSCLC by testing SB8 treatment as a covariate effect on relevant PK parameters in each population and performing model-based simulations of bevacizumab exposure following each treatment.

The population PK model was initially based on a published model for bevacizumab (Han et al. 2016), but was refined in a step-wise, partly data-driven fashion. The model was first estimated using phase I data, and subsequently extended including phase III data. Covariates were considered based on clinical judgment and mechanistic plausibility. They were analysed using a stepwise backward elimination to identify a more parsimonious model. Influential observations were identified and excluded. Predictive performance was assessed by visual predictive checks.

Objectives

The objectives of this analysis were to:

• Develop a population PK model to characterize the concentration-time profiles of bevacizumab in healthy male subjects and NSCLC patients

• Determine the effect of key extrinsic and intrinsic covariates on bevacizumab PK parameters

• Evaluate the effect of anti-drug antibody (ADA) incidence on the PK of bevacizumab

• Assess consistency in bevacizumab exposure between SB8 and Avastin (EU Sourced and US Sourced) in healthy subjects

• Assess consistency in bevacizumab exposure between EU Sourced and US Sourced Avastin in healthy subjects

• Assess consistency in bevacizumab exposure between SB8 and EU Sourced Avastin in the NSCLC patient population

Results

Model building results

The equations describing the final model disposition parameters are as follows:

$$CL = \theta_{CL} \cdot (1 + FLAGP1 \cdot \theta_{SB8-1}^{CL}) \cdot (1 + FLAGP3 \cdot \theta_{SB8-3}^{CL}) \cdot \left[\frac{BWT}{74.2}\right]^{\theta_{BWTCL}} \cdot \left[\frac{BALB}{41.8}\right]^{\theta_{BALB}} \cdot \left[\frac{CRCL}{92.99}\right]^{\theta_{CRCL}} \cdot (1 + Gender \cdot \theta_{GENCL}) \cdot (1 + Population \cdot \theta_{POPCL}) \cdot exp(\eta_{CL})$$

$$Vc = \theta_{Vc} \cdot \left[\frac{WT}{74.2}\right]^{\theta_{BWTVc}} \cdot (1 + Gender \cdot \theta_{GENVc}) \cdot (1 + Population \cdot \theta_{POPVc}) \cdot exp(\eta_{Vc})$$

$$Q = \theta_Q$$
$$Vp = \theta_{Vp}$$

The equation for CL originally included 16 covariates in the full model which were reduced to 7 covariates (θ_{SB8-1}^{CL}, θ_{SB8-3}^{CL}, Gender, Population, BALB, BWT, CRCL) by the application of a backward elimination procedure.

The equation for Vc originally included 3 covariates (BWT, Gender and Population) which all stayed in the model after the application of the backward elimination algorithm.

No covariates were included in the equations for Q and Vp which were simply estimated based on the whole data. Parameter estimates for the final model are provided in the table below.

Table 12: Final model parameter estimates with combined phase I and phase III study data

Parameter	Estimate	ASE	%RSE	95% CI	Units
CL	0.0116	0.000271	2.3	(0.0111, 0.0122)	L/h
Vc	4.08	0.0936	2.3	(3.90, 4.26)	L
Q	0.0220	0.00105	4.8	(0.0200, 0.0241)	L/h
Vp	2.12	0.0393	1.9	(2.05, 2.20)	L
Ph1 SB8 on CL	0.116	0.039164	33.8	(0.0391, 0.193)	
Ph3 SB8 on CL	0.0846	0.0310	36.6	(0.0239, 0.145)	
Female on CL	-0.191	0.0244	12.7	(-0.239, -0.143)	
Healthy on CL	-0.299	0.0229	7.7	(-0.344, -0.254)	
BWT on CL	0.375	0.0798	21.3	(0.218, 0.531)	
BALB on CL	-0.487	0.119	24.4	(-0.720, -0.255)	
CRCL on CL	0.192	0.0510	26.6	(0.0917, 0.292)	
Female on Vc	-0.109	0.0336	30.8	(-0.175, -0.0431)	
Healthy on Vc	-0.180	0.0248	13.8	(-0.228, -0.131)	
BWT on Vc	0.503	0.0841	16.7	(0.338, 0.668)	
Residual Variability					
RV-Log(Add) Phase I	0.140	0.00246	1.8	(0.135, 0.145)	
RV-Log(Add) Phase III	0.388	0.00718	1.9	(0.374, 0.402)	
IIV					
CL	17.5	--	--	(15.6, 19.2)	CV%
Vc	19.3	--	--	(17.1, 21.2)	CV%

ASE = asymptotic standard error; %RSE = percent relative standard error; CI = confidence interval; CL = clearance; Vc = central volume of distribution; Q = intercompartmental clearance; Vp = peripheral volume of distribution; Ph1 = Phase I; Ph3 = Phase III; BWT = baseline body weight; BALB = baseline albumin; CRCL = creatinine clearance; IIV = interindividual variability; RV = residual variability; CV = coefficient of variation; Log(Add) = additive error on the log-transformed DV; DV = dependent variable

Population PK parameter estimates in the final model (clearance [CL] = 0.0116 L/h; central volume of distribution [Vc] = 4.08 L; intercompartmental clearance [Q] = 0.0220 L/h; peripheral volume of distribution [Vp] = 2.12 L) were generally comparable with published values (CL = 0.0086 L/h; Vc = 2.678 L; Q = 0.0186 L/h; Vp = 2.423 L) and also consistent with known PK properties of monoclonal antibodies.

For assessing how the results of a statistical analysis can be generalize to an independent data set, cross-validation was applied to validate the predictive ability of the model. In case there is severe overfitting, e.g. high RMSE when using cross-validation, the results cannot be considered meaningful. The calculated root mean squared error of the model-predicted bevacizumab concentration (RMSE 0.276 (0.202, 0.347)) was of similar magnitude as the RSME of the model reported by Han et al. (2016). The cross-validation of the whole backward elimination process was provided to calculate the predictive error of the whole model building procedure. Three training data sets were used in the cross-validation. Depending on the training set baseline albumin on clearance (CL), female gender on central volume of distribution (Vc), creatinine clearance (CRCL), and Phase III SB8 on CL were either included or removed following the backward elimination procedure. These were excluded in addition to the same eliminated covariates as for the full data-set model, except for Phase III tumor size on CL and baseline alkaline phosphatase (BALP). In linear regression it is possible to directly compute the factor by which the training MSE underestimates the validation MSE under the assumption that the model specification is valid. For the original model the training MSE (0.073) was very close to the validation MSE (0.078).

In order to assess the robustness of the model results, avoid overfitting and detect possible differences between treatments, (i) the same analyses as for the final model was performed with the evaluated model by Han et al. adding terms for treatment and study and (ii) separate modelling of the PK parameters for SB8 and Avastin was done.

Table 13: Parameter estimates for population PK models for bevacizumab

Parameter	Original Model[a]		Ad-Hoc Model with Chemotherapy[a]		SB8-Avastin Data with Han model		Model by Han et al.[b]	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Fixed Effect								
CL (L/h)	0.0116	(0.0111, 0.0122)	0.0105	(0.00983, 0.0112)	0.00786	(0.00729, 0.00844)	0.0086	(0.00837, 0.00882)
Vc (L)	4.08	(3.90, 4.26)	4.07	(3.89, 4.25)	3.52	(3.32, 3.73)	2.678	(2.616, 2.736)
Q (L/h)	0.0220	(0.0200, 0.0241)	0.0221	(0.0201, 0.0242)	0.0208	(0.0188, 0.0227)	0.0187	(0.0166, 0.0213)
Vp (L)	2.12	(2.05, 2.20)	2.12	(2.04, 2.19)	2.00	(1.90, 2.10)	2.417	(2.291, 2.568)
Phase I SB8 on CL	0.116	(0.0391, 0.193)	0.116	(0.0395, 0.193)	0.122	(0.0326, 0.211)	-	-
Phas I US-Avastin on CL	-	-	-	-	0.011	(–0.0698, 0.0919)	-	-
Phase III SB8 on CL	0.0846	(0.0239, 0.145)	0.0820	(0.0214, 0.143)	0.0864	(0.0250, 0.148)	-	-
Female on CL	–0.191	(–0.239, –0.143)	–0.191	(–0.240, -0.143)	-	-	-	-
Male on CL	-	-	-	-	1.26[e]	(1.18, 1.33)[e]	1.15	(1.11, 1.19)
Healthy on CL	–0.299	(–0.344, –0.254)	–0.223	(–0.283, –0.163)	–0.164	(–0.242, –0.0862)	-	-
BWT on CL or CL/Q[c]	0.375	(0.218, 0.531)	0.367	(0.209, 0.525)	0.538	(0.396, 0.680)	0.586	(0.501, 0.666)
BALB on CL	–0.487	(–0.720, –0.255)	–0.495	(–0.729, –0.262)	–0.543	(–0.777, –0.309)	–0.474	(–0.619, –0.323)
BALP on CL	-	-	-	-	0.321	(0.0914, 0.551)	0.321	(0.132, 0.526)
CRCL on CL	0.192	(0.0917, 0.292)	0.196	(0.0939, 0.299)	-	-	-	-
Female on Vc	–0.109	(–0.175, –0.0431)	–0.108	(–0.175, –0.0415)	-	-	-	-
Male on Vc	-	-	-	-	1.13[f]	(1.04, 1.21)[f]	1.18	(1.13, 1.22)
Healthy on Vc	–0.180	(–0.228, –0.131)	–0.178	(–0.227, –0.129)	–0.177	(–0.225, –0.128)	-	-
BWT on Vc or Vc/Vp[d]	0.503	(0.338, 0.668)	0.502	(0.337, 0.667)	0.466	(0.309, 0.623)	0.469	(0.396, 0.541)
Chemotherapy on CL	-	-	0.156	(0.0874, 0.225)	0.152	(0.0824, 0.222)	-	-
IFNa on CL	-	-	-	-	-	-	0.843	(0.780, 0.905)
Residual Variability								
RV-Log(Add) Phase I	0.140	(0.135, 0.145)	0.140	(0.135, 0.145)	0.136	(0.131, 0.141)	-	-
RV-Log(Add) Phase III	0.388	(0.374, 0.402)	0.385	(0.371, 0.399)	0.386	(0.371, 0.399)	21.7%	(20.7, 22.9)%
Interindividual Variability								
CL (CV%)	17.5	(15.6, 19.2)	17.4	(15.6, 19.1)	17.5	(15.7, 19.2)	29.0	(27.2, 31.0)
Vc (CV%)	19.3	(17.1, 21.2)	19.3	(17.2, 21.3)	19.3	(17.1, 21.2)	18.2	(15.6, 20.9)
Vp (CV%)	-	-			15.5	(9.7, 19.7)	41.8	(33.2, 49.3)

CI = confidence interval; CL = clearance; Vc = central volume of distribution; Q = intercompartmental clearance; Vp = peripheral volume of distribution; BWT = baseline body weight; BALB = baseline albumin; CRCL = creatinine clearance; IFNa = interferon alpha treatment; RV = residual variability; CV = coefficient of variation; Log(Add) = additive error on the log-transformed dependent variable
[a] Source: Section 5.3.3.5 Report SB8-POPPK-01, Table 15 [b] Source: Section 5.3.3.5 Report SB8-POPPK-01, Table 17
[c] BWT on CL and Q in model by Han et al and SB8-Avastin data with Han model [d] BWT on Vc and Vp in model by Han et al and SB8-Avastin data with Han model [e] **Added 1 +** θ

Table 14: Full model parameter estimates for SB8 and Avastin (combined EU Avastin and US Avastin) using separate datasets

Parameter	SB8 Data		EU Avastin® and US Avastin® Data	
	Estimate	95% CI	Estimate	95% CI
Fixed Effect				
CL (L/h)	0.0134	(0.0122, 0.0147)	0.0115	(0.0104, 0.0127)
Vc (L)	4.13	(3.90, 4.36)	4.05	(3.77, 4.33)
Q (L/h)	0.0230	(0.0201, 0.0260)	0.0217	(0.0190, 0.0245)
Vp (L)	2.35	(2.23, 2.47)	2.01	(1.91, 2.11)
SMOK on CL	0.0239	(–0.0452, 0.0931)	0.0130	(–0.0505, 0.0764)
ECOG on CL	–0.121	(–0.190, –0 .0523)	–0.0235	(–0.109, 0.0623)
Asian on CL	–0.145	(–0.274, –0.0164)	–0.0577	(–0.202, 0.0868)
Female on CL	–0.165	(–0.238, –0.0915)	–0.206	(–0.280, –0.132)
Healthy on CL	–0.274	(–0.359, –0.189)	–0.233	(–0.329, -0.136)
BWT on CL	0.297	(0.0713, 0.523)	0.308	(0.0578, 0.559)
AGE on CL	0.0711	(–0.110, 0.253)	0.167	(0.0234, 0.310)
BALB on CL	–0.449	(–0.770, –0.127)	–0.389	(–0.750, –0.0288)
BAST on CL	–0.0707	(–0.147, 0.00576)	0.000331	(–0.0741, 0.0747)
BALP on CL	0.0208	(–0.0470, 0.0886)	0.0979	(0.0276, 0.168)
CRCL on CL	0.151	(–0.00607, 0.308)	0.300	(0.128, 0.472)
BILI on CL	0.00773	(–0.0625, 0.0780)	–0.0393	(–0.0982, 0.0196)
Female on Vc	–0.131	(–0.211, –0.0502)	–0.0867	(–0.192, 0.0187)
Healthy on Vc	–0.204	(–0.269, –0.139)	–0.164	(–0.238, –0.0908)
BWT on Vc	0.584	(0.380, 0.788)	0.428	(0.170, 0.686)
Baseline Tumor Size on CL	0.107	(0.0358, 0.178)	0.0314	(–0.0280, 0.0908)
Residual Variability				
RV-Log(Add) Phase I	0.120	(0.112, 0.127)	0.148	(0.141, 0.154)
RV-Log(Add) Phase III	0.320	(0.302, 0.338)	0.434	(0.413, 0.454)
Interindividual variability				
CL (CV%)	16.3	(13.6, 18.6)	16.6	(14.2, 18.7)
Vc (CV%)	17.2	(13.2, 20.5)	20.9	(18.0, 23.4)

CI = confidence interval; CL = clearance; Vc = central volume of distribution; Q = intercompartmental clearance; Vp = peripheral volume of distribution; SMOK = current smoker; ECOG = Eastern Cooperative Oncology Group performance status; BWT = baseline body weight; BALB = baseline albumin; BAST = baseline alanine aminotransferase; BALP = baseline alkaline phosphatase; CRCL = creatinine clearance; BILI = baseline total bilirubin; IIV = interindividual variability; RV = residual variability; CV = coefficient of variation; Log(Add) = additive error on the log-transformed DV; DV = dependent variable

Results for the effect of key extrinsic and intrinsic covariates

The final bevacizumab population PK model included the following statistically significant covariates: female gender, healthy subject (vs. NSCLC patient), body weight, baseline albumin and CRCL on CL; and female gender, healthy subject (vs. NSCLC patient) and body weight on Vc. SB8 treatment effect covariates for Phase I and Phase III PK comparisons with EU sourced Avastin were not identified as significant covariates in the backward elimination procedure (i.e., p>0.001), but were included in the final model for the assessment of PK similarity between SB8 and Avastin.

Results for PK comparability

PK similarity was assessed by testing a term representing the treatment arm that was included in the final model. The respective estimates for Phase I and Phase III of the treatment difference arm (e.g. Ph1 SB8 0.116 with 95% CI (0.0391, 0.193), Ph3 SB8 0.0846 with 95% CI (0.0239, 0.145)) confirmed the significantly higher than bevacizumab CL in the SB8 that have been observed in the primary non-compartmental analysis.

Individual concentration-time profiles were simulated for dosing of SB8, US sourced Avastin and EU sourced Avastin to steady state. From the simulated PK profiles, summary measures of exposure were calculated, including $C_{max,ss}$, $C_{min,ss}$ and $AUC_{0-\tau,ss}$. The mean exposure parameter ratios and corresponding prediction intervals of SB8 compared to EU or US sourced Avastin, and US compared to EU sourced Avastin, are provided in the below table.

Table 15: Model-predicted exposure parameter ratios

Population	Treatment	Reference	Mean (90% PI)		
			$AUC_{0-\tau,ss}$	$C_{max,ss}$	$C_{min,ss}$
NSCLC Patients	SB8	EU Sourced Avastin	0.91 (0.86, 0.96)	0.96 (0.92,0.99)	0.88 (0.80, 0.94)
Healthy Subjects	SB8	EU Sourced Avastin	0.90 (0.85, 0.96)	0.96 (0.91, 0.99)	0.86 (0.78, 0.96)
	SB8	US Sourced Avastin	0.91 (0.85, 0.96)	0.95 (0.92, 0.99)	0.87 (0.79, 0.95)
	US Sourced Avastin	EU Sourced Avastin	1.00 (0.96, 1.05)	1.00 (0.96, 1.04)	0.99 (0.93, 1.06)

PI = prediction interval; $AUC_{0-\tau,ss}$ = area under the concentration-time profile for a dosing interval (τ) at steady state; $C_{max,ss}$ = steady state maximum concentration; $C_{min,ss}$ = steady state minimum concentration

The final model did not include treatment effect covariates US Avastin versus EU Avastin. Thus, the mean exposure parameter ratios and corresponding confidence intervals of US Avastin to EU Avastin obtained from simulations only reflect the variability of the estimate, not the variability of the treatment ratio.

<u>Results for immunogenicity response and concomitant chemotherapy</u>

The effects of immunogenicity response and concomitant chemotherapy on bevacizumab CL were assessed in separate ad hoc model runs using the final population PK model. Of the 341 NSCLC patients included in the population PK analysis, 26 subjects (16.1%) in the SB8 treatment group and 23 subjects (12.8%) in the EU sourced Avastin treatment group had samples that were ADA-positive.

The impact of the immunogenicity response on clearance was assessed by inclusion of a time-dependent binary (ADA status positive/negative) variable. There was no statistically significant difference with an effect estimate of 5.6% [95% CI: -4.6%, 15.8%]. The final model without interaction terms was also updated by including the ADA titer effect on CL. For this more sensitive model a significant increase in clearance was observed (Titer on CL: 0.0426 (0.00145;0.0838) which was not seen in the original ad-hoc covariate analysis where a term for time-dependent ADA status was included. This makes sense as formation of anti-drug antibodies (ADA) could increase clearance (Impact of ADAs on pharmacokinetics). The Applicant could not include an interaction term of Titer on CL x model to judge the effect of different ADA formation on the comparison of CL between treatments due to computational issues. Covariate effects for the titer effect on CL were estimated, separately for each treatment group. The effect of titer on the CL of EU Avastin was not significant, whereas the estimate of the effect of titer on the CL in of SB8 was statistically significant.

Similarly, the impact of the concomitant chemotherapy (carboplatin or paclitaxel) was evaluated by including a time-dependent binary (Chemo status positive/negative) term for it in the model for CL. The result was statistically significant, increasing bevacizumab CL by an estimate (95% CI) of 15.6% (8.74%, 22.5%). As the clearance is influenced by chemotherapy a term for chemotherapy should have been included in the model building process right from the beginning. The Applicant performed the model building with a time-dependent term for chemotherapy included in the model.

Table 16: Final model parameter estimates including the effect of chemotherapy on clearance in the model used for *Ad-hoc* analysis and the new model

Parameter (Units)	Ad-Hoc Model with Chemotherapy[a]			New Model Including Chemotherapy Covariate in Model Build		
	Estimate	%RSE	95% CI	Estimate	%RSE	95% CI
Fixed Effect						
CL (L/h)	0.0105	3.2	(0.00983, 0.0112)	0.0105	3.2	(0.00980, 0.0111)
Vc (L)	4.07	2.3	(3.89, 4.25)	3.91	1.8	(3.77, 4.05)
Q (L/h)	0.0221	4.8	(0.0201, 0.0242)	0.0221	4.8	(0.0201, 0.0242)
Vp (L)	2.12	1.9	(2.04, 2.19)	2.12	1.9	(2.04, 2.19)
Phase I SB8 on CL	0.116	33.7	(0.0395, 0.193)	0.116	33.7	(0.0393, 0.193)
Phase III SB8 on CL	0.0820	37.7	(0.0214, 0.143)	0.0818	37.8	(0.0212, 0.142)
Female on CL	–0.191	12.8	(–0.240, –0.143)	–0.188	13.2	(–0.236, –0.139)
Healthy on CL	–0.223	13.7	(–0.283, –0.163)	–0.221	14.0	(–0.282, –0.160)
BWT on CL	0.367	22.0	(0.209, 0.525)	0.370	21.8	(0.212, 0.528)
BALB on CL	–0.495	24.0	(–0.729, –0.262)	–0.495	24.3	(–0.731, –0.259)
CRCL on CL	0.196	26.6	(0.0939, 0.299)	0.197	26.2	(0.0957, 0.297)
Female on Vc	–0.108	31.5	(–0.175, -0.0415)	-	-	-
Healthy on Vc	–0.178	14.0	(–0.227, –0.129)	–0.146	16.2	(–0.192, –0.0997)
BWT on Vc	0.502	16.7	(0.337, 0.667)	0.555	15.0	(0.392, 0.719)
Chemo on CL	0.156	22.5	(0.0874, 0.225)	**0.156**	**22.4**	**(0.0879, 0.225)**
Residual Variability						
RV-Log(Add) Phase I	0.140	1.8	(0.135, 0.145)	0.140	1.8	(0.135, 0.145)
RV-Log(Add) Phase III	0.385	1.8	(0.371, 0.399)	0.386	1.9	(0.372, 0.400)
Interindividual variability						
CL (%CV)	17.4	--	(15.6, 19.1)	17.4	--	(15.6, 19.1)
Vc (%CV)	19.3	--	(17.2, 21.3)	19.5	--	(17.3, 21.5)

%RSE = percent relative standard error; CI = confidence interval; CL = clearance; Vc = central volume of distribution; Q = intercompartmental clearance; Vp = peripheral volume of distribution; BWT = baseline body weight; BALB = baseline albumin; CRCL = creatinine clearance; RV = residual variability; CV = coefficient of variation; Log(Add) = additive error on the log-transformed dependent variable

[a] Source: Section 5.3.3.5 Report SB8-POPPK-01, Table 17

2.4.3. Pharmacodynamics

No new pharmacodynamic data have been submitted as part of this application (see discussion on clinical pharmacology).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

In accordance with the EMA guideline (EMA/CHMP/BMWP/403543/2010), the clinical Phase I study (SB8-G11-NHV) in healthy male subjects(following a 3 mg/ kg body weight single i.v. injection) is considered as the main comparative PK study to demonstrate the similarity between SB8 and EU-Avastin in terms of PK properties while the steady-state serum concentration data in the clinical Phase III study (SB8-G31-NSCLC) provides supportive evidence for the PK similarity in a representative patient population (metastatic or recurrent non-squamous NSCLC) by analysis of trough (pre-dose) and maximum (post-dose) plasma levels of SB8 or EU-Avastin following repeat dose IV administration of 15 mg/kg bevacizumab.

The validated PK assay method using SB8 as the reference standard had no differential effects on the results obtained from the SB8, EU Avastin, and US Avastin treatment groups. In the **Phase I PK study (SB8-G11-NHV)** the primary endpoint (AUC_{inf}) and the main secondary endpoints (AUC_{last}, C_{max}) with their 90% CIs were entirely within the predefined acceptance range of 80-125% indicating biosimilarity between the test and reference product. The geometric LSMean ratios (90% CI) for SB8 and EU sourced Avastin in AUC_{inf}, AUC_{last}, and C_{max} were 0.880 (0.8154 to 0.9498), 0.886 (0.8258 to 0.9516) and 0.996 (0.9333 to 1.0628), respectively.

It was noticed however, that the upper limit of the 90% CIs for AUC_{inf} and AUC_{last} did not include 1 implying a statistically significant difference between the two treatments.

For therapeutic proteins, it is known, that formation of anti-drug antibodies (ADA) can influence PK of a drug, especially clearance. The overall incidence of ADA proved to be comparable between the SB8 and EU-Avastin treatment groups. Thus, 1 subject (2.6%) in the SB8 group and 4 subjects (10.3%) in the EU-Avastin group exhibited post-dose ADA positive results. None of the subjects developed NAbs after administration of SB8 or EU-Avastin. A possible impact of ADAs on the PK parameters could not be assessed due to their overall low incidence in the treatment groups (see section 2.6 Clinical safety).

In the **Clinical Phase III study (SB8-G31-NSCLC)** the values obtained for C_{trough} and C_{max} at cycles 1, 3, 5 and 7 were largely comparable between SB8 and EU-Avastin. The C_{trough} and C_{max} values appear to increase steadily, converging to a steady state that seems to occur at Cycle 3. Even though a large variance was observed in each group (28 to 53% CV in the SB8 group, 28 to 67% CV in the EU Avastin group), at each of the time-points, with the exception of Cycle 1, it was noticed that the mean C_{trough} and C_{max} values were constantly lower for SB8 compared to EU Avastin. This difference is further confirmed in the subgroups of ADA positive and ADA negative patients (see Section Impact of ADAs on pharmacokinetics). The Applicant provided the 90% CIs for the geometric LSMean ratios in C_{trough} and C_{max}. The latter fell within the 0.8-1.25 range in all four cycles (1, 3, 5, 7) and the 90% CI contained 1. Two of the three ratios for C_{trough}, however, were lower than 0.8 (cycles 3 and 7) and the 90% CI range was below 1 in all cycles analysed (3, 5, 7). These results further enhance the notion that SB8 is less bioavailable than Avastin but the exposure is similar enough for the difference not to be clinically relevant.

It is important to note however, that the overall interpretation of the results of the PK substudy was hampered due to some inconsistencies found. Looking at the individual drug concentration data listing of the PK population, it was noted that in several patients pre-dose concentrations of bevacizumab were higher than the post-dose concentrations. This was observed in both treatment groups (SB8 and Avastin), in all treatment cycles (1, 3, 5 and 7) and in patients of different study sites. In addition, sometimes pre-dose and post-dose concentrations were found to be very similar. Validity of these data was questioned as samples might have been mixed up at the study site or the analytical site. It was unclear what impact these findings had on the overall interpretation of the results and on the reliability of the PK data generated in this study. The Applicant was therefore requested to investigate and discuss these issues in depth and to conduct an analysis of the PK data excluding these suspicious samples. The PK results after excluding suspicious samples showed comparable Ctrough and Cmax between SB8 and EU Avastin, and these data were also consistent with the PK data of the whole PK population. In addition, a GCP inspection was performed. No critical findings were observed in the inspected study sites. The inappropriate handling and documentation of biological samples at the investigation sites together with the deficiency of the procedure regarding the root cause analysis and the investigation of the anomalous PK results by the Sponsor could have led to the inconsistent PK data interpreted in the Clinical Study Report. Nevertheless, the outcome was that it has no negative impact on the reliability of data collected for this trial.

As formation of anti-drug antibodies increases clearance, a possible impact was investigated (see Section Impact of ADAs on pharmacokinetics). For the ADA negative subgroup the mean C_{trough} and C_{max} values were constantly lower for SB8 compared to EU Avastin studied at each of the time-points (except Cycle 1). Due to the lower sample size of the ADA positive subgroup, results are more variable, but except for Cycle 7 and Cycle 3 pre-dose, mean results were again lower for SB8 compared to EU Avastin. This indicates a higher clearance of SB8 independent of ADA status which fits to the clinical Phase I study (SB8-G11-NHV) results where also a higher clearance was observed with negligible ADA formation.

In addition, a **population PK analysis** on the PK data pooled from the clinical Phase I study in healthy volunteers and the clinical Phase III study in patients with NSCLC was performed. A model was developed in order to determine the effect of key extrinsic and intrinsic covariates on bevacizumab PK parameters, assess PK similarity between SB8 and EU Avastin and to evaluate the effect of anti-drug antibody (ADA) and chemotherapy incidence on the PK of bevacizumab. For model building the backward elimination procedure was applied to reduce the number of covariates in the model. This stepwise regression is prone to overfitting the data, i.e. the model fits much better in the sample it was derived from than it does on new data. The reported estimates may be biased and the confidence intervals do not have the correct coverage. To address this concern cross-validation was performed on the data set. For the original model the training MSE (0.073) was very close to the validation MSE (0.078). Nevertheless, it is still unclear if the original final model was used in these calculations or the resulting model when applying the backward elimination procedure to each training data set.

A good matching was observed between measured and predicted PK data in healthy volunteers. However, it is not clear whether the final model is sensitive (or more sensitive than the primary protocol-defined analysis) to detect differences between biosimilar and originator; the model was built in a data-driven way and may be subject to over-fitting. RMSE is given as a measure for the model fit which is the average deviation of the estimates from the observed values or is the square root of the variance of the residuals. In comparison the R2 is the fraction of the total sum of squares that is explained by the regression, related to the RMSE, but easier to interpret because its value always lies between 0 and one. Furthermore, R2 can be adjusted for the number of explanatory terms in a model relative to the number of data points. The high value of adjusted R^2 of the final model (0.885) indicates a good quality of the linear approximation.

Gender, healthy subject (versus patient), body weight, baseline albumin, and creatinine clearance were identified as statistically significant covariates for bevacizumab PK in the final population PK model on CL. Gender, healthy subject (versus patient), and body weight had statistically significant covariate effects on Vc.

The magnitude of most covariate effects (except for the gender effect which may be explainable by the addition of a chemotherapy term) were very similar for the new and the original Han model. The influence of body weight on clearance is considerably higher in the Han models compared to the original model with or without chemotherapy. The effect of CRCL was identified as a significant covariate in the final model of SB8 but not in the model by Han et al. Baseline ALP and treatment with interferon alpha were identified as the important predictor variable for CL in the model by Han et al. whereas it was eliminated in the final model of SB8. The Applicant explained this by a difference in demographics of the model-building population used in each model. Furthermore, the observed differences could be due to the fact that the model by Han et al. only included patients with solid tumor and the final model of SB8 included both healthy volunteers and patients with advanced NSCLC. They may be explained in part by target-mediated drug disposition of bevacizumab in patients. Separate models of the PK parameters for SB8 and Avastin data were implemented leading to the same significant covariates (gender, healthy/patient, body weight on CL; healthy/patient, body weight on Vc) except for baseline tumour size on Vc which was only significant in the SB8 model. BALB and

CRCL on CL were not significant covariates anymore in both separate models compared to the original final model. The adjusted CL estimate was only slightly higher for the SB8 group compared to the Avastin group (0.0125 versus 0.0118 L/h). The effect estimates of the covariates differ by at most 0.12 L/h and lie within the 95% CI of each other.

The original final PK population model also showed a significant difference in clearance between SB8 and EU Avastin (0.116 with 95% CI (0.0391, 0.193)) leading to a significant lower difference in $C_{max,ss}$, $C_{min,ss}$ and $AUC_{0-\tau,ss}$. This result is consistent with the results gained in the Phase I study for AUC and Phase III study for C_{max}. The impact of the immunogenicity response (ADA) on clearance was not statistically significant whereas the impact of the concomitant chemotherapy (carboplatin or paclitaxel) was statistically significant increasing bevacizumab CL. However, it is not clear whether the final model is sensitive (or more sensitive than the primary protocol-defined analysis) to detect differences between biosimilar and originator; the model was built in a data-driven way and may be subject to over-fitting. For deciding on the appropriateness of the model and the robustness of the results, the Applicant provided additional analyses (see Table 13 and Table 14).

Nevertheless, all models only slightly differ and for all models the 95% CIs for the effect on clearance of SB8 in Phase I and Phase III still excluded 0, thus, showing a significantly higher bevacizumab CL in the SB8 treatment arm.

Pharmacodynamics

No new pharmacodynamic data have been submitted as part of this application. Validated PD markers considered relevant to predicting efficacy of bevacizumab in patients do not exist. Therefore, no PD markers were included in the SB8-G11-NHV PK study, and clinical endpoints were utilised in the phase III study in NSCLC patients.

The primary mechanism of action of bevacizumab is the inhibition of tumour vessel growth by blocking VEGF. The mode of action of bevacizumab is considered to be the same across all approved cancer indications. Therefore, extrapolation to other cancer indications of the reference product than advanced NSCLC is considered acceptable as similarity of Aybintio/SB8 to the bevacizumab reference product (EU-Avastin) has been demonstrated.

2.4.5. Conclusions on clinical pharmacology

In the Phase I PK study the primary endpoint (AUC_{inf}) and the main secondary endpoints (AUC_{last}, C_{max}) with their 90% CIs were entirely within the predefined acceptance range of 80-125% indicating biosimilarity between the test and reference product and in the Phase III PK substudy the values obtained for C_{trough} and C_{max} at cycles 1, 3, 5 and 7 were largely comparable between SB8 and EU-Avastin. From the PK data presented of the Phase I and Phase III study it seems, that SB8 exhibits a faster clearance and a lower bioavailability/drug exposure than EU-Avastin. The observed difference in clearance between the two treatments is a possible contributing factor to the difference in the AUCs between SB8 and EU-Avastin in the Phase I study and could be related to an elevated content in %High mannose in SB8 as compared to Avastin. Based on the data provided it seems that the slight difference in ADA formation has no causal relationship to the observed lower exposure. The impact of a slightly lower exposure is, however, considered to have no visible impact on clinical efficacy.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

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

2.5.2. Main study

SB8-G31-NSCLC: A Phase III, Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB8 (proposed bevacizumab biosimilar) and Avastin in Subjects with Metastatic or Recurrent Non-squamous Non-small Cell Lung Cancer.

Methods

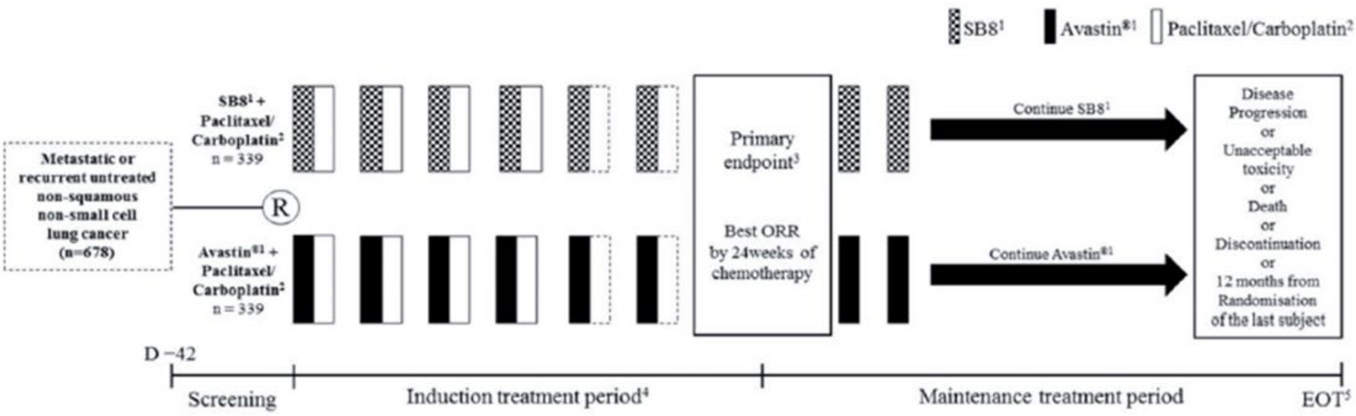


Figure 3: Study scheme for study SB8-G31-NSCLC

Study Participants

Patients must meet all of the following criteria to be eligible for the study:

• Patients aged ≥ 18 years (if local regulations are different in this regard, follow the local regulations).

• Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 at the screening

• Histologically and/or cytologically confirmed metastatic (American Joint Committee on Cancer (AJCC) 7th edition TNM stage IV) or recurrent non-squamous NSCLC or NSCLC not otherwise specified.

• At least 1 measurable lesion according to RECIST v1.1

• Adequate haematological function at screening defined as the following:

• Absolute neutrophil count (ANC) ≥ 1500/mm3 (≥ 1.5 × 109/L)

• Platelet count ≥ 100000/mm3

• Haemoglobin ≥ 9 g/dL (without transfusion within 14 days prior to randomization)

• Adequate hepatic function at screening defined as the following:

• Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (in cases of known Gilbert's syndrome ≤ 3 × ULN)

• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 × ULN (in case of liver metastases < 5 × ULN)

• Alkaline phosphatase (ALP) < 3 × ULN (in case of liver metastases < 5 × ULN)

• Adequate renal function at screening defined as the following:

• Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CCr) measured or calculated according to Cockcroft-Gault formula ≥ 50 mL/minute

• Urine dipstick for proteinuria < 2+ (other ways of urinalysis were also acceptable); if urine dipstick was ≥ 2+, 24-hour urine protein excretion should have been < 1 g or protein/creatinine ratio in spot urine should have been < 1 g/g creatinine (or < 226.0 mg/mmol creatinine)

• Patients and their partners of childbearing potential (female or male) including those with history of elective sterilization (e.g. fallopian tube ligation), who agreed to use at least 2 forms of appropriate contraception (e.g. established use of oral, injected or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine system, physical barrier, male sterilization or true abstinence) from screening until 6 months after the last administration of IP. A negative pregnancy test result was required for all women of childbearing potential including women who had menopause onset within 2 years prior to randomization. True abstinence was considered sufficient for patients who did not have a partner.

• Patients must have been able to provide informed consent, which had to be obtained prior to any study related procedures.

Treatments

IP: Patients were randomized to receive either SB8 or EU Avastin 15 mg/kg IV infusion every 3 weeks on Day 1 of every 3-week cycle for at least 4 cycles and up to 6 cycles. Supplied for use as a concentrate for solution (100 mg or 400 mg per vial).

Non-IP: Paclitaxel 200 mg/m2 IV infusion over 3 hours / carboplatin area under the curve (AUC) 6 IV infusion over 30 minutes on Day 1 of each cycle during the induction treatment period. Paclitaxel was to be administered after the completion of IP administration. Nab-paclitaxel or other formulation of paclitaxel was not allowed in this study. Carboplatin was to be administered after the completion of paclitaxel.

Study phases and conduct

Screening period: within 42 days before randomisation.

Induction treatment period: This period consists of 4 to 6 cycles of a 3-week cycle. SB8 or Avastin was to administered intravenously before starting chemotherapy (paclitaxel and carboplatin) at a dose of 15 mg/kg on Day 1 of every 3-week cycle for at least 4 cycles and up to 6 cycles.

Maintenance treatment period: In patients who showed a response to the treatment (defined as complete response (CR) or partial response (PR), or stable disease (SD) after completion of the induction treatment period, SB8 or Avastin was to be administered every 3 weeks until disease progression, unacceptable toxicity, death, or end of study occurs.

End of Treatment (EOT) was defined as discontinuation of the treatment due to disease progression, unacceptable toxicity, death, or last administration of the IP before the end of the study. EOT visit was performed at least 21 days after the last IP administration and prior to subsequent therapy.

Follow up: telephone contact every 3 months from EOT until discontinuation of the patient from the study (e.g., death, withdrawal of consent, lost to follow-up, or initiation of subsequent therapy for NSCLC) or EOS.

Objectives

The primary objective of this study was to demonstrate the equivalence of SB8 to Avastin in terms of the best Overall Response Rate (ORR) by 24 weeks of chemotherapy in patients with metastatic or recurrent non-squamous NSCLC.

The secondary objectives were:

• To evaluate the efficacy of SB8 compared to Avastin by PFS, OS and duration of response (DOR)

• To evaluate the safety and tolerability of SB8 compared to Avastin.

• To evaluate the PK of SB8 compared to Avastin.

• To evaluate the immunogenicity of SB8 compared to Avastin.

Outcomes/endpoints

- Primary efficacy endpoint

Best ORR by 24 weeks of chemotherapy (best ORR was defined as the proportion of subjects whose best overall response was either complete response [CR] or partial response [PR] according to RECIST v1.1 during the induction treatment period by 24 weeks).

Tumour assessment (MRT or CT assessment of disease status according to RECIST v1.1) was performed before planned Day 1 of Cycle 3, 5, and 7 and then every 4 cycles and assessed by both Investigators and independent central reviewer. The primary efficacy analysis was based on the data from the independent central review.

For EMA, the primary efficacy analysis was to be performed in the per-protocol set (PPS) for the difference of the best ORR (best ORR of SB8 – best ORR of Avastin) by 24 weeks, and the equivalence between the two treatment groups will be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [-12.5%, 12.5%]. Similar analysis was to be performed for the FAS to support the primary analysis.

The primary efficacy analysis was performed using the log binomial model with treatment. The sensitivity analysis was performed using the log binomial model with the covariates of age (< 70, ≥ 70 years), sex (female, male), region (EU or non-EU) and treatment to explore the robustness of the primary efficacy results.

- Secondary efficacy endpoints:

- PFS (defined as the time from the date of Randomisation to disease progression or death regardless of cause. Subjects who were not progressed at the time of analysis were censored at the date of EOT visit or the last tumour assessment date if the date of EOT was not available).

- OS (defined as the time from the date of Randomisation to the date of death regardless of the cause of death. Subjects who were alive at the time of analysis were censored at the date of last known alive).

- Duration of response (DOR) (defined as the time from documented tumour response (complete or partial) until documented disease progression. Only the subjects who achieved an initial tumour response were evaluated for DOR).

- Exploratory efficacy endpoint:

Best ORR by 11 weeks and 17 weeks of chemotherapy.

Further endpoints concerned safety and tolerability of SB8 compared to Avastin, evaluated the PK of SB8 compared to Avastin (C_{trough} at pre-dose of Cycle 1, 3, 5, and 7 and C_{max} at post-dose of Cycle 1, 3, 5, and 7), evaluated the immunogenicity of SB8 compared to Avastin (ADAs at pre-dose of Cycle 1, 3, 5, 7, and at the EOT visit.

Other efficacy parameters were evaluated post-hoc. These considered ORR at cycle 2, 4 and 6; response rate-time curves, Tumour burden and ORR at cycle 6 regardless of period.

Sample size

With 305 patients in each treatment group, the two-sided 90% CI of the best ORR ratio was expected to lie within [0.737, 1.357] with approximately 80% power, and the two-sided 95% CI of the best ORR difference between SB8 and EU Avastin was expected to lie within [−12.5%, 12.5%] with 80% power when the expected best ORR was assumed to be 35%. Assuming a 10% drop-out rate, a total of 678 patients (339 patients per treatment group) were planned to be randomized.

Randomisation

Eligible patients were randomized in a 1:1 ratio to receive either SB8 or EU Avastin (15 mg/kg administered by IV infusion on Day 1 of every 3-week cycle) concurrently with PC chemotherapy (paclitaxel 200 mg/mg2 and carboplatin AUC 6 by IV infusion on Day 1 of every 3-week cycle) for at least 4 cycles and up to 6 cycles of the induction treatment period. The randomization was stratified by age group (< 70 years and ≥ 70 years at the time of the randomization) and gender.

A subject randomisation list was produced by the Interactive Web Recognition System (IWRS)

Blinding (masking)

The subjects, Investigators, and site personnel involved in the study were blinded to the assignment of the IP. The IP remained blinded throughout the study period except staffs designated for unblinding after the interim analysis.

Statistical methods

Analysis sets

• Enrolled Set (ENR): all subjects who provided informed consent for this study.

• Randomised Set (RAN): all subjects who received a randomisation number at the randomisation.

• Full Analysis Set (FAS): all randomised subjects. The subjects were analysed based on the treatment they were randomised to by intention-to-treat principle. Missing data from subjects who withdrew from the study due to PD, lack of efficacy and AEs without any tumour assessment were considered as non-responder.

• Per-protocol Set (PPS): all FAS subjects who completed at least first 2 cycles of combination chemotherapy with a tumour assessment and did not have any major protocol deviations that impacted the primary efficacy assessment. The PPS is the primary analysis set.

• Safety Set (SAF): all subjects who received the study drug at least once.

• Pharmacokinetic Population (PK Population): This set consisted of subjects allocated to PK sub-study who had at least one measured serum concentration of bevacizumab.

Analysis methods

Primary efficacy comparison

The primary efficacy analysis aims at demonstrating equivalence in the ORR between SB8 and Avastin in the PPS. The null hypothesis tested for the primary efficacy analysis will be either (1) SB8 is inferior to Avastin or (2) SB8 is superior to Avastin based on a pre-specified equivalence margin.

For the EMA submission the primary efficacy analysis will be performed in the PPS for the difference of the best ORR (best ORR of SB8 – best ORR of Avastin) by 24 weeks.

The tumour response is assessed by independent central review and by Investigator, but the primary efficacy analysis will be based on the data from the independent central review. The difference in best ORR (best ORR of SB8 – best ORR of Avastin) and its 95% CI for the PPS are estimated by the binomial regression model with treatment group as an explanatory variable. The equivalence is declared if the two-sided 95% CI lies within the pre-defined equivalence margin of [-12.5%, 12.5%].

Secondary efficacy comparisons

The secondary efficacy endpoints of PFS, OS and DOR are analysed for PPS and FAS.

Median survival times and the corresponding 95% CI for Progression-Free Survival (PFS) and Overall Survival (OS) are estimated using the Kaplan-Meier method in the FAS and PPS and visualized with Kaplan-Meier plots.

Results

Participant flow

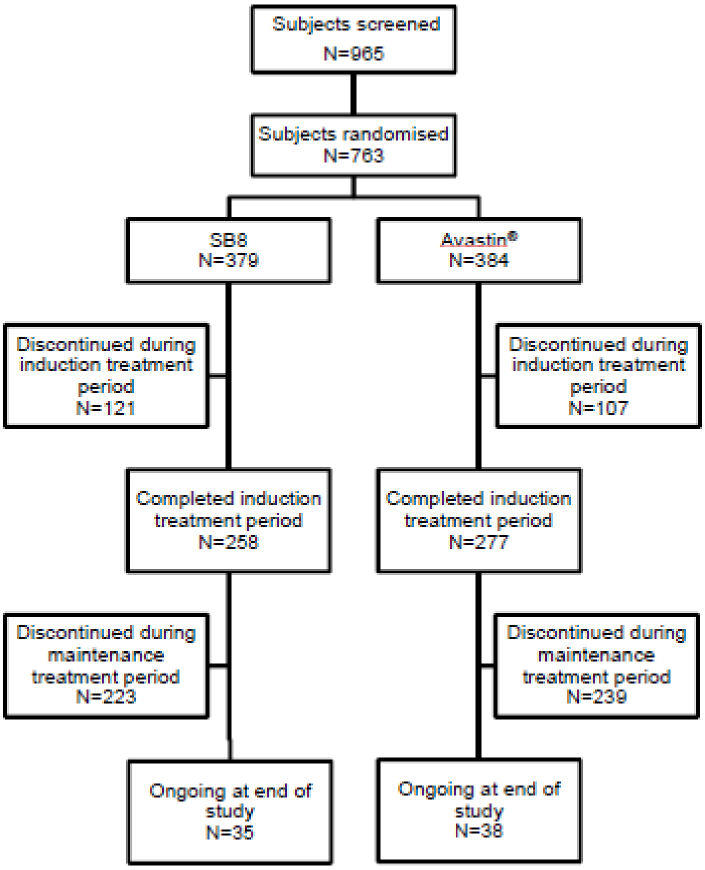


Figure 4: Subject Disposition (Study SB8-G31-NSCLC)

Seven hundred and sixty three (763) patients with metastatic or recurrent non-squamous NSCLC stage IV or recurrent without known activating epidermal growth factor receptor (EGFR) gene mutations or anaplastic lymphoma kinase (ALK) gene translocations were randomized in a 1:1 ratio, stratified by age group (< 70 and ≥ 70 years) and gender.

Recruitment

The study was conducted in 100 study centers, located in Belarus, Georgia, Germany, Hungary, Republic of Korea, Poland, Romania, Russia, Serbia, Spain, Taiwan, Thailand and Ukraine. First subject signed informed consent on 5 July, 2016 and the last subject last visit was on 9 August 2018.

Conduct of the study

Two global amendments and 2 country-specific amendments were made to the original protocol (dated 5 October 2015).
Protocol deviations were classified as major and minor. Protocol deviations did not lead to subject withdrawal unless they indicated a significant risk to the subject's safety. A total of 451 (59.1%) subjects had at least one major protocol deviation (224 [59.1%] subjects in the SB8 treatment group and 227 [59.1%]) subjects in the Avastin treatment group). A total of 14 (1.8%) subjects were

excluded from the PPS due to major protocol deviations. The most common major protocol deviation that led to exclusion from the PPS was associated with efficacy criteria (6 [1.6%] subjects in the SB8 treatment group and 7 [1.8%] subjects in the Avastin treatment group).

Baseline data

Table 17: Demographic Characteristics (Randomized Set, Study SB8-G31-NSCLC)

Characteristics	SB8 N = 379	EU Avastin® N = 384	Total N = 763
Age (years)			
n	379	384	763
Mean (SD)	60.2 (8.95)	60.0 (9.18)	60.1 (9.06)
Median	61.0	61.0	61.0
Min, Max	31,82	20,84	20,84
Age group, n (%)			
< 65 years	255 (67.3)	269 (70.1)	524 (68.7)
≥ 65 years	124 (32.7)	115 (29.9)	239 (31.3)
< 70 years	326 (86.0)	334 (87.0)	660 (86.5)
≥ 70 years	53 (14.0)	50 (13.0)	103 (13.5)
Gender, n (%)			
Male	252 (66.5)	256 (66.7)	508 (66.6)
Female	127 (33.5)	128 (33.3)	255 (33.4)
Race, n (%)			
White	347 (91.6)	348 (90.6)	695 (91.1)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	32 (8.4)	35 (9.1)	67 (8.8)
Black or African American	0 (0.0)	1 (0.3)	1 (0.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)			
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Chinese	5 (1.3)	6 (1.6)	11 (1.4)
Indian (Indian subcontinent)	0 (0.0)	0 (0.0)	0 (0.0)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)
Mixed Ethnicity	1 (0.3)	0 (0.0)	1 (0.1)
Other	373 (98.4)	378 (98.4)	751 (98.4)
Region, n (%)			
EU	77 (20.3)	78 (20.3)	155 (20.3)
Non-EU	302 (79.7)	306 (79.7)	608 (79.7)
Weight (kg)			
n	379	384	763
Mean (SD)	72.53 (15.160)	72.67 (14.615)	72.60 (14.878)
Median	70.00	71.00	70.50
Min, Max	37.9,128.0	38.2,127.0	37.9,128.0
Height (cm)			
n	379	384	763
Mean (SD)	168.51 (8.892)	168.80 (8.957)	168.66 (8.920)
Median	170.00	170.00	170.00
Min, Max	140.0,193.0	145.0,190.0	140.0,193.0
BMI (kg/m²)			
n	379	384	763
Mean (SD)	25.50 (4.809)	25.49 (4.707)	25.50 (4.755)
Median	24.90	24.80	24.90
Min, Max	15.8,46.7	13.5,42.2	13.5,46.7
BSA (m²)			

Characteristics	SB8 N = 379	EU Avastin® N = 384	Total N = 763
n	379	384	763
Mean (SD)	1.83 (0.217)	1.84 (0.212)	1.84 (0.214)
Median	1.80	1.80	1.80
Min, Max	1.3,2.5	1.3,2.6	1.3,2.6
ECOG performance status, n (%)			
0	106 (28.0)	107 (27.9)	213 (27.9)
1	272 (71.8)	277 (72.1)	549 (72.0)
≥ 2	1 (0.3)	0 (0.0)	1 (0.1)
Smoking status, n (%)			
Never smoked	143 (37.7)	148 (38.5)	291 (38.1)
Former smoker	100 (26.4)	102 (26.6)	202 (26.5)
Current smoker	136 (35.9)	134 (34.9)	270 (35.4)

BMI = body mass index; BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; EU = European Union; Max – maximum; Min = minimum; SD = standard deviation; N = number of patients in the Randomized set (RAN); n = number of patients.
Age was calculated based on the date of randomization.
Body Mass Index (kg/m^2) = weight (kg) / $(height[m])^2$
Body Surface Area (m^2) = $(height\ [cm] \times weight\ [kg]\ /\ 3600)^{1/2}$
Percentages were based on the number of patients in the RAN.

Table 18: Baseline Disease Characteristics (Randomized Set, Study SB8-G31-NSCLC)

Characteristics	SB8 N = 379	EU Avastin® N = 384	Total N = 763
Cancer type (dominant histological classification), n (%)			
Adenocarcinoma	364 (96.0)	363 (94.5)	727 (95.3)
Large cell neuroendocrine carcinoma	0 (0.0)	2 (0.5)	2 (0.3)
Large cell carcinoma	2 (0.5)	7 (1.8)	9 (1.2)
Adenosquamous carcinoma	2 (0.5)	2 (0.5)	4 (0.5)
Pleomorphic carcinoma	0 (0.0)	1 (0.3)	1 (0.1)
Spindle cell carcinoma	1 (0.3)	0 (0.0)	1 (0.1)
Giant cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)
Carcinosarcoma	0 (0.0)	0 (0.0)	0 (0.0)
Not otherwise specified	10 (2.6)	9 (2.3)	19 (2.5)
Stage of disease, n (%)			
Stage 0	0 (0.0)	0 (0.0)	0 (0.0)
Stage IA	0 (0.0)	0 (0.0)	0 (0.0)
Stage IB	1 (0.3)	1 (0.3)	2 (0.3)
Stage IIA	1 (0.3)	1 (0.3)	2 (0.3)
Stage IIB	0 (0.0)	1 (0.3)	1 (0.1)
Stage IIIA	0 (0.0)	1 (0.3)	1 (0.1)
Stage IIIB	0 (0.0)	0 (0.0)	0 (0.0)
Stage IV	375 (98.9)	380 (99.0)	755 (99.0)
TNM Incomplete	0 (0.0)	0 (0.0)	0 (0.0)
Non-categorized	2 (0.5)	0 (0.0)	2 (0.3)
EGFR gene status, n (%)			
Positive	0 (0.0)	1 (0.3)	1 (0.1)
Negative	98 (25.9)	92 (24.0)	190 (24.9)
Unknown	281 (74.1)	291 (75.8)	572 (75.0)
ALK gene status, n (%)			
Positive	0 (0.0)	0 (0.0)	0 (0.0)
Negative	65 (17.2)	67 (17.4)	132 (17.3)
Unknown	314 (82.8)	317 (82.6)	631 (82.7)
Duration of disease (month)			
N	379	384	763
Mean (SD)	7.19 (21.618)	5.08 (13.384)	6.13 (17.971)
Median	1.10	1.10	1.10
Min, Max	0.1, 214.5	0.2, 121.5	0.1, 214.5

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; Max = maximum; Min = minimum; SD = standard deviation; N = number of patients in the randomized set (RAN); n = number of patients.
TNM Incomplete: patients with missing values of any state assessments, T (primary tumor), N (regional lymph nodes), and M (distant metastasis).
Percentages were based on the number of patients in the RAN.

EGFR activating mutation testing results were available for the majority of patients in South Korea (93%), Taiwan (91%,), Spain (81%) and Germany (69%), whereas EGFR mutation status was known for one of 155 patients in Ukraine, and for 19.3% (49/254) of patients treated in Russian sites. ALK rearrangement testing was carried out for the majority of patients in South Korea (89.7%), Spain (86.7%) and Germany (69.2%), whereas ALK rearrangement status was known for 1 out of 155 patients in Ukraine and for 12.2% (31/254) of patients at Russian sites.

Numbers analysed

Table 19: Data sets analysed (Randomised set, study SB8-G31-NSCLC)

	SB8		EU Avastin®		Total	
	n	(%)	n	(%)	n	(%)
Randomized Set	379	(100.0)	384	(100.0)	763	(100.0)
Full Analysis Set	379	(100.0)	383	(99.7)	762	(99.9)
Per-protocol Set	337	(88.9)	328	(85.4)	665	(87.2)
Safety Set	378	(99.7)	380	(99.0)	758	(99.3)
Pharmacokinetic population	161	(42.5)	180	(46.9)	341	(44.7)

n = number of patients in the respective analysis set.
Percentages were based on the number of randomized patients.
Source: Section 5.3.5.1 Final CSR, SB8-G31-NSCLC, Table 11-1, Table 14.1-2.1

Outcomes and estimation

Primary endpoint

Table 20: Primary analysis of difference in best overall response rate during induction treatment period by 24 weeks (Per-protocol set)

Parameter	SB8 N = 337 n (%)	Avastin N = 328 n (%)
Best Overall Response Rate (Best ORR)		
CR+PR	169 (50.1)	147 (44.8)
Difference of Best ORR		
Difference (SB8-Avastin®)	5.3%	
95% CI	[-2.2%, 12.9%]	

CI = confidence interval; CR = complete response; ORR = overall response rate; PR = partial response;
N = number of subjects in the Per-protocol set; n = number of subjects.
The best ORR was defined as the proportion of subjects whose best overall response was either CR or PR according to RECIST v1.1 during the induction treatment period by 24 weeks.

Sensitivity analyses and post-hoc performed additional analyses are provided in section "Ancillary analyses".

Secondary Efficacy Results

Progression-free Survival and Overall Survival:

At the time of the EOS (Aug 09, 2018), the median follow-up duration was 15.2 months (range 0-24.4 months).

Table 21: Summary of PFS and OS (Per-protocol set)

	SB8 N = 337	Avastin® N = 328
Progression-free Survival		
Number of subjects with event, n (%)	230 (68.2)	223 (68.0)
Median PFS (months) [95% CI]	8.50 [7.20, 9.70]	7.90 [7.30, 9.40]
Overall Survival		
Number of subjects with events, n (%)	152 (45.1)	146 (44.5)
Median OS (months) [95% CI]	14.80 [13.00, 17.10]	15.80 [13.80, 17.70]
Kaplan-Meier Estimates [95% CI]		

Results were similar for FAS.

The 6-month and 12-month PFS rates [95% CI] calculated using Kaplan-Meier method were 73% [68%, 78%] and 34% [28%, 39%] in the SB8 treatment group and 76% [71%, 80%] and 30% [24%, 35%] in the Avastin treatment group in the PPS. Results were similar for FAS.

In the PPS the 6-month, 12-month, and 18-month OS rates [95% CI] were 85% [80%, 88%], 61% [55%, 66%], and 43% [36%, 50%] in the SB8 treatment group and 89% [85%, 92%], 63% [57%, 68%], and 43% [36%, 50%] in the Avastin treatment group. Results were similar for FAS.

Duration of response

Table 22: Summary of duration of response (month)

Analysis Set	Treatment	n (%)	Median	Mean	SD
FAS	SB8 (N = 379)	179 (47.2)	5.60	6.38	3.773
	Avastin® (N = 383)	164 (42.8)	5.85	6.79	4.117
PPS	SB8 (N = 337)	175 (51.9)	5.60	6.33	3.784
	Avastin® (N = 328)	159 (48.5)	5.90	6.81	4.177

FAS = Full analysis set; PPS = Per-protocol set; SD = standard deviation; N = number of subjects in analysis set; n = number of subjects.
Source: Table 14.2-2.9.1 and Table 14.2-2.9.2

Exploratory Efficacy Results

Table 23: Analysis of difference in best overall response rate during induction treatment period by 11 weeks and 17 weeks (Full analysis set, study SB8-G31- NSCLC)

Parameter		FAS		PPS	
		SB8 (N=379)	EU Avastin® (N=383)	SB8 (N=337)	EU Avastin® (N=328)
By 11 weeks	Best ORR, n (%)	107 (28.2%)	100 (26.2%)	99 (29.4%)	89 (27.1%)
	Difference [95% CI]	2.0% [−4.3%, 8.4%]		2.2% [−4.6%, 9.1%]	
By 17 weeks	Best ORR, n (%)	159 (42.1%)	152 (39.7%)	149 (44.2%)	137 (41.8%)
	Difference [95% CI]	2.4% [−4.6%, 9.3%]		2.4% [−5.1%, 10.0%]	

CI = confidence interval; FAS = full analysis set; N = number of patients in the full analysis set or per-protocol set; n = number of patients; ORR = overall response rate; PPS = per-protocol set.
Percentages were based on the number of patients in the FAS or PPS.
The best ORR was defined as the proportion of patients whose best overall response was either complete response (CR) or partial response (PR) according to RECIST v1.1 during the induction treatment period by 11weeks and 17 weeks.
In the FAS, missing data from patients who withdrew the study due to disease progression and Adverse Events (AEs) without any tumor assessment were considered as a non-responder.
In the FAS, missing data from patients who withdrew the study with reasons other than disease progression and AEs and remained in the study, without any tumor assessment were imputed using a multiple imputation method.
Source: Section 5.3.5.1 Final CSR SB8-G31-NSCLC, Table 11-14, Table 11-16, Table 14.2-5.2.1, Table 14.2-5.2.2, Table 14.2-5.4.1, Table 14.2-5.4.2

Post-hoc performed additional analyses concerning secondary endpoints are provided in section "post hoc analyses".

Ancillary analyses

Sensitivity Analysis of the Primary Efficacy Variable

To explore the robustness of the primary efficacy result, the primary efficacy analysis for the ratio in the PPS and the difference in the FAS in the best ORR was performed.

Table 24: Analysis of ratio and difference in best overall response rate during induction treatment period by 24 weeks

Analysis Set	Treatment	n	(%)	Difference	95% CI
FAS	SB8 (N = 379)	181	(47.6)	4.8%	[-2.3%, 11.9%][a]
	Avastin® (N =383)	164	(42.8)		
Analysis Set	**Treatment**	**n**	**(%)**	**Ratio**	**90% CI**
PPS	SB8 (N = 337)	169	(50.1)	1.12	[0.978, 1.280][b]
	Avastin® (N = 328)	147	(44.8)		

CI = confidence interval; FAS = Full analysis set; PPS = Per-protocol set; N = number of subjects in analysis set; n = number of subjects.
The best ORR was defined as the proportion of subjects whose best overall response was either complete response or partial response according to RECIST v1.1 during the induction treatment period by 24 weeks.
Missing data from subjects who withdrew the study due to disease progression and Adverse Events (AEs) without any tumour assessment were considered as non-responder for the FAS.
Missing data from subjects who withdrew the study with reasons other than disease progression and AEs and remained in the study, without any tumour assessment were imputed using multiple imputation method for the FAS.
[a] Represent the confidence interval was fully within the equivalence margin [-12.5%, 12.5%].
[b] Represent the confidence interval was fully within the equivalence margin [0.737, 1.357].
Source: Table 14.2-2.1.2 and Table 14.2-2.2.1

Table 25: Sensitivity analysis of ratio in best overall response rate during induction treatment period by 24 weeks

Analysis Set	Treatment	n	(%)	Ratio	90% CI
FAS	SB8 (N = 379)	181	(47.6)	1.11	[0.977, 1.270][a]
	Avastin® (N = 383)	164	(42.8)		
PPS	SB8 (N = 337)	169	(50.1)	1.12	[0.977, 1.278][a]
	Avastin® (N = 328)	147	(44.8)		

CI = confidence interval; FAS = Full analysis set; PPS = Per-protocol set; N = number of subjects in analysis set; n = number of subjects.
The best ORR was defined as the proportion of subjects whose best overall response was either complete response or partial response according to RECIST v1.1 during the induction treatment period by 24 weeks.
Missing data from subjects who withdrew the study due to disease progression and Adverse Events (AEs) without any tumour assessment were considered as non-responder for the FAS.
Missing data from subjects who withdrew the study with reasons other than disease progression and AEs and remained in the study, without any tumour assessment were imputed using multiple imputation method for the FAS.
[a] Represent the confidence interval was fully within the equivalence margin [0.737, 1.357].
Source: Table 14.2-2.3.1 and Table 14.2-2.3.2

In the sensitivity analysis equivalence in terms of the adjusted difference in best ORR, results were similar.

Analysis imputing for patients without tumour assessment

More conservative imputation methods on all patients without tumour assessment to estimate the effect difference between SB8 and Avastin was provided post-hoc for the primary endpoint best ORR by week 24 of the ORR at Cycle 6 in the induction period as well as for ORR at week 24.

Table 26: Analysis of difference in best overall response rate by 24 weeks of the induction period (Per-protocol set, study SB8-G31- NSCLC) (*Ad-hoc* analysis)

Parameter	SB8 N=337	EU Avastin® N=328
Best Overall Response Rate (Best ORR)		
CR+PR [n(%)][a]	148 (43.8%)	126 (38.5%)
Difference of Best ORR		
Difference (SB8 – EU Avastin®)	5.3%	
95% CI	[−2.2%, 12.7%]	

CI = confidence interval; CR = complete response; N = number of patients in the Per-protocol Set (PPS); n = number of patients; ORR = overall response rate; PR = partial response; Percentages were based on the number of patients in the PPS.
[a] The best ORR was defined as the proportion of patients whose best overall response was either complete response (CR) or partial response (PR) according to RECIST v1.1 during the induction treatment period by 24 weeks.
Missing data from patients who withdrew the study with primary discontinuation reasons other than death and disease progression without any tumor assessment were imputed using a multiple imputation method.
Missing data from patients who withdrew the study primarily due to death or disease progression without any tumor assessment were considered as non-responders.
Difference and 95% CI were estimated by the binomial regression model with treatment group as an explanatory variable.

For the FAS, the difference [95% CI] in best ORR by 24 weeks of the induction period after missing data imputation of 332 patients was 6.0% [−0.9%, 12.9%] (table not presented).

The other provided analyses took Cycle 2, 4 and 6 or just Cycle 2 and 4 as predictor variables for best ORR using a non-monotone missing pattern (not presented). Nevertheless, results showed that the 95% CI of the difference in best ORR would be within the comparability range of 12.5% for both, the FAS and PPS.

The *ad-hoc* analysis of ORR at Cycle 6 in the induction period was performed for the PPS after imputation of 278 patients without ORR at Cycle 6 in the induction period. The difference [95% CI] in ORR at Cycle 6 in the induction period for the PPS was 5.6% [−1.8%, 13.0%]. The results indicated no statistically significant difference between the two treatment groups with the 95% CI including zero.

Table 27: Analysis of difference in overall response rate at cycle 6 in the induction period (Per-protocol set, study SB8-G31- NSCLC) (*Ad-hoc* analysis)

Parameter	SB8 N=337	EU Avastin® N=328
ORR at Cycle 6 in Induction Period		
CR+PR [n(%)][a]	143 (42.6%)	121 (36.9%)
Difference of ORR		
Difference (SB8 – EU Avastin®)	5.6%	
95% CI	[−1.8%, 13.0%]	

CI = confidence interval; CR = complete response; N = number of patients in the Per-protocol Set (PPS); n = number of patients; ORR = overall response rate; PR = partial response
[a] The ORR at Cycle 6 in induction period was defined as the proportion of patients whose overall response was either complete response (CR) or partial response (PR) according to RECIST v1.1 at Cycle 6 in induction period.
Missing data from patients who withdrew the study with reasons other than death and disease progression without any tumor assessment were imputed using multiple imputation method.
Missing data from patients who withdrew the study due to death and disease progression without any tumor assessment were considered as non-responder.
Difference and 95% CI were estimated by the binomial regression model with treatment group as an explanatory variable.

The difference [95% CI] in ORR at Cycle 6 in the induction period for the FAS was 6.2% [−0.6%, 13.1%]. The results indicated no statistically significant difference between the two treatment groups.

Results for PPS and FAS were similar and indicated no statistically significant difference between the two treatment groups. Furthermore, the difference was smaller than in the analysis without missing data imputation for the subset of patients completing 6 cycles in the induction period presented in the initial dossier (former results showed a difference of 7.1% [95% CI: −3.5%, 17.7%] for the PPS).

For justification of the clinical relevance of the margin, the applicant performed three different weighted linear regression of best ORR to median PFS. For two regression analyses (First results of the clinical Phase III study (SB8-G31-NSCLC) in addition to the results from four clinical studies with

Avastin (Botrel et al., 2011), with 6 data points) and an analysis of weighted linear regression based on 18 Observations adding 12 Clinical Studies in Advanced NSCLC (Blumenthal et al., 2015) to the previous data points), the pre-defined upper equivalence margin of a 13% margin corresponded to estimated PFS < 3 months. With the third analysis of weighted linear regression based on 16 Observations excluding the results of SB8-G31-NSCLC, a 13% margin corresponded to 3.01-month estimated PFS. The 95% bootstrap CI for the difference in median PFS between the SB8 and EU Avastin treatment groups was calculated as [−1.5, 2.0] months.

<u>Analysis of ORR at cycle 6 regardless of study period</u>

Analysis of ORR at cycle 6 regardless of study period with imputed missing values was presented, similar to the imputation method requested for the primary endpoint. The number of patients with non-responder imputation was comparable between treatment arms. Slightly more patients discontinued the study for primary reasons other than death or disease progression without any tumour assessment with SB8 (12.8% vs. 9.1%), multiple imputation was used for these patients, as requested. ORR at Cycle 6 regardless of study period results in a difference of 4.8% [95% CI: –2.8%, 12.3%] between treatment arms for the PPS. For the FAS the difference in ORR at Cycle 6 regardless of study period were 4.9% [95% CI: –2.0%, 11.9%]. These analysis results are within the pre-defined equivalence margin of 12.5% in contrast to ORR at Cycle 6 in the induction period.

Table 28: Difference in overall response rate at Cycle 6 regardless of study period (Per-protocol set, study SB8-G31- NSCLC) (*Ad-hoc* analysis)

Parameter	SB8 N=337	EU Avastin® N=328
ORR at Cycle 6 regardless of study period		
CR+PR [n(%)][a]	152 (45.0%)	132 (40.3%)
Difference of ORR		
Difference (SB8 – Avastin®)	4.8%	
95% CI	[–2.8%, 12.3%][b]	

CI = confidence interval; CR = complete response; N = number of patients in the Per-protocol Set (PPS); n = number of patients; ORR = overall response rate; PR = partial response
Percentages were based on the number of patients in the PPS.
[a] The ORR at Cycle 6 was defined as the proportion of patients whose overall response was either CR or PR according to RECIST v1.1 at Cycle 6.
[b] Represent the confidence interval was fully within the equivalence margin [–12.5%, 12.5%].
Missing data from patients who withdrew the study due to death or disease progression without any tumor assessment were considered as non-responders.
Missing data from patients who withdrew the study with reasons other than death and disease progression, without any tumor assessment, were imputed using the multiple imputation method.
Difference and 95% CI were estimated by the binomial regression model with treatment group as an explanatory variable.

<u>Analysis of primary endpoint assessed by Investigators:</u>

In addition tumour lesions were assessed by investigators whose results strongly differ from the independent central review.

Table 29: Analysis of difference in best overall response rate during induction treatment period by 24 weeks by investigators

Analysis Set	Treatment	n	(%)	Difference	95% CI
FAS	SB8 (N = 379)	177	(46.8)	-3.6%	[-10.7%, 3.5%]
	Avastin® (N =383)	193	(50.4)		
PPS	SB8 (N = 337)	159	(47.2)	-0.7%	[-8.3%, 6.9%]
	Avastin® (N = 328)	157	(47.9)		

CI = confidence interval; FAS = Full analysis set; PPS = Per-protocol set; N = number of subjects in analysis set; n = number of subjects.
The best ORR was defined as the proportion of subjects whose best overall response was either complete response or partial response according to RECIST v1.1 during the induction treatment period by 24 weeks.
Missing data from subjects who withdrew the study due to disease progression and Adverse Events (AEs) without any tumour assessment were considered as non-responder for the FAS.
Missing data from subjects who withdrew the study with reasons other than disease progression and AEs and remained in the study, without any tumour assessment were imputed using multiple imputation method for the FAS.
Source: Table 14.2-4.2.1 and Table 14.2-4.2.2

Table 30: Summary of concordance between central review and investigator review for best overall response during the induction treatment period by 24 weeks (RECIST 1.1) - (Full analysis set, study SB8-G31-NSCLC)

Treatment	Independent Central Review	Investigator Review		Concordance Rate
		Response, n (%)	No Response, n (%)	
SB8	Response, n (%)	**131 (34.7)**	41 (10.8)	79.1%
	No response, n (%)	38 (10.1)	**168 (44.4)**	
EU Avastin®	Response, n (%)	**119 (31.2)**	33 (8.6)	75.5%
	No response, n (%)	60 (15.7)	**170 (44.5)**	

Response: Patient with a best overall response during induction treatment period by 24 weeks of either complete response (CR) or partial response (PR) at least once.
No response: Patient without a best overall response during induction treatment period by 24 weeks of either CR or PR.
Two patients were excluded from the calculation of concordance since one (patient from EU Avastin®) assessment did not belong to the induction period and the other (patient from SB8) had no best ORR due to the absence of target lesion at baseline by central review.
Concordance rate = (Number of agreed assessments by both reviewers)/(Total number of assessments for both reviewers) × 100

The applicant performed an ad-hoc sensitivity analysis to explore the robustness of the primary efficacy result by imputing the results of the patients who stop due to PD, but got evaluated as SD by central review as responders (except at cycle 6). This concerned almost equally as many patients in the SB8 as in the EU Avastin group (11/12 patients in the FAS and 10/10 in the PPS).

Table 31: Sensitivity analysis of difference in best overall response rate during the induction period by 24 weeks (RECIST 1.1) – Responder imputation for 20 identified patients – Central review (Per-protocol set, study SB8-G31- NSCLC)

Parameter	SB8 N=337	EU Avastin® N=328
Best Overall Response Rate (Best ORR)		
CR+PR [n (%)]	179 (53.1%)	157 (47.9%)
95% CI within treatment group	[47.6%, 58.5%]	[42.3%, 53.4%]
Difference of Best ORR		
Difference (SB8 – EU Avastin®)	5.2%	
95% CI	[–2.3%, 12.8%]	

CI = confidence interval; CR = complete response; ORR = overall response rate; PR = partial response
The best ORR was defined as the proportion of subjects whose best overall response was either CR or PR according to RECIST v1.1 during the induction treatment period by 24 weeks.
A total of 20 identified patients were considered as responder
Difference and 95% CI were estimated by the binomial regression model with treatment group as an explanatory variable.

The percentage of non-evaluable lesions (NE) was higher in the central review compared to the local investigator based tumour evaluation. The number of unevaluable lesions differed especially in the reference arm (15% NE by central review and 8.6% by local review). Patients with non-evaluable (NE) lesions continued to receive study treatment.

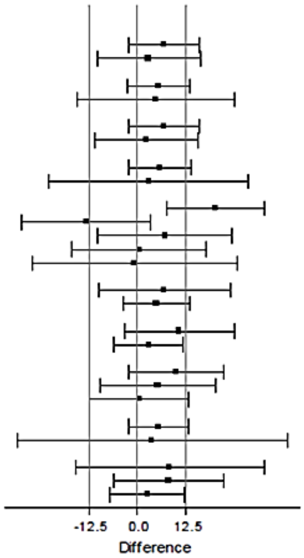
Further post hoc analyses

<u>Subgroup Analyses of the Primary Efficacy Variables by Demographics</u>

Overall there were no relevant differences between the two treatment groups, with exception of the Russian population, where a difference in Best ORR of 20.1% [7.5%, 32.7%] was observed (SB8-Avastin).

The Applicant further investigated reasons for the difference. Russian patients in the SB8 group were slightly younger (90.8% versus 90.0% age <70 years) and included more women (31.1% versus 30.9%) than in the SB8 subgroup. This could have been a contributing factor.

Subgroup	SB8 Events/N (%)		Avastin Events/N (%)		Difference (95% CI)
Age Group 1					
< 65 years	121/226	(53.5%)	107/229	(46.7%)	6.8% [-2.4%, 16.0%]
≥ 65 years	48/111	(43.2%)	40/ 99	(40.4%)	2.8% [-10.5%, 16.2%]
Age Group 2					
< 70 years	149/291	(51.2%)	130/284	(45.8%)	5.4% [-2.7%, 13.6%]
≥ 70 years	20/ 46	(43.5%)	17/ 44	(38.6%)	4.8% [-15.5%, 25.1%]
Gender					
Male	112/227	(49.3%)	94/221	(42.5%)	6.8% [-2.4%, 16.0%]
Female	57/110	(51.8%)	53/107	(49.5%)	2.3% [-11.0%, 15.6%]
Race					
White	154/311	(49.5%)	130/297	(43.8%)	5.7% [-2.2%, 13.7%]
Other	15/ 26	(57.7%)	17/ 31	(54.8%)	2.9% [-23.0%, 28.7%]
Country					
Russia	65/119	(54.6%)	38/110	(34.5%)	20.1% [7.5%, 32.7%]
Ukraine	28/ 68	(41.2%)	37/ 68	(54.4%)	-13.2% [-29.9%, 3.4%]
Georgia, Hungary, Spain, Germany	25/ 61	(41.0%)	20/ 59	(33.9%)	7.1% [-10.2%, 24.4%]
Belarus, Romania, Serbia, Poland	37/ 64	(57.8%)	35/ 61	(57.4%)	0.4% [-16.9%, 17.8%]
Korea, Thailand, Taiwan	14/ 25	(56.0%)	17/ 30	(56.7%)	-0.7% [-27.0%, 25.7%]
Region					
EU	34/ 67	(50.7%)	28/ 64	(43.8%)	7.0% [-10.1%, 24.1%]
Non-EU	135/270	(50.0%)	119/264	(45.1%)	4.9% [-3.5%, 13.4%]
ECOG Performance Status					
0	59/ 98	(60.2%)	44/ 89	(49.4%)	10.8% [-3.4%, 25.0%]
1	110/239	(46.0%)	103/239	(43.1%)	2.9% [-6.0%, 11.8%]*
Smoking Status					
Never smoked	66/126	(52.4%)	56/132	(42.4%)	10.0% [-2.2%, 22.1%]
Former smoker	43/ 91	(47.3%)	34/ 81	(42.0%)	5.3% [-9.6%, 20.1%]
Current smoker	60/120	(50.0%)	57/115	(49.6%)	0.4% [-12.4%, 13.2%]
Cancer Type					
Adenocarcinoma	162/324	(50.0%)	137/308	(44.5%)	5.5% [-2.3%, 13.3%]
Other	7/ 13	(53.8%)	10/ 20	(50.0%)	3.8% [-31.0%, 38.7%]
Distant Metastasis					
M0	23/ 36	(63.9%)	15/ 27	(55.6%)	8.3% [-16.1%, 32.8%]
M1a	57/103	(55.3%)	42/ 89	(47.2%)	8.1% [-6.0%, 22.3%]
M1b	89/198	(44.9%)	90/212	(42.5%)	2.5% [-7.1%, 12.1%]*



The best overall response rate (ORR) was defined as the proportion of patients whose best overall response was either complete response (CR) or partial response (PR) according to RECIST v1.1 during the induction treatment period by 24 weeks.
Difference and 95% confidence interval were estimated by the binomial regression model with treatment group as an explanatory variable.
* Represent the confidence interval was fully within the equivalence margin [−12.5%, 12.5%].

Figure 5: Forest plot for subgroup analysis of difference in best overall response rate during induction treatment period by 24 weeks (Per-protocol set, study SB8-G31- NSCLC)

<u>Maximum change in tumour burden from baseline</u>

The mean of the maximum percentage change from baseline in tumour burden by 24 weeks of chemotherapy was −27.8% for the SB8 treatment group and −27.3% for EU Avastin treatment group. The difference between the two treatment groups was 0.6% with the 95% CI of [−4.18%, 2.99%].

Results were comparable by w11 and w17: Differences were 0.5% and 0.7%, respectively.

ORR at different cycles

Table 32: Analysis of overall response at Cycle 2 of the induction treatment period (RECIST v1.1) – Central review (Per-protocol set, study SB8-G31- NSCLC)

Parameter	SB8 N=337 n (%)	EU Avastin® N=328 n (%)
At Cycle 2		
Responder Rate (CR+PR of overall response)		
CR+PR [n (%)]	96 (28.5)	88 (26.8)
Difference in Best ORR		
Difference (SB8 - EU Avastin®)	1.7%	
95% CI	[−5.1%, 8.5%]	

CI = confidence interval; N = number of patients in Per-protocol Set with available assessments at each time point; n = number of patients; Percentages were based on N. The responder rate was defined as the proportion of patients whose overall response was either complete response (CR) or partial response (PR) according to RECIST v1.1 during the induction treatment period at each cycle. Difference and the 95% CI were estimated using a binomial regression model with treatment group as an explanatory variable.

Table 33: Analysis of overall response at Cycle 4 of the induction treatment period (RECIST v1.1) – Central review (Per-protocol set, study SB8-G31- NSCLC)

Parameter	SB8 N=280 n (%)	EU Avastin® N=276 n (%)
At Cycle 4		
Responder Rate (CR+PR of overall response)		
CR+PR [n (%)]	137 (48.9)	126 (45.7)
Difference in Best ORR		
Difference (SB8 - EU Avastin®)	3.3%	
95% CI	[−5.0%, 11.6%]	

CI = confidence interval; N = number of patients in Per-protocol Set with available assessments at each time point; n = number of patients; Percentages were based on N. The responder rate was defined as the proportion of patients whose overall response was either complete response (CR) or partial response (PR) according to RECIST v1.1 during the induction treatment period at each cycle. Difference and the 95% CI were estimated using a binomial regression model with treatment group as an explanatory variable.

Table 34: Analysis of overall response at Cycle 6 of the induction treatment period (RECIST v1.1) – Central review (Per-protocol set, study SB8-G31- NSCLC)

Parameter	SB8 N=170 n (%)	EU Avastin® N=168 n (%)
At Cycle 6		
Responder Rate (CR+PR of overall response)		
CR+PR [n (%)]	97 (57.1)	84 (50.0)
Difference in Best ORR		
Difference (SB8 - EU Avastin®)	7.1	
95% CI	[−3.5%, 17.7%]	

CI = confidence interval; N = number of patients in Per-protocol Set with available assessments at each time point; n = number of patients; Percentages were based on N. The responder rate was defined as the proportion of patients whose overall response was either complete response (CR) or partial response (PR) according to RECIST v1.1 during the induction treatment period at each cycle. Difference and the 95% CI were estimated using a binomial regression model with treatment group as an explanatory variable.

The Applicant provided *ad-hoc* analyses for overall response rate (ORR) at Cycle 2 and Cycle 4 with the same imputation method asked for the *ad-hoc* analysis of ORR at Cycle 6. For these ad-hoc analyses, multiple imputation for datasets with monotone missing patterns was first performed and subsequently, non-responder imputation was performed for patients whose primary discontinuation reason was death or progressive disease. Treatment group (SB8, EU Avastin), age group (< 70 years, ≥ 70 years), sex (male, female), and tumour measurements of overall response at Cycle 2 (for ad-hoc analysis at Cycle 4 only) were included as important predictor variables in the multiple imputation model. Multiple imputation was performed separately for each treatment group using logistic regression model.

The *ad-hoc* analysis of ORR at Cycle 2 in the induction period was performed for the PPS after imputation for patients without tumour measurements for overall response at Cycle 2 during the induction period (see Table 35). The 95% CI included zero, indicating no statistically significant difference between the two treatment groups. These results were also consistent with the difference [95% CI] in ORR at Cycle 2 in the induction period (1.7% [−5.1%, 8.5%]) in patients with available assessments (no imputation) at this time point (see Table 32). Results were similar for the FAS.

Table 35: Analysis of difference in overall response rate at Cycle 2 in the induction period (Per-protocol set, study SB8-G31- NSCLC) (*Ad-hoc* analysis)

Parameter	SB8 N=337	EU Avastin® N=328
ORR at Cycle 2 in the induction Period		
CR+PR [n(%)][a]	98 (29.1%)	89 (27.2%)
Difference of ORR		
Difference (SB8 – Avastin®)	1.9%	
95% CI	[–4.9%, 8.7%][b]	

CI = confidence interval; CR = complete response; N = number of patients in the Per-protocol Set (PPS); n = number of patients; ORR = overall response rate; PR = partial response
Percentages were based on the number of patients in the PPS.
[a] The ORR at Cycle 2 in the induction period was defined as the proportion of subjects whose overall response was either CR or PR according to RECIST v1.1 at Cycle 2 in induction period.
[b] Represent the confidence interval was fully within the equivalence margin [–12.5%, 12.5%].
Missing data from patients who withdrew the study with reasons other than death or disease progression without any tumor assessment were imputed using multiple imputation method.
Missing data from patients who withdrew the study due to death or disease progression without any tumor assessment were considered as non-responder.

Table 36: Analysis of difference in overall response rate at Cycle 4 in the induction period (Per-protocol set, study SB8-G31- NSCLC) (*Ad-hoc* analysis)

Parameter	SB8 N=337	EU Avastin® N=328
ORR at Cycle 4 in the induction Period		
CR+PR [n(%)][a]	150 (44.5%)	134 (41.0%)
Difference of ORR		
Difference (SB8 – Avastin®)	3.5%	
95% CI	[–4.0%, 11.0%][b]	

CI = confidence interval; CR = complete response; N = number of patients in the Per-protocol Set (PPS); n = number of patients; ORR = overall response rate; PR = partial response
Percentages were based on the number of patients in the PPS.
[a] The ORR at Cycle 4 in the induction period was defined as the proportion of subjects whose overall response was either CR or PR according to RECIST v1.1 at Cycle 4 in induction period.
[b] Represent the confidence interval was fully within the equivalence margin [–12.5%, 12.5%].
Missing data from patients who withdrew the study with reasons other than death and disease progression without any tumor assessment were imputed using multiple imputation method.
Missing data from patients who withdrew the study due to death and disease progression without any tumor assessment were considered as non-responder.

Table 37: Difference in overall response rate at Cycle 4 in the induction period (Full analysis set, study SB8-G31- NSCLC) (*Ad-hoc* analysis)

Parameter	SB8 N=379	EU Avastin® N=383
ORR at Cycle 4 in the induction Period		
CR+PR [n(%)][a]	159 (41.9%)	143 (37.2%)
Difference of ORR		
Difference (SB8 – Avastin®)	4.7%	
95% CI	[–2.2%, 11.6%][b]	

CI = confidence interval; CR = complete response; N = number of patients in the Full Analysis Set (FAS); n = number of patients; ORR = overall response rate; PR = partial response
Percentages were based on the number of patients in the FAS.
[a] The ORR at Cycle 4 in the induction period was defined as the proportion of subjects whose overall response was either CR or PR according to RECIST v1.1 at Cycle 4 in induction period.
[b] Represent the confidence interval was fully within the equivalence margin [–12.5%, 12.5%].
Missing data from patients who withdrew the study with reasons other than death and disease progression without any tumor assessment were imputed using multiple imputation method.
Missing data from patients who withdrew the study due to death and disease progression without any tumor assessment were considered as non-responder.

The 95% CI included zero, indicating no statistically significant difference between the two treatment groups. These results were also consistent with the difference [95% CI] in ORR at Cycle 4 in the induction period (3.3% [−5.0%, 11.6%]) in patients with available assessment (no imputation) at this time point.

In addition to the primary analysis being performed on the imputed data for ORR, the Applicant performed a Mixed-effect Model for Repeated Measures (MMRM) for treatment differences in terms of the continuous endpoint changes in tumour burden from baseline to post-baseline.

Table 38: Analysis of mixed-effect model for repeated measures in Induction period (Full analysis set – Multiple imputation, study SB8-G31-NSCLC) (Ad-hoc analysis)

				Difference, (mm) (SB8–EU Avastin®)	
Treatment	N	n	LSMean (SE)	Estimate	95% CI
SB8	379	379	61.7 (1.18)	–1.84	–4.566; 0.885
EU Avastin®	383	383	63.5 (1.19)		

CI = confidence interval; LSMean = least squares mean; N = number of patients in the Full Analysis Set; n = number of patients with available assessment results at baseline; SE = standard error
Missing values for the sum of diameters of target lesions at each visit for the induction period were imputed using a multiple imputation method.
Difference and 95% CI were estimated by the MMRM model with the covariates of age group ([< 70, ≥ 70], sex [male, female]), time, time by treatment interaction, baseline of sum of diameter and treatment group. Time included Cycle 2, Cycle 4 and Cycle 6 for the induction period.

Table 39: Analysis of mixed-effect model for repeated measures in Maintenance period (Full analysis set – Multiple imputation, study SB8-G31-NSCLC) (Ad-hoc analysis)

				Difference, (mm) (SB8–EU Avastin®)	
Treatment	N	n	LSMean (SE)	Estimate	95% CI
SB8	379	379	65.5 (1.37)	–1.52	–4.826; 1.794
EU Avastin®	383	383	67.0 (1.38)		

CI = confidence interval; LSMean = least squares mean; N = number of patients in the Full Analysis Set; n = number of patients with available assessment results at baseline; SE = standard error
Missing values for the sum of diameters of target lesions at each visit for the maintenance period were imputed using a multiple imputation method.
Difference and 95% CI were estimated by the MMRM model with the covariates of age group ([< 70, ≥ 70], sex [male, female]), time, time by treatment interaction, baseline of sum of diameter and treatment group. Time included Cycle 6, Cycle 10, Cycle 14, Cycle 18, Cycle 22, Cycle 26 and Cycle 30 for the maintenance period.

The adjusted difference [95% CI] in change of tumour burden from baseline during the whole period was –1.96 [95% CI: –5.804, 1.891]. None of these differences were significant and all point estimates pointed to a higher change of tumour burden from baseline in the Avastin group compared to the SB8 group.

Difference in best ORR adjusted by the subcategory of distant metastasis

The site of metastases and lymph node involvement were reported to play a crucial role in predicting the treatment outcome in advanced NSCLC (Eberhardt et al., 2015; Lim et al., 2018; Gress et al., 2017). The ad-hoc sensitivity analysis of the difference in best ORR adjusted by the subcategory of distant metastasis showed an adjusted difference of 4.7%, with the two-sided 95%CI of [−2.9%, 12.2%], which was entirely contained within the pre-defined equivalence margin of [−12.5%, 12.5%].

Subgroup analyses for each distant metastasis subcategory were performed in addition.

Table 40: Subgroup analysis of difference in Best Overall Response rate in induction period by 24 weeks (RECIST 1.1) – central review (Per-protocol set, study SB8-G31-NSCLC) (Ad-hoc analysis)

		SB8 N = 337	EU Avastin® N = 328
Subgroup: M0	Number of Patients	36	27
Best ORR[a]	CR+PR [n (%)]	23 (63.9%)	15 (55.6%)
	95% CI within group	[46.2%, 79.2%]	[35.3%, 74.5%]
Difference of Best ORR	Difference (SB8 - Avastin)	8.3%	
	95% CI	[−16.1%, 32.8%]	
Subgroup: M1a	Number of Patients	103	89
Best ORR[a]	CR+PR [n (%)]	57 (55.3%)	42 (47.2%)
	95% CI within group	[45.2%, 65.1%]	[36.5%, 58.1%]
Difference of Best ORR	Difference (SB8 - Avastin)	8.1%	
	95% CI	[−6.0%, 22.3%]	
Subgroup: M1b	Number of Patients	198	212
Best ORR[a]	CR+PR [n (%)]	89 (44.9%)	90 (42.5%)
	95% CI within group	[37.9%, 52.2%]	[35.7%, 49.4%]
Difference of Best ORR	Difference (SB8 - Avastin)	2.5%	
	95% CI	[−7.1%, 12.1%]	

CI = confidence interval; CR = complete response; N = number of patients in the Per-protocol Set (PPS); n = number of patients; Percentages were based on the number of patients in the respective subgroup; PR = partial response

[a] The best overall response rate (ORR) was defined as the proportion of subjects whose best overall response was either complete response (CR) or partial response (PR) according to RECIST v1.1 during the induction treatment period by 24 weeks.

Difference and 95% confidence interval (CI) were estimated by the binomial regression model with treatment group as an explanatory variable.

Post-hoc analysis of response patterns in the induction period

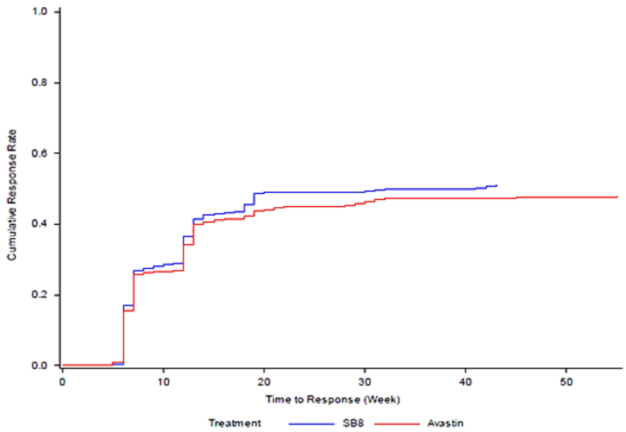
The number of patients with each possible response pattern has been provided per treatment arm for the induction period.

Table 41: Each possible response pattern in the induction period by treatment group (Per-protocol set, study SB8-G31-NSCLC) (Ad-hoc analysis)

Pattern	SB8 N=337		EU Avastin® N=328		Total N=665	
	n	%	n	%	n	%
PR-CR-CR	0	(0.0)	1	(0.3)	1	(0.2)
PR-PR-PR	50	(14.8)	44	(13.4)	94	(14.1)
PR-PR-PD	1	(0.3)	0	(0.0)	1	(0.2)
PR-PR	35	(10.4)	33	(10.1)	68	(10.2)
PR-SD	0	(0.0)	1	(0.3)	1	(0.2)
PR-PD-SD	0	(0.0)	1	(0.3)	1	(0.2)
PR-PD	2	(0.6)	0	(0.0)	2	(0.3)
PR	8	(2.4)	8	(2.4)	16	(2.4)
SD-PR-PR	30	(8.9)	28	(8.5)	58	(8.7)
SD-PR-SD	0	(0.0)	1	(0.3)	1	(0.2)
SD-PR-PD	0	(0.0)	1	(0.3)	1	(0.2)
SD-PR	20	(5.9)	15	(4.6)	35	(5.3)
SD-SD-PR	17	(5.0)	9	(2.7)	26	(3.9)
SD-SD-SD	60	(17.8)	68	(20.7)	128	(19.2)
SD-SD-PD	3	(0.9)	6	(1.8)	9	(1.4)
SD-SD	39	(11.6)	41	(12.5)	80	(12.0)
SD-PD-PD	3	(0.9)	4	(1.2)	7	(1.1)
SD-PD	5	(1.5)	8	(2.4)	13	(2.0)
SD-NE	1	(0.3)	0	(0.0)	1	(0.2)
SD	24	(7.1)	20	(6.1)	44	(6.6)
PD-SD-SD	0	(0.0)	1	(0.3)	1	(0.2)
PD-PD-PD	5	(1.5)	3	(0.9)	8	(1.2)
PD-PD	7	(2.1)	5	(1.5)	12	(1.8)
PD	13	(3.9)	12	(3.7)	25	(3.8)
NE-PR-PR	0	(0.0)	2	(0.6)	2	(0.3)
NE-PR-PD	1	(0.3)	0	(0.0)	1	(0.2)
NE-PR	0	(0.0)	1	(0.3)	1	(0.2)
NE-SD	0	(0.0)	1	(0.3)	1	(0.2)
NE-NE	1	(0.3)	2	(0.6)	3	(0.5)
NE	12	(3.6)	12	(3.7)	24	(3.6)

CR = complete response; N=number of patients in the Per-protocol Set; n=number of patients; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease ;
Overall response was reported as last tumor assessments including values of unscheduled in each cycle.
Percentages were based on N.

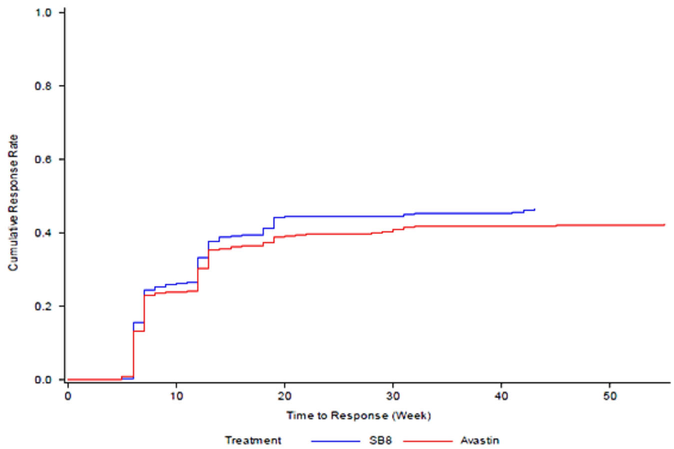
Response rate-time curves of best ORR for both the FAS and the PPS considering both responders and non-responders were presented upon request.



Time to response only for the last tumor assessment was considered, and response rates were based on available cases.
Time to response (weeks) were calculated by integer value of (date of tumor assessment - date of randomization + 1)/7

In the PPS, cumulative response of the SB8 treatment group = 0.5104; cumulative response of the EU Avastin® treatment group = 0.4787.

Figure 6: Response rate-Time curve for the responders and non-responder – central review (Per-protocol set, study SB8-G31-NSCLC) (*Ad-hoc* analysis)



Time to response only for the last tumor assessment was considered, and response rates were based on available cases.
Time to response (weeks) were calculated by integer value of (date of tumor assessment - date of randomization + 1)/7
In the FAS, cumulative response of the SB8 treatment group = 0.4644; cumulative response of the EU Avastin® treatment group = 0.4230.

Figure 7: Response rate-Time curve for the responders and non-responder – central review (Full analysis set, study SB8-G31-NSCLC) (*Ad-hoc* analysis)

Table 42: Comparison of cumulative response rate – central review (per-protocol set, study SB8-G31-NSCLC) (*Ad-hoc* analysis)

	Responder + Non-Responder		
	SB8 (N=337)	EU Avastin® (N=328)	
Week Duration	Cumulative Response Rate	Cumulative Response Rate	*P*-Value
≤ 10 weeks	0.2849	0.2652	0.5711
≤ 20 weeks	0.4896	0.4421	0.2192
≤ 30 weeks	0.4926	0.4634	0.4516
≤ 40 weeks	0.4985	0.4726	0.5032
≤ 50 weeks	0.5104	0.4756	0.3698
≤ 60 weeks	NA[a]	0.4787	NA[a]
Overall	0.5104	0.4787	0.4133

N = the number of patients in the Per-protocol Set
Time to response only for the last tumor assessment is considered, and response rate is based on available cases.
Time to response (weeks) were calculated by integer value of (date of tumor assessment - date of randomization + 1)/7.
P-value was estimated based on Chi-square test.
[a] The maximum of time to response in SB8 treatment group are within ≤ 50 weeks. Thus, it is not applicable for the analysis in this week duration.

<u>Ad-hoc analysis of PFS and OS using a Cox regression model on PPS</u>

Event rates for PFS were similar between SB8 and Avastin. Regarding OS, 152 (45.1%) patients and 146 (44.5%) patients in the SB8 and EU Avastin treatment groups, respectively experienced the events.

The 6-month, 12-month, and 24-month PFS rates and the corresponding 95% CIs were similar for PFS and OS.

The HR of PFS and the corresponding 95% CI was 1.01 [0.84, 1.22]. The HR of death and the corresponding 95% CI was 1.08 [0.86, 1.35].

<u>Ad-hoc analysis of DOR</u>

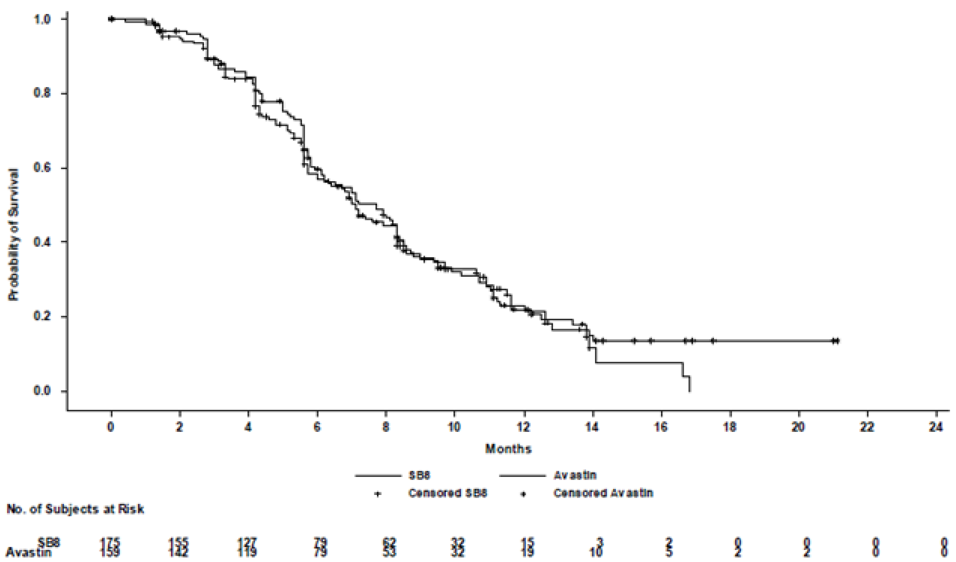


Figure 8: Kaplan-Meier plot for duration of response – central review (per-protocol set, study SB8-G31-NSCLC) (Ad-hoc analysis)

The median [95% CI] DOR was 7.70 [6.00, 8.30] in the SB8 treatment group and 7.10 [6.10, 8.30] in the EU Avastin treatment group in the PPS (Figure 8 and Table 43).

Table 43: Analysis of duration of response using Kaplan-Meier method – central review (per-protocol set, study SB8-G31-NSCLC) (Ad-hoc analysis)

Parameter	SB8 N=337	EU Avastin® N=328	Total N=665
Duration of Response (DOR), n (%)	175 (51.9%)	159 (48.5%)	334 (50.2%)
Patients with events, n (%)	112 (33.2%)	106 (32.3%)	218 (32.8%)
Disease Progression, n (%)	80 (23.7%)	78 (23.8%)	158 (23.8%)
Death, n (%)	32 (9.5%)	28 (8.5%)	60 (9.0%)
Patients censored, n (%)	63 (18.7%)	53 (16.2%)	116 (17.4%)
Kaplan-Meier Estimates [95% CI]			
2 months	0.95 [0.91, 0.98]	0.97 [0.93, 0.99]	0.96 [0.93, 0.98]
4 months	0.84 [0.77, 0.89]	0.84 [0.77, 0.89]	0.84 [0.79, 0.88]
6 months	0.59 [0.50, 0.66]	0.60 [0.51, 0.67]	0.59 [0.53, 0.64]
8 months	0.47 [0.39, 0.55]	0.45 [0.36, 0.53]	0.46 [0.40, 0.52]
10 months	0.33 [0.25, 0.41]	0.32 [0.24, 0.40]	0.32 [0.27, 0.38]
12 months	0.23 [0.15, 0.31]	0.22 [0.15, 0.30]	0.22 [0.17, 0.28]
14 months	0.12 [0.05, 0.21]	0.15 [0.09, 0.23]	0.14 [0.09, 0.19]
16 months	0.08 [0.02, 0.18]	0.13 [0.07, 0.21]	0.12 [0.07, 0.17]
18 months	NA	0.13 [0.07, 0.21]	0.08 [0.03, 0.15]
20 months	NA	0.13 [0.07, 0.21]	0.08 [0.03, 0.15]
22 months	NA	0.13 [0.07, 0.21]	0.08 [0.03, 0.15]
24 months	NA	NA	NA
Median DOR (months) [95% CI]	7.70 [6.00, 8.30]	7.10 [6.10, 8.30]	7.10 [6.30, 8.30]
25th and 75th percentile	4.30; 11.60	5.00; 11.30	4.80; 11.30
Min; Max	0.00; 16.80	0.00; 21.10	0.00; 21.10

CI = confidence interval; DOR = duration of response; Max = maximum; Min = minimum; NA = not available; N = number of patients in the Per-protocol Set (PPS); n = number of patients
Percentages were based on the number of patients in the PPS.
All estimate, including 25th percentile, median, 75th percentile, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 months DOR rate and their corresponding 95% CI were calculated using Kaplan-Meier method.

Upon request, the applicant presented the study discontinuation reasons per treatment group and in total for the patients who are responders, but nevertheless leave the study without PD or death being observed (discontinuation due to AE was similar but erroneously stated as 1.1% with SB8):

Table 44: Summary of discontinuation reason for censored patients in duration of response – central review (per-protocol set, study SB8-G31-NSCLC) (Ad-hoc analysis)

	SB8 N=337 n (%)	EU Avastin® N=328 n (%)
Censored Patients in Duration of Response (DOR)	63 (18.7%)	53 (16.2%)
Withdrawal by subject	7 (11.1%)	8 (15.1%)
End of study	12 (19.0%)	13 (24.5%)
Adverse event	7 (1.1%)	7 (13.2%)
Lost to follow-up	0 (0.0%)	1 (1.9%)
Pregnancy	0 (0.0%)	0 (0.0%)
Progressive disease	31 (49.2%)	21 (39.6%)
Non-compliance with study treatment	2 (3.2%)	0 (0.0%)
Death	NA	NA
Other	4 (6.3%)	3 (5.7%)

DOR = duration of response; NA = Not Applicable; N = number of patients in the Per-protocol Set (PPS); n = number of patients; PD = disease progression; Percentages were based on the number of patients in the PPS.

The censoring reasons 'new anticancer treatment without documented PD', 'treatment discontinuation for undocumented PD' and 'no post- baseline tumor assessment' were classified as informative censoring. The treatment groups were comparable concerning the percentage of informative and non-informative censoring in the FAS and the PPS.

Table 45: Summary of non-informative censoring and informative censoring for the duration of response – central review (per-protocol set, study SB8-G31-NSCLC) (*Ad-hoc* analysis)

	SB8 N=337 n (%)	EU Avastin® N=328 n (%)
Patients with DOR censored	63 (18.7%)	53 (16.2%)
Informative Censoring[a]	40 (11.9%)	27 (8.2%)
Non-informative Censoring	23 (6.8%)	26 (7.9%)

[a] If patient had both 'Informative Censoring' and 'Non-informative Censoring', censoring cases, the patient was considered as 'Informative Censoring'.
Informative Censoring Cases: 'New anticancer treatment started without documented PD' or 'Treatment discontinuation for undocumented PD'; Non-informative Censoring Cases: 'No PD' or 'Treatment discontinuation for toxicity or other reason'; Percentages were based on the Per-protocol Set.

A Therneau-Grambsch nonproportionality test for the Cox model for PFS, OS, and DOR showed, that the proportional hazard assumption of the Cox regression model was not violated. The effect of treatment on PFS and DOR seems to increase with time from around Month 10 onwards whereas the effect of treatment on OS rather seems to decrease.

Ad-hoc Sensitivity Analysis to Assess the Impact of Key Quality Attributes Related to Efficacy of Bevacizumab on the Observed Difference in Best ORR

The observed difference in best ORR was assessed from the quality perspective to investigate whether any quality attributes may have any impact on treatment outcome. Among the quality attributes assessed for the development of SB8, the quality attributes in relation to the efficacy of bevacizumab were selected as covariates.

To assess the impact of these quality attributes on the observed difference in best ORR, the sensitivity analysis was performed in the PPS, using the binomial model with the covariates of each selected quality attribute, treatment, and its interaction term by treatment. The sensitivity analysis was summarized as the effect estimates with p-value based on the Wald test (alpha level of 0.05).

Individual values of all 7 SB8 batches used during the induction treatment period were used for the ad-hoc analysis. Of 14 EU Avastin lots used during the induction treatment period, 5 lots could not be characterized. For HUVEC anti-proliferation, VEGF-A 165 binding, VEGF neutralization, and FcRn binding assay, the missing values were imputed using a median from the individual values of the other

9 EU Avastin lots. For protein concentration, the values for 4 EU Avastin lots were from the Certificate of Analysis (CoA), and the remaining one lot was imputed using the median.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 46: Summary of Efficacy for Study SB8-G31-NSCLC

Title: A Phase III, Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB8 (proposed bevacizumab biosimilar) and Avastin in Subjects with Metastatic or Recurrent Non-squamous Non-small Cell Lung Cancer			
Study identifier	EudraCT number: 2015-004026-34 Protocol Number: SB8-G31-NSCLC		
Design	Randomised, double blind, parallel group, multicentre study		
	Duration of induction period:		4 up to 6 cycles a 3-6 weeks
	Duration of maintenance period:		From end of induction period to EOS
			(12 months from random. of last patient
Hypothesis	Equivalence		
Treatments groups	A (n=379 randomized)		SB8, IV infusion, 15 mg/kg Q3W (4-6 cycles) with IV carboplatin AUC of 6 and paclitaxel (200 mg/m^2) (4 – 6 cycles)
	B (n=384 randomized)		Avastin(EU), IV infusion, 15 mg/kg Q3W (4-6 cycles) with IV carboplatin AUC of 6 and paclitaxel (200 mg/m^2) (4 – 6 cycles)
Endpoints and definitions	Primary endpoint PP set	Difference in Best ORR by w24	proportion of subjects whose best overall response was either CR or PR according to RECIST v1.1 during the induction treatment period by 24 weeks
	Secondary endpoint	PFS	Progression free survival
	Secondary endpoint	OS	Overall survival
	Secondary endpoint	DOR	Duration of response
Interim database lock	May 02, 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Per Protocol set; PEP evaluation by w24, Sec. EP Evaluation by EOT/EOS		
Descriptive statistics and estimate variability	Treatment group	SB8	Avastin (EU)
	Number of patients	337	328
Primary endpoint	Best ORR	169 (50.1%)	147 (44.8%)
	Difference (95% CI)	5.3% (-2.2%, 12.9%)	
Secondary endpoint	PFS months (95% CI)	8.50 (7.20, 9.70)	7.90 (7.30, 9.40)
Secondary endpoint	Median OS months (95% CI)	14.80 (13.00, 17.00)	15.80 (13.80, 17.70)
Secondary endpoint	Mean DOR months (SD)	6.33 (3.784)	6.81 (4.177)

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

Not applicable.

Clinical studies in special populations

In study SB8-G31-NSCLC, 239 patients ≥ 65 years were included. 124 received SB8 and 115 received EU sourced Avastin, of these, 103 patients were ≥70 years.

Supportive study(ies)

Not applicable.

2.5.3. Discussion on clinical efficacy

Clinical efficacy comparison is based on a single active-controlled multicenter efficacy/safety study (SB8-G31-NSCLC) in NSCLC patients, an approved indication for Avastin (EU) as first line treatment for non-squamous NSCLC with carboplatin and paclitaxel.

The Applicant claimed all therapeutic indications currently authorised for the reference product EU Avastin with the exception of the treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel. A justification for extrapolation of indications (such as metastatic carcinoma of the colon or rectum, advanced/metastatic renal cell cancer, and persistent, recurrent, or metastatic cervical cancer) was provided by the Applicant, see section 3.5.

Design and conduct of clinical studies

In total 763 patients were 1:1 randomized to receive either SB8 or EU sourced Avastin. Age group (< 70 years vs ≥ 70 years) at randomisation and gender were used as stratification factors. The study was conducted in nearly 100 centers, including 80% patients from non-EU countries. A GCP inspection of the clinical study SB8-G31-NSCLC was performed at two investigator sites (located in Hungary and Russia) and the sponsor site (located in the Republic of Korea) in January and February 2020. No critical findings were observed at any of the inspection sites. The trial has been conducted according to GCP and ethical standards. The data obtained at the sites inspected are reliable and can be accepted as support of the marketing Authorisation Application.

The general study design was in line with previous scientific advice. Patients with metastatic or recurrent non-squamous NSCLC are considered appropriate to sensitively compare efficacy between Avastin and the proposed biosimilar candidate. The used treatment regimens for bevacizumab and chemotherapy was in line with the Avastin SmPC. In- and exclusion criteria are considered appropriate and known baseline demographic and disease characteristics were comparable. Randomisation was performed according to the stratification factors age and gender balancing for country.

Patients with known positive EGFR/ALK status were not randomized according to the exclusion criteria, but only about 30% of patients had known EGFR or ALK status, leaving a high percentage of randomized patients with unknown EGFR/ALK status. Testing for EGFR mutation and ALK gene translocations was not included in the screening phase, which does not comply with current standards, as genotyping is now routinely incorporated in many clinical settings. However, it was not yet standard in the planning phase of this study. Frequency of EGFR/ALK mutation testing showed remarkable differences between countries during SB8 clinical development. Patients with ALK rearrangements might be found among the subpopulation of unknown ALK status with a lower probability.

In the induction period patients received 15 mg/kg bevacizumab concurrently with PC chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC 6) by IV infusion on Day 1 of every 3-week cycle for at least 4 cycles and up to 6 cycles. Dose reduction with predefined dose levels, schedule modifications or cessation of chemotherapy was permitted for toxicity. Tumour measurements after every second cycle (until cycle 7) and every 4 cycles thereafter until EOT or EOS are acceptable. The first tumour measurement was after a median of 44 days (Cycle 3) and the second after a median of 86 days (Cycle 5). If eligible, patients received bevacizumab in the maintenance period every 3 weeks until disease progression, unacceptable toxicity, death, or end of study. Treatment was discontinued by disease progression, unacceptable toxicity, death, or last administration of the IP before the end of the study.

The number of cycles of the IP (Avastin/SB8) and non-IP (Paclitaxel/Carboplatin) as well as timing of cycles and duration of IP exposure was comparable between treatment groups in the FAS and PPS. Over 50% of patients in each treatment arm were treated for 6 cycles in the induction period.

Endpoints:

The primary endpoint was risk difference in best overall response rate in the PP set by w24 with a comparability range of 12.5% for the 95% CI of the difference. Secondary endpoints were PFS, OS and DOR. Further endpoints were best ORR by w11 and by w17.

- Best ORR maximizes the binary outcome and might be selected to reduce the confounding factors of variant cycles and delayed application due to AEs. Non-responder imputation or analysis of available data are often attractive because they are simple to implement but can easily produce invalid results in equivalence trials. ORR at w19 was prior recommended as primary endpoint in the scientific advice (EMA/CHMP/SAWP/85315/2015).
- A more conservative imputation method on all patients without tumour assessment was presented by the applicant upon request for the sensitive and clinically relevant endpoints "ORR at cycle 6 of the induction period" with non-responder imputation for patients discontinuing due to death or PD according to tumor assessment and multiple imputation for all other patients who discontinue the trial prior to week 24 (FAS and PPS). This analysis was requested with the same imputation for the primary endpoint "best ORR by w24" of the induction period. In addition this analysis was also requested for the endpoint "ORR at cycle 6 regardless of study period", as this treatment policy estimand ignores a change of the treatment period (induction/maintenance) within the observation period of the primary endpoint of 24 weeks, i.e. if concurrent chemotherapy was still applied. As patients will change to the maintenance phase prior to 24 weeks also in clinical practice, it reflects the comparison described in the ICH E9 Glossary (under Intention to Treat Principle) as the effect of a treatment policy.
- The applicant discussed the comparability margin of the primary endpoint and the observed 95% CI of the difference between SB8 and EU Avastin: According to a weighted linear regression analysis, a difference in 12.5% of best ORR corresponds to a change in PFS of 2.5 months whereas for a response rate of 13% an increase of 2.6 months can be achieved.

Efficacy data and additional analyses

The difference in best ORR by w24 was 5.3%, [-2.2%, 12.9%] for the PPS, the upper limit of the 95% CI slightly exceeding the pre-defined comparability margin of [-12.5%, 12.5%]. In the sensitivity analysis performed with the FAS, the difference was 4.8%, the 95% CI (-2.3%, 11.9%) being within the comparability margin. The risk ratio of best ORR including 90% CI, which was the primary endpoint for FDA filing, was also within the predefined comparability margin of [0.737, 1.357] in both, the FAS and PPS. The number of patients with disease progression (PD), complete response (CR) and partial response (PR) was similar between treatment arms.

The secondary endpoints and further analyses are largely in support of biosimilarity. The secondary endpoint median PFS was 8.5 [7.20, 9.70] vs. 7.9 [7.30, 9.40] months for SB8 and Avastin, respectively, HR 1.02. The median OS was 14.80 [13.00, 17.00] vs. 15.80 [13.80, 17.70] for SB8 and Avastin, respectively and a HR of 1.08. The PFS and OS rates of 6-month, 12 month (and 18 month in case of OS) were comparable. The Difference in DOR was 0.48 in favour of EU Avastin, but in contrast with the results of the primary endpoint. The requested post-hoc analysis with an alternative imputation method showed slightly higher result of DOR in the SB8 group, which is more consistent with the outcome of the primary analysis suggesting a slightly higher efficacy of SB8. An explanation is given for the difference to the median DOR from the original descriptive statistics where Avastin had an outcome of 5.90 months and SB8 of 5.60 months. The Kaplan Meier estimate of the median gives the number of months when the probability of survival is 0.5 and considers also censoring. Furthermore, endpoints of best ORR by w11 and w17 were similar, the 95% CI of the difference being within a ±12.5% margin.

The presented post-hoc analyses of ORR at cycle 2 and cycle 4 were comparable. Analyses of PFS and OS using a Cox regression model showed similar results as the initial analysis, in support of biosimilarity. In addition, the maximum change in tumour burden from baseline was investigated post-hoc, showing similar results between treatments. The mean of the maximum percentage change from baseline in tumour burden by 24 weeks of chemotherapy was −27.8% for SB8 and −27.3% for EU-sourced Avastin. The difference between the two treatment groups was small (0.6% [95% CI of −4.18%, 2.99%]). The ad-hoc sensitivity analysis of the difference in best ORR adjusted by the subcategory of distant metastasis showed an adjusted difference of 4.7%, with the two-sided 95%CI of [−2.9%, 12.2%], which was entirely contained within the pre-defined equivalence margin of [−12.5%, 12.5%].

In the forest plot of demographic subgroup analyses for best ORR at cycle 6 the point estimates for the difference in best ORR during induction period lied within the equivalence margins (except for the Russian subgroup), but mostly showed a higher efficacy of SB8 compared to Avastin. An in-depth investigation of the data indicated that the very slight differences between prognostic baseline characteristics, as age, gender or histological type of carcinoma could have some small influence on the higher observed response rate with SB8 compared to Avastin, but do not fully explain the higher difference in ORR of this subgroup. A chance finding can only be assumed, if all the other (at least known) factors were ruled out, which is plausible in this case.

The primary efficacy data were based on the independent central review (ICR) assessment, nevertheless results based on the investigator review assessment pointed to a slightly lower response rate of SB8 compared to EU Avastin. The discrepancy was explained by the applicant, that tumour assessments were conducted independently and vary between individual reviewers. Similarly, rather low concordance rates (about 75%) were observed in the literature. Patients discontinued the study due to PD assessed by the investigator and in this case, no further tumour assessments were performed. Patients which stopped due to PD but got evaluated as SD by central review were balanced between treatment arms and did only marginally change Best ORR results. For patients who were assessed as first PD by Central Review, more than 50% were assessed differently by investigators review in both treatment arms. The concordance in assessment of first PD by both review groups was slightly higher in the Avastin arm (49.1%) compared to 42.6% in the SB8 arm. Nevertheless, an impact on the response rate from such cases can be excluded, as only 3 patients were assessed as 'other than PD' in the subsequent assessment results in the induction period, but none of them was later determined as responders by central review.

There seems to be a slight difference between SB8 and Avastin relative to VEGF neutralization potency of batches used in this study, as batch results nearly did not overlap, although they were within the EU similarity range. In the overall VEGF neutralization assay comparing various batches, which were not restricted to clinical batches, this difference was not observed (see section 2.2 Quality aspects), therefore this difference is not of concern in the demonstration of biosimilarity on quality level. Results of all quality attribute VEGF-A 165 binding, HUVEC anti-proliferation, VEGF neutralization, as well as in vitro assays were within the pre-defined similarity range between the biosimilar candidate and the reference product. In addition, the ad-hoc analysis of the best ORR with the quality attributes as covariates showed that no contributing factor was identified from the quality aspects.

A more conservative imputation method on all patients without tumour assessment for best ORR by w24 of the induction period and for ORR at cycle 6 were presented upon request. These imputation analyses were further provided for ORR at cycle 2, and 4, for ORR at cycle 6 regardless of study period, and for the ADA positive vs. ADA negative subgroups:

- In the most appropriate analysis (imputing for patients without ORR at Cycle 6 in the Induction Period (MI with Monotone Missing Patterns), the difference in best ORR (SB8 – EU Avastin) was 5.3% with a 95% CI of [−2.2%, 12.7%] for PPS and 6.0% with 95% CI of [−0.9%, 12.9%] for the FAS. The imputation therefore revealed a lower difference between treatment arms compared to the initial analysis, which is reassuring. The response rate-time curves showed that the difference in response favoured SB8 and was highest between w20 and w30 and then slightly decreased till w40. With other imputation methods presented (using ORR at Cycle 2, 4 and 6 or just ORR at Cycle 2 and 4 as predictor variables for best ORR using a non-monotone missing pattern, which were not considered most appropriate), the difference in best ORR would be completely within a comparability range of ±12.5%.

- The analysis of ORR at Cycle 6 in the induction showed a difference (SB8 – EU Avastin) of 5.6% [95% CI: -1.8%, 13.0%] for PPS and 6.2% [95% CI: −0.6%, 13.1%] for the FAS. Results for PPS and FAS were similar and indicated no statistically significant difference between the two treatment groups. Also, in this analysis the difference was smaller than in the analysis without missing data imputation.
- Using the same kind of imputation, the analysis for the difference in ORR at Cycle 6 regardless of study period could be interpreted as a treatment policy estimand and better reflect the outcome in clinical practice after 6 cycles. The difference in ORR at Cycle 6 regardless of study period resulted in 4.8% [95% CI: –2.8%, 12.3%] for the PPS and in 4.9% [95% CI: –2.0%, 11.9%] for the FAS, which was entirely within a comparability range of ±12.5%.
- The analyses for ORR at cycle 2 and 4 showed only slight difference in ORR, which is similar to the initially presented results.
- The analysis of best ORR by 24 weeks in the induction period of ADA positive and ADA negative patients showed similar results as the ad-hoc analysis presented before. The response was higher in ADA positive patients compared to ADA negative patients in the Avastin treatment arm. In contrast, response was lower in ADA positive patients compared to ADA negative patients with SB8. ORR at each Cycle showed no consistent trend. Beside a chance finding due to the low sample size in the ADA positive subgroup, some influence of unfavourable prognostic factors detected in the ADA positive patients with SB8 cannot be excluded. Comparison of PFS and DOR showed no relevant effect of ADA development on these efficacy endpoints in both treatment groups.

The impact of ADA on efficacy is also further presented in the sub-section on immunological events in section 2.6. Clinical safety

2.5.4. Conclusions on the clinical efficacy

The difference in (best) ORR seems to slightly favour SB8 with an upper bound of the 95% CI around 13% in the induction period.

Nevertheless, the analysis for the difference in ORR at Cycle 6 regardless of study period for the PPS resulted in an upper bound of 12.3%. This endpoint could be interpreted as a treatment policy estimand and better reflect the outcome in clinical practice after 6 cycles, as it ignores a change of the treatment period (induction/maintenance) within the observation period of the primary endpoint of 24 weeks, i.e. if concurrent chemotherapy was still applied. As patients will change to the maintenance period prior to 24 weeks also in clinical practice, it reflects the comparison described in the ICH E9 Glossary (Intention to Treat Principle) as the effect of a treatment policy. Moreover, further efficacy endpoints as PFS, OS, DOR and change in tumour burden were similar. Further analyses evaluating the robustness of the study data were performed including ad-hoc sensitivity analyses after adjusting the covariates (e.g. tumour burden or number of Cycles for IP and non-IP), best ORR based on the data from Investigator's review or different assessment time points (e.g. by Week 11 and Week 17), and ORR at Cycle 2, Cycle 4 and Cycle 6 (regardless of study period). All of these analyses results showed that the treatment effect of SB8 and EU Avastin was largely comparable.

Based on the totality of data, comparability on efficacy level can be concluded.

2.6. Clinical safety

Patient exposure

The Applicant has provided safety data from clinical Phase I single-dose PK trial in healthy male volunteers (Study SB8-G11-NHV), and one clinical Phase III trial in male and female NSCLC patients (Study SB8-G31-NSCLC).

In the Phase I Study SB8-G11-NSCLC the subjects were randomized to one of three arms (SB8, EU Avastin or US-Avastin) to receive a single IV dose of 3 mg/kg bevacizumab.

In the Phase III Study SB8-G31-NSCLC patients were randomized in a 1:1 ratio to receive either an IV dose of 15 mg/kg of SB8 or EU Avastin plus paclitaxel and carboplatin (every three weeks) for at least 4 and no more than 6 cycles (induction treatment phase). Patients who responded to treatment continued with bevacizumab as monotherapy in the maintenance treatment phase until evidence of disease progression (PD), unacceptable toxicity, death, or 12 months from the randomization of the last patient (End of Study [EOS]), whichever occurred first. Due to the heterogeneity of the study populations and the different treatment schemes used in both studies, no pooled safety analysis was provided.

In the **Phase I study**, the safety population consisted of all 119 healthy male subjects aged 18 to 59 years who were exposed to a single dose of 3mg/kg bevacizumab i.v. (SB8 40 subjects; EU sourced Avastin 40 subjects; US sourced Avastin 39 subjects).

In the **Phase III study**, the safety population consisted of all NSCLC patients who received bevacizumab (either SB8 or EU-Avastin) at a dose of 15mg/kg i.v. at least once. Hence, a total of 758 out of the 763 randomized patients were included in the SAF (SB8 group: 378 patients [99.7%]; EU-Avastin group: 380 patients [99%]). In the below table, the exposure to the IP is summarized for the safety set of Phase III Study SB8-G31-NSCLC.

Table 47: Summary of exposure to investigational product (Safety set, study SB8-G31-NSCLC)

	SB8 N = 378		EU Avastin® N = 380	
Duration of IP exposure (weeks)				
n	378		380	
Mean	34.26		35.26	
Min, Max	3.0, 105.4		3.0, 101.3	
Number of Patients received infusion, n (%)				
Cycle 1	378	(100.0)	380	(100.0)
Cycle 2	362	(95.8)	363	(95.5)
Cycle 3	329	(87.0)	323	(85.0)
Cycle 4	311	(82.3)	315	(82.9)
Cycle 5	288	(76.2)	295	(77.6)
Cycle 6	278	(73.5)	288	(75.8)
Cycle 7	248	(65.6)	265	(69.7)
Cycle 8	233	(61.6)	260	(68.4)
Cycle 9	218	(57.7)	248	(65.3)
Cycle 10	206	(54.5)	232	(61.1)
Cycle 11	144	(38.1)	167	(43.9)
Cycle 12	142	(37.6)	159	(41.8)
Cycle 13	137	(36.2)	150	(39.5)
Cycle 14	133	(35.2)	145	(38.2)
Cycle 15	107	(28.3)	102	(26.8)
Cycle 16	104	(27.5)	101	(26.6)
Cycle 17	101	(26.7)	95	(25.0)
Cycle 18	99	(26.2)	90	(23.7)
Cycle 19	69	(18.3)	60	(15.8)
Cycle 20	63	(16.7)	54	(14.2)
Cycle 21	55	(14.6)	50	(13.2)
Cycle 22	47	(12.4)	47	(12.4)
Cycle 23	28	(7.4)	30	(7.9)
Cycle 24	28	(7.4)	27	(7.1)
Cycle 25	27	(7.1)	25	(6.6)
Cycle 26	25	(6.6)	20	(5.3)
Cycle 27	15	(4.0)	17	(4.5)
Cycle 28	13	(3.4)	14	(3.7)
Cycle 29	12	(3.2)	12	(3.2)
Cycle 30	10	(2.6)	9	(2.4)
Cycle 31	5	(1.3)	7	(1.8)
Cycle 32	5	(1.3)	4	(1.1)
Cycle 33	5	(1.3)	4	(1.1)
Cycle 34	3	(0.8)	0	(0.0)
Cycle 35	2	(0.5)	0	(0.0)
Cycle 36	1	(0.3)	0	(0.0)
Number of cycles received				
Induction treatment period				
N	378		380	
Mean	4.8		4.8	
Min, Max	1, 6		1, 6	
Maintenance treatment period				
N	258		277	
Mean	9.3		9.1	
Min, Max	1, 31		1, 27	
Overall treatment period				
N	378		380	
Mean	11.2		11.5	
Min, Max	1, 36		1, 33	

IP = investigational product; Max = maximum; Min = minimum; N = number of patients in the Safety Set; n = number of patients.

A summary of IP administration by treatment group in the SAF is presented in the below table.

Table 48: Summary of administration of investigational product by treatment group (Safety set, study SB8-G31-NSCLC)

	SB8 N = 378	EU Avastin® N = 380
Induction treatment period		
Cumulative actual dose of IP (mg)		
n	378	380
Mean (SD)	5282.29 (2058.582)	5268.55 (2111.156)
Min, Max	666.0, 10590.0	675.0, 10545.0
Relative dose intensity of IP (%)		
n	378	380
Mean (SD)	100.01 (0.152)	100.05 (0.611)
Min, Max	99.3, 101.4	97.4, 109.3
Dose delay of IP, n (%)	85 (22.5)	84 (22.1)
Adverse event	66 (17.5)	55 (14.5)
Maintenance treatment period		
Cumulative actual dose of IP (mg)		
n	258	277
Mean (SD)	10306.80 (7794.330)	9965.53 (7170.415)
Min, Max	765.0, 38340.0	660.0, 35748.0
Relative dose intensity of IP (%)		
n	258	277
Mean (SD)	100.05 (0.314)	99.97 (0.666)
Min, Max	99.0, 103.1	93.4, 103.4
Dose delay of IP, n (%)	75 (19.8)	92 (24.2)
Adverse event	40 (10.6)	55 (14.5)
Overall treatment period		
Cumulative actual dose of IP (mg)		
n	378	380
Mean (SD)	12317.09 (9233.938)	12532.89 (8752.988)
Min, Max	666.0, 48270.0	675.0, 43190.5
Relative dose intensity of IP (%)		
n	378	380
Mean (SD)	100.02 (0.161)	100.02 (0.647)
Min, Max	99.4, 101.4	94.4, 109.3

IP = investigational product; Max = maximum; Min = minimum; N = number of patients in the Safety Set; n = number of patients; SD = standard deviation
Relative dose intensity (%) = actual dose intensity/planned dose intensity × 100.
Reasons of dose modifications were counted individually for patients with more than 1 dose modification.
Source: Section 5.3.5.1 Final CSR, SB8-G31-NSCLC, Table 12-2, Table 14.3-1.5

A summary of administration of non-investigational product during the induction treatment period by treatment group is displayed in the table below.

Table 49: Summary of administration of non-investigational product during induction treatment period by treatment group (Safety set, study SB8-G31-NSCLC)

	SB8 N = 378	EU Avastin® N = 380
Paclitaxel		
Cumulative actual dose of Paclitaxel (mg)		
n	378	380
Mean (SD)	1752.32 (619.786)	1738.84 (651.921)
Min, Max	17.5, 2830.0	280.0, 2868.0
Relative dose intensity of Paclitaxel (%)		
n	378	380
Mean (SD)	98.22 (7.320)	98.29 (6.496)
Min, Max	5.2, 102.2	49.9, 104.2
Dose reduction of Paclitaxel, n (%)	36 (9.5)	36 (9.5)
Adverse event	36 (9.5)	35 (9.2)
Carboplatin		
Cumulative actual dose of Carboplatin (mg)		
n	377	380
Mean (SD)	3232.59 (1237.718)	3227.79 (1252.997)
Min, Max	408.2, 5400.0	428.4, 5400.0
Relative dose intensity of Carboplatin (%)		
n	377	380
Mean (SD)	98.44 (5.001)	97.70 (6.524)
Min, Max	63.6, 112.9	56.1, 116.9
Dose reduction of Carboplatin, n (%)	23 (6.1)	31 (8.2)
Adverse events	23 (6.1)	31 (8.2)

Max = maximum; Min = minimum; SD = standard deviation; N = number of patients in the Safety Set; n = number of patients;
Relative dose intensity (%) = actual dose intensity/planned dose intensity × 100.
Reasons of dose reductions were counted individually for patients with more than 1 dose reduction
Source: Section 5.3.5.1 Final CSR, SB8-G31-NSCLC, Table 12-3, Table 14.3-1.5

Disposition of subjects/patients

Phase I Study SB8-G11-NHV

Of the 119 subjects who were randomized, 113 subjects completed the study, and 6 subjects discontinued the study. 1 subject discontinued due to withdrawal of informed consent, 5 subjects discontinued due to other reasons (i.e. not meeting inclusion or exclusion criteria after dosing, one subject received an incorrect dose of the IP and one subject was administered disallowed therapy). None of the subjects discontinued the study due to AEs or other safety issues.

Phase III Study SB8-G31-NSCLC

A total of 965 patients were screened, of which 763 patients were randomised. The most common reason for screening failure was not meeting the eligibility criteria. The patient disposition was well balanced between the two treatment groups: 379 patients were randomised to the SB8 treatment group and 384 patients were randomized to the EU Avastin treatment group.

Among randomised patients, 70.1% (535/763) of subjects completed the induction treatment period (68.1% [258/379] in the SB8 treatment group and 72.1% [277/384] in the Avastin treatment group). 60.6% (462/763) of the patients discontinued during the maintenance treatment period in both treatment groups (58.8% [223/379] in the SB8 group; 62.2% [239/384] in the EU Avastin group). At the time of EOS (Aug 09, 2018) the proportion of patients who were ongoing in the maintenance treatment period was 9.2% (35/379) in the SB8 treatment group and 9.9% (38/384) in Avastin treatment group. The main reasons for discontinuation in the induction and maintenance treatment period in both groups were disease progression (10.9% in the induction period, 47.6% in the maintenance period), AEs (6.9% in the induction period, 4.3% in the maintenance period) and death (5.5% in the induction period, 2.8% in the maintenance period). The numbers of the patients terminating treatment because of disease progression, AEs or death were comparable between both groups.

Adverse events

<u>Phase I Study SB8-G11-NHV</u>

Treatment-emergent adverse events for the phase I study SB8-G11-NHV were defined as AEs which started after IP administration or pre-existed before IP administration and worsened in severity after IP administration. A summary of the TEAEs in the clinical Phase I study is presented in the below table.

Table 50: Summary of adverse events (Safety set, study SB8-G11-NHV)

	Treatment							
	SB8 N = 40		EU Avastin® N = 40		US Avastin® N=39		Total N=119	
Category	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any AE	23 (57.5)	38	15 (37.5)	19	22 (56.4)	40	60 (50.4)	97
Any TEAE	20 (50.0)	32	15 (37.5)	17	21 (53.8)	36	56 (47.1)	85
TEAE Severity								
Grade 1	19 (47.5)	31	15 (37.5)	17	20 (51.3)	35	54 (45.4)	83
Grade 2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Grade 3	1 (2.5)	1	0 (0.0)	0	1 (2.6)	1	2 (1.7)	2
Grade 4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Grade 5	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
TEAE Causality								
Not related	19 (47.5)	31	14 (35.0)	16	18 (46.2)	33	51 (42.9)	80
Related	1 (2.5)	1	1 (2.5)	1	3 (7.7)	3	5 (4.2)	5
Any SAE	1 (2.5)	1	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1
Any TEAE leading to discontinuation of IP	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Any TEAE leading to death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Any infusion-related reaction	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

AE = adverse events; E = number of events; N = number of subjects in the Safety set; n = number of subjects with that observation; TEAE = treatment-emergent adverse event; SAE = serious adverse event
Percentages were based on the number of subjects in the Safety Set.

The majority of TEAEs were Grade 1 (mild) in severity. A total of 2 (1.7%) subjects experienced Grade 3 (severe) TEAEs: 1 (2.5%) subject in the SB8 group and 1 (2.6%) subject in the US sourced Avastin group:

• One subject (SB8 group) had Grade 3 (severe) perirectal abscess which was considered serious and not related to the IP by the Investigator.

• Another subject (US sourced Avastin group) had Grade 3 (severe) syncope which was considered non-serious and not related to the IP by the Investigator.

No SAEs were reported in the EU Avastin treatment group and US Avastin treatment group. No TEAEs were reported with severity Grade 4 (life-threatening) or Grade 5 (death) in any treatment group. There were no deaths or discontinuations due to TEAEs during the study.

TEAEs considered to be related to the IP were reported in 1 (2.5%) subject in the SB8 treatment group (diarrhoea), 1 (2.5%) subject in the EU Avastin treatment group (acne) and 3 (7.7%) subjects in the US Avastin treatment group (musculoskeletal stiffness in 1 subject and headache in 2 subjects).

No infusion related reaction symptoms were observed.

Treatment-emergent Adverse Events (TEAEs) occurring in > 5% of subjects in any treatment group reported during the study are provided in the table below.

Table 51: Number (%) of subjects with TEAEs in ≥ 5% of subjects in any treatment group (Safety set, study SB8-G11-NHV)

	Treatment							
	SB8 N = 40		EU Avastin® N = 40		US Avastin® N=39		Total N=119	
Preferred Term	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any TEAE	20 (50.0)	32	15 (37.5)	17	21 (53.8)	36	56 (47.1)	85
Nasopharyngitis	3 (7.5)	3	6 (15.0)	6	6 (15.4)	6	15 (12.6)	15
Headache	3 (7.5)	6	0 (0.0)	0	7 (17.9)	10	10 (8.4)	16
Diarrhoea	4 (10.0)	5	2 (5.0)	2	0 (0.0)	0	6 (5.0)	7
Back pain	2 (5.0)	2	1 (2.5)	1	2 (5.1)	2	5 (4.2)	5
Oropharyngeal pain	2 (5.0)	2	0 (0.0)	0	2 (5.1)	2	4 (3.4)	4

E = number of events; N = number of subjects in the Safety Set; n = number of subjects with event;
TEAE = treatment-emergent adverse event
Percentages were based on the number of subject in the Safety Set.
Adverse events were coded by preferred term using the MedDRA Version 18.0 coding dictionary.
Source: Section 5.3.3.1 CSR SB8-G11-NHV, Table 12-2, Table 14.3.1-1.2

The most frequently affected SOCs among the treatment groups were infections and infestations (4 [10.0%] subjects in the SB8, 8 [20.0%] subjects in the EU Avastin and 7 [17.9%] subjects in the US Avastin treatment groups) and gastrointestinal disorders (9 [22.5%] subjects in the SB8, 2 [5.0%] subjects in the EU Avastin and 2 [5.1%] subjects in the US Avastin treatment groups).

Phase III Study SB8-G31-NSCLC

A TEAE was defined as any AE with an onset date on or after the date of the first administration of IP. AEs which were already present before the first IP and increased in severity after the first IP were considered as TEAEs. Pre-existing AEs before the first IP with no increase in severity after the first IP were not considered as TEAEs.

A total of 694 (91.6%) patients reported 5284 TEAEs at any time after the first dose of the IP during the overall study period (summarized in Table 52 below).

The majority of TEAEs were grade 1 or 2 in severity; i.e. there were 1470 grade 1 and 883 grade 2 events in the SB8 treatment group, and 1383 grade 1 and 862 grade 2 events in the Avastin treatment group.

Table 52: Summary of adverse events (Safety set, study SB8-G31-NSCLC)

Treatment	SB8 N=378			EU Avastin® N=380		
Number of patient experiencing	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Adverse events	351	(92.9)	2955	352	(92.6)	2819
TEAEs	348	(92.1)	2703	346	(91.1)	2581
CTCAE Grade						
Grade 1	47	(12.4)	1470	57	(15.0)	1383
Grade 2	127	(33.6)	883	134	(35.3)	862
Grade 3	119	(31.5)	285	97	(25.5)	259
Grade 4	33	(8.7)	43	31	(8.2)	50
Grade 5	22	(5.8)	22	27	(7.1)	27
TEAEs related to IP	160	(42.3)	628	177	(46.6)	651
TEAEs related to Paclitaxel	305	(80.7)	1492	297	(78.2)	1488
TEAEs related to Carboplatin	289	(76.5)	1312	283	(74.5)	1325
TEAEs of special interest	31	(8.2)	39	20	(5.3)	30
Hypertension	29	(7.7)	37	16	(4.2)	22
Proteinuria	2	(0.5)	2	7	(1.8)	8
TEAEs leading to IP discontinuation	50	(13.2)	58	36	(9.5)	43
Drug related TEAE leading to IP discontinuation	4	(1.1)	4	1	(0.3)	1
TEAEs leading to Paclitaxel discontinuation	43	(11.4)	49	42	(11.1)	50
TEAEs leading to Carboplatin discontinuation	44	(11.6)	50	37	(9.7)	45
Infusion-related reaction of TEAE	20	(5.3)	23	11	(2.9)	24
SAEs						
All SAEs	75	(19.8)	104	81	(21.3)	111
Serious TEAEs	75	(19.8)	104	81	(21.3)	111
SAE related to IP	16	(4.2)	20	23	(6.1)	27
Fatal TEAEs	22	(5.8)	22	27	(7.1)	27

CTCAE = Common Terminology Criteria for Adverse Events; E = frequency of adverse events; IP = investigational product; N = number of patients in the Safety Set; n = number of patients who experienced at least one event; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Adverse events were coded to system organ class and preferred term using the MedDRA version 20.0.
Severity assessment was classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
If a patient had more than one event of the same severity or relationship, then the events were counted only once in that severity or relationship. If a patient had more than one event with different severity or relationship, then the patient was counted only once for more severe adverse events or related adverse events. If a patient had more than one action taken within a system organ class, preferred term and verbatim term, the patient was counted only once for the permanent discontinuation.
Source: Section 5.3.5.1 Final CSR SB8-G31-NSCLC, Table 12-4, Table 14.3.1-1.1

A total of 215 SAEs were reported in 156 (20.6%) patients, all of which were treatment-emergent (i.e. serious TEAEs). In the SB8 treatment group, 104 SAEs were reported in 75 (19.8%) patients and in the Avastin treatment group, 111 SAEs were reported in 81 (21.3%) patients.

There were 69 TEAEs considered to be of special interest (hypertension, proteinuria) reported during the overall study period. In the SB8 treatment group, 39 TEAEs of special interest were reported in 31 (8.2%) patients and in the Avastin group, 30 TEAEs of special interest were reported in 20 (5.3%) patients.

Overall, there were 101 TEAEs leading to IP discontinuation; 58 events were reported in 50 (13.2%) patients in the SB8 treatment group and 43 events were reported in 36 (9.5%) patients in the Avastin group.

A total of 22 (5.8%) patients in the SB8 treatment group and 27 (7.1%) patients in the Avastin treatment group had fatal TEAEs.

TEAEs occurring ≥ 5% of the patients in any treatment group by Preferred Term (PT) are presented in the table below.

Table 53: Number (%) of patients with TEAEs and number of events by preferred term during the overall study period in ≥ 5% of patients in any treatment group (Safety set, study SB8-G31-NSCLC)

Preferred term	SB8 N = 378 n (%) E	Avastin® N = 380 n (%) E	Total N = 758 n (%) E
Any TEAE with incidence ≥ 5% of subjects in any treatment group	328 (86.8) 1768	318 (83.7) 1741	646 (85.2) 3509
Alopecia	184 (48.7) 185	183 (48.2) 184	367 (48.4) 369
Anaemia	92 (24.3) 111	90 (23.7) 111	182 (24.0) 222
Nausea	74 (19.6) 177	80 (21.1) 225	154 (20.3) 402
Neutropenia	74 (19.6) 122	71 (18.7) 125	145 (19.1) 247
Thrombocytopenia	58 (15.3) 98	46 (12.1) 69	104 (13.7) 167
Asthenia	49 (13.0) 58	44 (11.6) 56	93 (12.3) 114
Arthralgia	46 (12.2) 117	46 (12.1) 92	92 (12.1) 209
Fatigue	46 (12.2) 56	48 (12.6) 60	94 (12.4) 116
Hypertension	46 (12.2) 62	36 (9.5) 46	82 (10.8) 108
Leukopenia	40 (10.6) 61	24 (6.3) 46	64 (8.4) 107
Neuropathy peripheral	38 (10.1) 39	54 (14.2) 59	92 (12.1) 98
Weight decreased	37 (9.8) 37	28 (7.4) 30	65 (8.6) 67
Decreased appetite	36 (9.5) 39	34 (8.9) 47	70 (9.2) 86
Aspartate aminotransferase increased	32 (8.5) 48	24 (6.3) 38	56 (7.4) 86
Paraesthesia	32 (8.5) 33	32 (8.4) 34	64 (8.4) 67
Diarrhoea	31 (8.2) 40	25 (6.6) 27	56 (7.4) 67
Alanine aminotransferase increased	29 (7.7) 47	30 (7.9) 42	59 (7.8) 89
Blood urea increased	28 (7.4) 50	18 (4.7) 37	46 (6.1) 87
Blood alkaline phosphatase increased	26 (6.9) 36	27 (7.1) 34	53 (7.0) 70

Headache	26 (6.9) 29	27 (7.1) 49	53 (7.0) 78
Dysphonia	24 (6.3) 26	16 (4.2) 16	40 (5.3) 42
Myalgia	24 (6.3) 37	35 (9.2) 57	59 (7.8) 94
Peripheral sensory neuropathy	24 (6.3) 25	35 (9.2) 36	59 (7.8) 61
Vomiting	24 (6.3) 32	22 (5.8) 26	46 (6.1) 58
Cough	23 (6.1) 25	20 (5.3) 21	43 (5.7) 46
Dyspnoea	22 (5.8) 22	30 (7.9) 31	52 (6.9) 53
Constipation	21 (5.6) 25	18 (4.7) 24	39 (5.1) 49
Epistaxis	20 (5.3) 28	14 (3.7) 16	34 (4.5) 44
Musculoskeletal pain	19 (5.0) 55	16 (4.2) 32	35 (4.6) 87
Platelet count decreased	18 (4.8) 22	19 (5.0) 31	37 (4.9) 53
Proteinuria	17 (4.5) 26	24 (6.3) 40	41 (5.4) 66

TEAE = treatment-emergent adverse event; N = number of subjects in the Safety set; n = number of subjects with TEAEs; E = frequency of the adverse events.
Adverse events were coded to system organ class and preferred term (PT) using the MedDRA version 20.0.
PTs are sorted in descending order of subject frequency in the SB8 treatment group. If the frequencies of the PTs were the same, the PTs are sorted alphabetically.
Source: Table 14.3.1-1.5

The most frequently affected SOCs in both treatment groups were skin and subcutaneous tissue disorders (48.7% in the SB8 and 48.2% in the EU Avastin treatment groups), blood and lymphatic system disorders (42.9% and 41.3%, respectively), and nervous system disorders (29.6% and 35.8%, respectively).

Severe (Grade ≥ 3) TEAEs

In the SB8 treatment group, 350 severe TEAEs in 174 (46.0%) patients were reported: 44 SAEs (33 [8.7%] patients) of Grade 3, 19 SAEs (13 [3.4%] patients) of Grade 4, and 22 SAEs (22 [5.8%] patients) of Grade 5, respectively.

In the Avastin treatment group, 336 severe TEAEs in 155 (40.8%) patients were reported: 42 SAEs (27 [7.1%] patients) of Grade 3, 26 SAEs (18 [4.7%] patients) of Grade 4, and 27 SAEs (27 [7.1%] patients) of Grade 5, respectively.

The most frequently occurring severe TEAEs were neutropenia (8.7% in the SB8 and 9.5% in the Avastin treatment groups), hypertension (6.3% and 3.7%, respectively), anaemia (4.8% and 5.5%, respectively), and neutrophil count decreased (4.0% and 3.2% respectively).

Relationship of TEAEs to Study Treatment

In the SB8 treatment group, 628 TEAEs were reported to be related to the IP in 160 (42.3%) patients and in the Avastin treatment group, 651 TEAEs were reported to be related to the IP in 177 (46.6%) patients.

At the SOC level, the most commonly reported TEAEs considered to be related to the IP were blood and lymphatic system disorders (14.8% in the SB8 and 11.6% in the Avastin treatment groups), investigations (13.8% and 14.7%, respectively), and gastrointestinal disorders (10.1% and 11.3%, respectively).

In the SB8 treatment group, 1492 TEAEs were reported to be related to paclitaxel in 305 (80.7%) patients and in the Avastin treatment group, 1488 TEAEs were reported to be related to paclitaxel in 297 (78.2%) patients.

In the SB8 treatment group, 1312 TEAEs were reported to be related to carboplatin in 289 (76.5%) patients and in the Avastin treatment group, 1325 TEAEs were reported to be related to carboplatin in 283 (74.5%) patients.

- **Adverse events of special interest (AESI)**

Phase I Study SB8-G11-NHV

AESI were not analysed.

Phase III Study SB8-G31-NSCLC

The following TEAEs were considered as adverse events of special interest.

- Hypertension: Hypertension NCI-CTCAE v4.03 Grade ≥ 3 was classified as AESI.
- Proteinuria: If a patient was discovered to have ≥ 2+ proteinuria on urine dipstick (or other ways of urinalysis) and demonstrated 24 hours urine protein excretion ≥ 1 g or protein/creatinine ratio in spot urine ≥ 1g/g creatinine (or ≥ 226.0 mg/mmol creatinine), this was classified as AESI.

Other AESIs reported for bevacizumab have not been listed. An ad-hoc analyses of AESIs by induction and maintenance period was provided. Among the AESIs (all Grades) occurring in ≥ 0.5% of patients, the overall AESIs showing ≥ 1% difference between treatments were ATE, hypertension, cardiac disorders (excluding CHF and ATE) (higher in the SB8 treatment group), and pulmonary haemorrhage, pulmonary hypertension and peripheral sensory neuropathy (higher in the EU Avastin treatment group) (data not shown).

A total of 51 (6.7%) patients reported 69 TEAEs of special interest. In the SB8 treatment group, 39 TEAEs of special interest were reported in 31 (8.2%) patients and in the Avastin treatment group, 30 TEAEs of special interest were reported in 20 (5.3%) patients.

- In the SB8 treatment group, 37 TEAEs of hypertension were reported in 29 (7.7%) patients and in the Avastin treatment group, 22 TEAEs of hypertension were reported in 16 (4.2%) patients.
- In the SB8 treatment group, 2 TEAEs of proteinuria were reported in 2 (0.5%) patients and in the Avastin treatment group, 8 TEAEs of proteinuria were reported in 7 (1.8%) patients.

The overall incidences of hypertension ≥ Grade 3 and proteinuria in both treatment groups is displayed in the below tables.

Table 54: Incidence of hypertension (all preferred terms) (≥ Grade 3) (Safety set, study SB8-G31-NSCLC)

Preferred term	SB8 N = 378 n (%) E	Avastin® N = 380 n (%) E	Total N = 758 n (%) E
Blood pressure increased grade ≥ 3	4 (1.1) 5	2 (0.5) 2	6 (0.8) 7
Hypertension grade ≥ 3	24 (6.3) 30	14 (3.7) 18	38 (5.0) 48
Hypertensive crisis grade ≥ 3	2 (0.5) 2	1 (0.3) 1	3 (0.4) 3
Essential hypertension grade ≥ 3	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1

N = number of subjects in the Safety set; n = number of subjects with treatment-emergent adverse events;
E = frequency of adverse events.
Adverse events were coded to system organ class and preferred term using MedDRA version 20.0 coding dictionary.
If a subject had more than one adverse event within a system organ class and preferred term, the subject was counted only once for the maximum CTCAE grade.
Source: Table 14.3.1-2.6

Table 55: Incidence of proteinuria (all preferred terms) (Safety set, study SB8-G31-NSCLC)

Preferred term Grade	SB8 N = 378 n (%) E	Avastin® N = 380 n (%) E	Total N = 758 n (%) E
Protein urine	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Grade 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Grade 2	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Grade 3	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Grade 4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Grade 5	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Proteinuria	2 (0.5) 2	6 (1.6) 7	8 (1.1) 9
Grade 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Grade 2	0 (0.0) 0	4 (1.1) 5	4 (0.5) 5
Grade 3	2 (0.5) 2	2 (0.5) 2	4 (0.5) 4
Grade 4	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Grade 5	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0

N = number of subjects in the Safety set; n = number of subjects with treatment-emergent adverse events;
E = frequency of adverse events
Adverse events were coded to system organ class and preferred term using MedDRA version 20.0 coding dictionary.
If a subject had more than one adverse event within a system organ class and preferred term, the subject was counted only once for the maximum CTCAE grade.
Proteinuria: ≥ 2+ proteinuria on urine dipstick (or other ways of urinalysis) and 24 hours urine protein excretion ≥ 1 g or protein/creatinine ratio in spot urine ≥ 1 g/g creatinine (or ≥ 226.0 mg/mmol creatinine).
Source: Table 14.3.1-2.6

- **Infusion-related Reactions**

A total of 31 (4.1%) subjects reported 47 TEAEs associated with infusion-related reactions.

The most common symptoms of infusion-related reactions reported as PTs were dyspnoea, hypersensitivity, and drug hypersensitivity.

The incidence of infusion-related reaction was observed up to cycle 10 for IP and cycle 3 for non-IP, for both treatment groups. The incidence decreased over time in both treatment groups.

Table 56: Infusion-related reaction of TEAEs by system organ class and preferred term (Safety set, study SB8-G31-NSCLC)

System organ class Preferred term	SB8 N = 378 n (%) E	Avastin® N = 380 n (%) E	Total N = 758 n (%) E
Any infusion-related reaction of TEAE	20 (5.3) 23	11 (2.9) 24	31 (4.1) 47
Cardiac disorders	**0 (0.0) 0**	**1 (0.3) 1**	**1 (0.1) 1**
Palpitations	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Gastrointestinal disorders	**1 (0.3) 1**	**1 (0.3) 1**	**2 (0.3) 2**
Nausea	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Abdominal pain upper	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
General disorders and administration site conditions	**0 (0.0) 0**	**1 (0.3) 1**	**1 (0.1) 1**
Asthenia	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Immune system disorders	**7 (1.9) 7**	**3 (0.8) 4**	**10 (1.3) 11**
Hypersensitivity	3 (0.8) 3	1 (0.3) 1	4 (0.5) 4
Drug hypersensitivity	2 (0.5) 2	1 (0.3) 2	3 (0.4) 4
Anaphylactic reaction	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Anaphylactic shock	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Injury, poisoning and procedural complications	**0 (0.0) 0**	**1 (0.3) 3**	**1 (0.1) 3**
Infusion related reaction	0 (0.0) 0	1 (0.3) 3	1 (0.1) 3
Investigations	**3 (0.8) 3**	**0 (0.0) 0**	**3 (0.4) 3**
Blood pressure increased	2 (0.5) 2	0 (0.0) 0	2 (0.3) 2
Neutrophil count decreased	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Metabolism and nutrition disorders	**0 (0.0) 0**	**1 (0.3) 1**	**1 (0.1) 1**
Decreased appetite	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Musculoskeletal and connective tissue disorders	**1 (0.3) 1**	**1 (0.3) 2**	**2 (0.3) 3**
Spinal pain	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Arthralgia	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Muscle spasms	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Nervous system disorders	**0 (0.0) 0**	**1 (0.3) 1**	**1 (0.1) 1**
Migraine	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Psychiatric disorders	**1 (0.3) 1**	**0 (0.0) 0**	**1 (0.1) 1**
Nervousness	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Respiratory, thoracic and mediastinal disorders	**2 (0.5) 2**	**4 (1.1) 4**	**6 (0.8) 6**
Dyspnoea	2 (0.5) 2	4 (1.1) 4	6 (0.8) 6
Skin and subcutaneous tissue disorders	**4 (1.1) 5**	**1 (0.3) 5**	**5 (0.7) 10**
Dermatitis allergic	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Rash	1 (0.3) 1	1 (0.3) 5	2 (0.3) 6
Rash erythematous	1 (0.3) 2	0 (0.0) 0	1 (0.1) 2
Urticaria	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Vascular disorders	**3 (0.8) 3**	**1 (0.3) 1**	**4 (0.5) 4**
Flushing	2 (0.5) 2	0 (0.0) 0	2 (0.3) 2
Hypertension	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2

TEAE = treatment-emergent adverse event; N = number of subjects in the Safety set; n = number of subjects with infusion-related reactions; E = frequency of the infusion-related reactions.
Adverse events were coded to system organ class (SOC) and preferred term (PT) using the MedDRA version

Table 57: Incidence of infusion-related reaction for investigational product and non-investigational product by cycle (Safety set, study SB8-G31-NSCLC)

Timepoint	SB8 N = 378 n (%)	Avastin® N = 380 n (%)	Total N = 758 n (%)
IP			
Cycle 1	1 (0.3)	0 (0.0)	1 (0.1)
Cycle 2	2 (0.5)	0 (0.0)	2 (0.3)
Cycle 3	0 (0.0)	1 (0.3)	1 (0.1)
Cycle 4	0 (0.0)	1 (0.3)	1 (0.1)
Cycle 5	0 (0.0)	1 (0.3)	1 (0.1)
Cycle 6	0 (0.0)	1 (0.3)	1 (0.1)
Cycle 7	1 (0.3)	1 (0.3)	2 (0.3)
Cycle 8	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 9	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 10	1 (0.3)	0 (0.0)	1 (0.1)
Cycles 11-36	0 (0.0)	0 (0.0)	0 (0.0)
Non-IP			
Cycle 1	3 (0.8)	3 (0.8)	6 (0.8)
Cycle 2	3 (0.8)	6 (1.6)	9 (1.2)
Cycle 3	3 (0.8)	0 (0.0)	3 (0.4)
Cycle 4	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 5	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 6	0 (0.0)	0 (0.0)	0 (0.0)

IP = Investigational product; N = number of subjects in the Safety set; n = number of subjects with infusion-related reactions.
Source: Table 14.3-2.5 and Table 14.3-2.6

Serious adverse event/deaths/other significant events

Phase I Study SB8-G11-NHV

One SAE was reported in 1 (2.5%) subject in the SB8 treatment group during the study (one subject: perirectal abscess, not considered to be treatment related by the investigator, narrative was provided). No SAEs were reported in the EU Avastin and US Avastin treatment groups.

No deaths occurred during the study.

Phase III Study SB8-G31-NSCLC

Serious Adverse Events

A total of 215 SAEs were reported in 156 (20.6%) patients, all of which were treatment-emergent. In the SB8 treatment group, 104 SAEs in 75 (19.8%) patients were reported. In the Avastin treatment group, 111 SAEs in 81 (21.3%) subjects were reported.

Table 58: Serious treatment-emergent adverse events by system organ class (>1% in any treatment group) and preferred term (Safety set, study SB8-G31-NSCLC)

System organ class Preferred term	SB8 N = 378 n (%) E	Avastin® N = 380 n (%) E	Total N = 758 n (%) E
Any serious TEAE	75 (19.8) 104	81 (21.3) 111	156 (20.6) 215
Blood and lymphatic system disorders	**11 (2.9) 15**	**13 (3.4) 20**	**24 (3.2) 35**
Anaemia	6 (1.6) 9	4 (1.1) 4	10 (1.3) 13
Febrile neutropenia	2 (0.5) 2	6 (1.6) 7	8 (1.1) 9
Leukopenia	2 (0.5) 2	2 (0.5) 2	4 (0.5) 4
Thrombocytopenia	2 (0.5) 2	1 (0.3) 1	3 (0.4) 3
Neutropenia	0 (0.0) 0	3 (0.8) 6	3 (0.4) 6
Cardiac disorders	**6 (1.6) 6**	**5 (1.3) 5**	**11 (1.5) 11**
Acute coronary syndrome	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Acute myocardial infarction	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Angina pectoris	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Atrial fibrillation	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Atrial flutter	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Myocardial ischaemia	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Cardiac arrest	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Cardiovascular insufficiency	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Myocardial infarction	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Right ventricular failure	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Gastrointestinal disorders	**9 (2.4) 9**	**11 (2.9) 13**	**20 (2.6) 22**
Diarrhoea	2 (0.5) 2	1 (0.3) 1	3 (0.4) 3
Abdominal pain	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Constipation	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Ileus paralytic	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Inguinal hernia strangulated	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Intestinal ischaemia	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1

System organ class Preferred term	SB8 N = 378 n (%) E	Avastin® N = 380 n (%) E	Total N = 758 n (%) E
Pancreatitis acute	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Small intestinal perforation	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Colitis	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Gastric hypomotility	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Gastric ulcer haemorrhage	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Gastritis	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Haemorrhoidal haemorrhage	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Large intestinal haemorrhage	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Nausea	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Pancreatitis chronic	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Vomiting	0 (0.0) 0	2 (0.5) 3	2 (0.3) 3
General disorders and administration site conditions	**8 (2.1) 8**	**9 (2.4) 9**	**17 (2.2) 17**
Sudden death	4 (1.1) 4	6 (1.6) 6	10 (1.3) 10
Infusion site extravasation	2 (0.5) 2	0 (0.0) 0	2 (0.3) 2
Death	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
General physical health deterioration	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Asthenia	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Fatigue	0 (0.0) 0	2 (0.5) 2	2 (0.3) 2
Immune system disorders	**4 (1.1) 4**	**2 (0.5) 2**	**6 (0.8) 6**
Hypersensitivity	2 (0.5) 2	0 (0.0) 0	2 (0.3) 2
Anaphylactic reaction	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Anaphylactic shock	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Drug hypersensitivity	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Infections and infestations	**13 (3.4) 16**	**9 (2.4) 10**	**22 (2.9) 26**
Pneumonia	7 (1.9) 8	0 (0.0) 0	7 (0.9) 8
Influenza	2 (0.5) 2	0 (0.0) 0	2 (0.3) 2
Atypical pneumonia	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Bronchitis	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Cellulitis	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Herpes zoster	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Infectious pleural effusion	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Septic shock	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Device related infection	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Enterocolitis infectious	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1

System organ class Preferred term	N = 378 n (%) E	N = 380 n (%) E	N = 758 n (%) E
Gastroenteritis	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Infection	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Lung abscess	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Pyelonephritis chronic	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Sepsis	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Wound infection	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Nervous system disorders	**8 (2.1) 9**	**5 (1.3) 5**	**13 (1.7) 14**
Carotid artery occlusion	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Cerebral ischaemia	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Cerebrovascular accident	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Cognitive disorder	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Encephalopathy	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Haemorrhagic stroke	1 (0.3) 1	3 (0.8) 3	4 (0.5) 4
Intercostal neuralgia	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Ischaemic stroke	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Transient ischaemic attack	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Brachial plexopathy	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Respiratory, thoracic and mediastinal disorders	**13 (3.4) 13**	**21 (5.5) 24**	**34 (4.5) 37**
Pulmonary embolism	4 (1.1) 4	9 (2.4) 9	13 (1.7) 13
Pneumothorax	3 (0.8) 3	3 (0.8) 4	6 (0.8) 7
Pulmonary haemorrhage	3 (0.8) 3	5 (1.3) 5	8 (1.1) 8
Dyspnoea	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Haemoptysis	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Pneumonia aspiration	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Atelectasis	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Chronic obstructive pulmonary disease	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Pulmonary oedema	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Respiratory failure	0 (0.0) 0	2 (0.5) 2	2 (0.3) 2
Vascular disorders	**9 (2.4) 11**	**5 (1.3) 5**	**14 (1.8) 16**
Shock haemorrhagic	3 (0.8) 3	0 (0.0) 0	3 (0.4) 3
Hypertension	2 (0.5) 2	1 (0.3) 1	3 (0.4) 3
Hypertensive crisis	2 (0.5) 2	1 (0.3) 1	3 (0.4) 3
Internal haemorrhage	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Jugular vein thrombosis	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Peripheral artery thrombosis	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Superior vena cava syndrome	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Circulatory collapse	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Deep vein thrombosis	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Essential hypertension	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1

PT = preferred term; TEAE = treatment-emergent adverse event; N = number of subjects in the Safety set; n = number of subjects with TEAEs; E = frequency of the adverse events.
Adverse events were coded to system organ class (SOC) and preferred term (PT) using the MedDRA version 20.0 coding dictionary.
SOCs are presented alphabetically. Only SOCs with incidence of >1% in any treatment group are presented. PTs are sorted within the SOC in descending order of subject frequency in the SB8 treatment group. If the frequencies of the PTs are the same, the PTs are sorted alphabetically.
Source: Table 14.3.1-2.2

<u>Severe (Grade ≥ 3) SAEs</u>

In the SB8 treatment group, 44 SAEs (33 [8.7%] patients) of grade 3, 19 SAEs (13 [3.4%] patients) of grade 4, and 22 SAEs (22 [5.8%] patients) of grade 5 were reported.

In the Avastin treatment group, 42 SAEs (27 [7.1%] patients) of grade 3, 26 SAEs (18 [4.7%] patients) of grade 4, and 27 SAEs (27 [7.1%] subjects) of grade 5 were reported.

When a patient experienced more than 1 adverse events, the patient was only counted once for the maximum CTCAE grade.

Relationship of SAEs to Study Treatment

In the SB8 treatment group, 20 SAEs (16 [4.2%] patients) were considered to be related to IP, 28 events (20 [5.3%] patients) were related to paclitaxel, and 27 events (20 [5.3%] patients) were related to carboplatin.

In the Avastin treatment group, 27 SAEs (23 [6.1%] patients) were considered to be related to IP, 43 events (33 [8.7%] patients) were related to paclitaxel and 39 events (29 [7.6%] patients) were related to carboplatin.

Outcomes of SAEs/ Deaths

Of the 215 SAEs reported, there were 49 fatal SAEs (22 patients in the SB8 treatment group and 27 patients in the Avastin group.

At the SOC level, the most commonly reported TEAEs leading to death were respiratory, thoracic and mediastinal disorders (1.3% in the SB8 and 2.9% in the Avastin treatment groups), general disorders and administration site conditions (1.3% and 1.6%, respectively), and nervous system disorders (0.8% and 1.1%, respectively).

Summary of Deaths during the Study Period

Overall, 44.5% (337/758) of the patients died (43.9%, 166/378 patients in the SB8 group; 45%, 171/380 patients in the EU-Avastin group). The primary cause of death was the study indication (35.4% in the SB8 group; 35.5% in the EU-Avastin group), AEs (4.5% in the SB8 group; 6.1% in the EU-Avastin group) and other reasons (4% in the SB8 group; 3.4% in the EU-Avastin group).

Laboratory findings

Phase I Study SB8-G11-NHV

Laboratory data (haematology, biochemistry, coagulation, urine analysis) did not show any significant changes over time which might be considered to be related to the IPs. In addition, no out-of-range vital sign values were identified by the Investigator as being clinically significant.

Interpretation of the ECG recordings showed some abnormalities, but most of these abnormalities did not reach clinical relevance as judged by the Investigator. No abnormalities were found during the physical examinations by the Investigator.

Phase III Study SB8-G31-NSCLC

- **Clinical Laboratory evaluation**

  - **Haematology:** The most frequently reported significant abnormal (Grade ≥ 3) haematology parameters were neutrophils (up to 8.5% of patients in any cycle in the SB8 treatment group and 6.8% in the EU Avastin treatment group), lymphocytes (3.3% and 4.0%, respectively), leukocytes (2.2% and 3.0%, respectively), and haemoglobin (1.7% and 1.9%, respectively).

  - **Biochemistry:** The most frequently reported significant abnormal (Grade ≥ 3) biochemistry parameters were sodium (up to 16.7% of patients in any cycle in the SB8 treatment group and 1.9% in the EU Avastin treatment group), potassium (4.0% and 1.7%, respectively), bilirubin

(1.7% and 0.0%, respectively), AST (1.7% and 0.9%, respectively), ALT (1.0% and 4.0%, respectively), creatinine (1.0% and 0.4%, respectively).

- o **Coagulation, Urine Protein:** there were no notable differences in the mean and median values of coagulation parameters and no notable differences in the urine parameters (dipstick results) observed between the SB8 and EU Avastin treatment groups.

- **Vital Signs, 12-Lead Electrocardiogramm, Physical Examination Findings, other Observations:** there was no evidence of clinically relevant differences in any parameter between the two treatment groups over time. There were no notable changes in the vital signs during the study, there were no notable shifts in 12-lead ECG parameters from baseline, there were also no notable changes in the physical examination findings during the study and no notable shifts in the ECOG performance status from the baseline.

Safety in special populations

Specific studies assessing the potential impact of safety in special groups of SB8, have not been conducted.

Immunological events

Immunogenicity assay validation

For detection of anti-drug antibodies (ADAs) against SB8 and the reference product Avastin, the applicant proposed a 3-tiered single-assay approach including screening, confirmation, and neutralization assays, as well as characterization of potential neutralizing ADAs (ADA titer assay).

<u>Screening assay</u>:

Human serum ADA levels were analysed using methods validated with respect to sensitivity, specificity, intra- and inter-assay precision, and short-term stability. Assay selectivity was shown in the presence of haemolyzed and lipemic matrix components. Drug tolerance was established in the presence of varying concentrations of SB8. Assays were also successfully validated for prozone/hook effect.

<u>Neutralization assay</u>:

Neutralizing antibodies (nAbs) in the clinical Phase I and Phase III study were determined using assays validated with regard to sensitivity, selectivity, short-term stability, inter- and intra-assay precision, drug tolerance and interference. No hook effect was observed.

PK Study SB8-G11-NHV

Blood samples of all 119 randomized patients (40 subjects in SB8, 40 subjects in EU Avastin and 39 subjects in US Avastin treatment groups) were collected on Day 1 (pre-dose), Day 22, Day 57, and Day 85 (single dose of SB8, EU Avastin or US Avastin) for determination of ADA to bevacizumab and NAbs.

In the SAF, the post-dose incidence of the subjects with ADAs to bevacizumab was reported as 1 (2.6%), 4 (10.3%), and 1 (2.6%) in the SB8, EU Avastin, and US Avastin treatment groups, respectively. The overall incidence of the subjects with ADA to bevacizumab was comparable among the three treatment groups. No subject in any treatment group was positive for NAbs.

Study SB8-G31-NSCLC

The SAF comprised of 758 patients: 378 patients in the SB8 treatment group and 380 patients in the EU Avastin treatment group. Blood samples were collected at pre-dose of Cycle 1, 3, 5, 7 and the End of Treatment (EOT) visit (at least 21 days after the last dose of IP administration and prior to initiation of subsequent therapy for NSCLC).

Overall ADA results (up to the relevant time point) were determined as positive for a subject with a negative ADA at pre-dose Cycle 1 who had at least one positive result after pre-dose of Cycle 1, and for subjects with a positive ADA at pre-dose Cycle 1, who had at least one positive result with higher titre level compared with baseline (i.e., treatment-boosted ADA).

Table 59: Incidence of ADA and NAbs by visit (Safety set, study SB8-G31-NSCLC)

Timepoint	Parameter	Assessment	SB8 N = 378		EU Avastin® N = 380		Total N = 758	
			n/n'	(%)	n/n'	(%)	n/n'	(%)
Cycle 1 (BL)	ADA	Positive	15/372	(4.0)	15/371	(4.0)	30/743	(4.0)
		Negative	357/372	(96.0)	356/371	(96.0)	713/743	(96.0)
	NAb	Positive	0/15	(0.0)	1/15	(6.7)	1/30	(3.3)
		Negative	15/15	(100.0)	14/15	(93.3)	29/30	(96.7)
Cycle 3	ADA	Positive	29/338	(8.6)	22/338	(6.5)	51/676	(7.5)
		Negative	309/338	(91.4)	316/338	(93.5)	625/676	(92.5)
	NAb	Positive	9/29	(31.0)	9/22	(40.9)	18/51	(35.3)
		Negative	20/29	(69.0)	13/22	(59.1)	33/51	(64.7)
Cycle 5	ADA	Positive	15/301	(5.0)	21/296	(7.1)	36/597	(6.0)
		Negative	286/301	(95.0)	275/296	(92.9)	561/597	(94.0)
	NAb	Positive	5/15	(33.3)	8/21	(38.1)	13/36	(36.1)
		Negative	10/15	(66.7)	13/21	(61.9)	23/36	(63.9)
Cycle 7	ADA	Positive	28/266	(10.5)	20/279	(7.2)	48/545	(8.8)
		Negative	238/266	(89.5)	259/279	(92.8)	497/545	(91.2)
	NAb	Positive	12/28	(42.9)	11/20	(55.0)	23/48	(47.9)
		Negative	16/28	(57.1)	9/20	(45.0)	25/48	(52.1)
EOT	ADA	Positive	21/150	(14.0)	9/161	(5.6)	30/311	(9.6)
		Negative	129/150	(86.0)	152/161	(94.4)	281/311	(90.4)
	NAb	Positive	9/21	(42.9)	5/9	(55.6)	14/30	(46.7)
		Negative	12/21	(57.1)	4/9	(44.4)	16/30	(53.3)
Cycle 7 Overall	ADA	Positive	46/341	(13.5)	34/337	(10.1)	80/678	(11.8)
		Negative	284/341	(83.3)	294/337	(87.2)	578/678	(85.3)
		Inconclusive	11/341	(3.2)	9/337	(2.7)	20/678	(2.9)
EOT Overall	ADA	Positive	55/341	(16.1)	37/337	(11.0)	92/678	(13.6)
		Negative	276/341	(80.9)	291/337	(86.4)	567/678	(83.6)
		Inconclusive	10/341	(2.9)	9/337	(2.7)	19/678	(2.8)

ADA = anti-drug antibody; BL = Baseline; NAb = neutralizing antibody; EOT = end of treatment; N = number of patients in the Safety Set; n = number of patients; n' = Number of patients with available assessment results at each time point; Percentages were based on n'.
NAb results only for patients with ADA positive against SB8 were used for the summary.
Overall ADA results were determined as 'Positive' for a patient with treatment-induced or treatment-boosted ADA where treatment-induced ADA indicates at least one positive result after pre-dose of Cycle 1 for patients with negative ADA at pre-dose of Cycle 1, and treatment-boosted ADA indicates at least one positive result with higher titer level compared to the pre-dose of Cycle 1 after pre-dose of Cycle 1 for patients with positive ADA at pre-dose of Cycle 1.
Overall ADA result was defined as 'Negative' for a patient without positive ADA until Cycle 7 and EOT.
Overall ADA result was defined as 'Inconclusive' for a patient with positive ADA at Cycle 1 and without a positive result with a higher titer level observed after pre-dose of Cycle 1 up to Cycle 7 and EOT.
Source: Section 5.3.5.1 Final CSR SB8-G31-NSCLC, Table 12-14, Table 14.3-3.1 and Table 14.3-3.3

ADA formation was similar at each time point, being 13.5% vs. 10.1% with SB8 and EU Avastin, respectively by cycle 7. At EOT the difference was more pronounced: 14% of patients were tested ADA positive with SB8 compared to 5.6% with EU sourced Avastin, with statistically significant association between treatments and the ADA status at EOT (p=0.0121).

Overall 16.1% vs. 11.0 % of subjects with SB8 and EU Avastin, respectively, had ADA formation up to EOT. A respectable proportion of ADA positive patients also tested positive for neutralizing antibodies (up to 42.9% of ADA pos. patients with SB8 compared to 55.6% of ADA pos. patients with EU Avastin at EOT). Distribution of high and low titres were comparable at each cycle except for EOT, where one patient each had a titre of 128, 256, 512 with SB8 compared to none with EU Avastin.

Table 60: Incidence of overall neutralising antibody (Nab) result at EOT by treatment group (safety set, study SB8-G31-NSCLC)[a]

Parameter	Assessment	SB8 N = 378 n (%)	EU Avastin® N = 380 n (%)	Total N = 758 n (%)
Overall NAb	Positive	28 (7.4%)	26 (6.8%)	54 (7.1%)
	Negative	39 (10.3%)	24 (6.3%)	63 (8.3%)

N = number of patients in the Safety Set (SAF); n = number of patients; NAb = neutralizing antibody; Percentages were based on the number of patients in the Safety Set.
NAb results only for patients with anti-drug antibody positive to SB8 or EU Avastin® were used for the summary.
Percentage were based on the Safety Set of each treatment group.

Table 61: Incidence of overall neutralising antibody result up to EOT by treatment group (safety set, study SB8-G31-NSCLC) (*Ad-hoc* analysis)

Parameter	Assessment	SB8 N=378 n (%)	EU Avastin® N=380 n (%)	Total N=758 n (%)
Overall NAb	Positive	26 (6.9%)	23 (6.1%)	49 (6.5%)
	Negative	29 (7.7%)	14 (3.7%)	43 (5.7%)

N = number of patients in the Safety Set (SAF); n = number of patients; NAb = neutralizing antibody
Percentages were based on the number of patients in the Safety Set.
NAb results only for patients with overall ADA positive up to EOT against SB8 or EU Avastin® were used for the summary.

Table 62: Incidence of overall neutralising antibody result up to cycle 7 by treatment group (safety set, study SB8-G31-NSCLC) (*Ad-hoc* analysis)

Parameter	Assessment	SB8 N=378 n (%)	EU Avastin® N=380 n (%)	Total N=758 n (%)
Overall NAb	Positive	19 (5.0%)	20 (5.3%)	39 (5.1%)
	Negative	27 (7.1%)	14 (3.7%)	41 (5.4%)

N = number of patients in the Safety Set (SAF); n = number of patients; NAb = neutralizing antibody
Percentages were based on the number of patients in the Safety Set.
NAb results only for patients with overall ADA positive up to Cycle 7 against SB8 or EU Avastin® were used for the summary.

The applicant presented the requested NAb results by cycle 7 (overall), by EOT and up to EOT.

Impact of ADAs on pharmacokinetics:

In the pivotal Phase I PK study SB8-G11-NSCLC, the overall incidence of ADA was comparable between the SB8 and EU Avastin treatment groups. One subject (2.6%) in the SB8 group and 4 subjects

(10.3%) in the EU-Avastin group exhibited post-dose ADA positive results. None of the subjects developed NAbs after administration of SB8 or EU-Avastin.

In the PK substudy of the Phase III trial SB8-G31-NSCLC, it was noticed, that the mean C_{trough} and C_{max} values were constantly lower for SB8 compared to EU Avastin. This difference was further confirmed in the subgroups of ADA positive and ADA negative patients.

Table 63: Number of positive titre observations by cycle in study SB8-G31-NSCLC

Timepoint	Parameter	Assessment	SB8 N=161 n/n' (%)	EU Avastin® N=180 n/n' (%)	Total N=341 n/n' (%)
Cycle 1 (Baseline)	ADA	Positive	9/159 (5.7)	8/178 (4.5)	17/337 (5.0)
		1	3/9 (33.3)	1/8 (12.5)	4/17 (23.5)
		2	1/9 (11.1)	0/8 (0.0)	1/17 (5.9)
		4	1/9 (11.1)	2/8 (25.0)	3/17 (17.6)
		8	2/9 (22.2)	2/8 (25.0)	4/17 (23.5)
		16	0/9 (0.0)	1/8 (12.5)	1/17 (5.9)
		32	2/9 (22.2)	2/8 (25.0)	4/17 (23.5)
		64	0/9 (0.0)	0/8 (0.0)	0/17 (0.0)
		128	0/9 (0.0)	0/8 (0.0)	0/17 (0.0)
		256	0/9 (0.0)	0/8 (0.0)	0/17 (0.0)
		512	0/9 (0.0)	0/8 (0.0)	0/17 (0.0)
Cycle 3	ADA	Positive	15/144 (10.4)	11/160 (6.9)	26/304 (8.6)
		1	2/15 (13.3)	2/11 (18.2)	4/26 (15.4)
		2	3/15 (20.0)	1/11 (9.1)	4/26 (15.4)
		4	5/15 (33.3)	3/11 (27.3)	8/26 (30.8)
		8	3/15 (20.0)	2/11 (18.2)	5/26 (19.2)
		16	0/15 (0.0)	1/11 (9.1)	1/26 (3.8)
		32	1/15 (6.7)	2/11 (18.2)	3/26 (11.5)
		64	0/15 (0.0)	0/11 (0.0)	0/26 (0.0)
		128	0/15 (0.0)	0/11 (0.0)	0/26 (0.0)
		256	0/15 (0.0)	0/11 (0.0)	0/26 (0.0)
		512	1/15 (6.7)	0/11 (0.0)	1/26 (3.8)
Cycle 5	ADA	Positive	8/125 (6.4)	9/142 (6.3)	17/267 (6.4)
		1	3/8 (37.5)	1/9 (11.1)	4/17 (23.5)
		2	1/8 (12.5)	1/9 (11.1)	2/17 (11.8)
		4	3/8 (37.5)	1/9 (11.1)	4/17 (23.5)
		8	0/8 (0.0)	2/9 (22.2)	2/17 (11.8)
		16	0/8 (0.0)	1/9 (11.1)	1/17 (5.9)
		32	0/8 (0.0)	1/9 (11.1)	1/17 (5.9)
		64	1/8 (12.5)	1/9 (11.1)	2/17 (11.8)

		128	0/8 (0.0)	1/9 (11.1)	1/17 (5.9)
		256	0/8 (0.0)	0/9 (0.0)	0/17 (0.0)
		512	0/8 (0.0)	0/9 (0.0)	0/17 (0.0)
Cycle 7	ADA	Positive	10/111 (9.0)	11/131 (8.4)	21/242 (8.7)
		1	2/10 (20.0)	1/11 (9.1)	3/21 (14.3)
		2	0/10 (0.0)	1/11 (9.1)	1/21 (4.8)
		4	1/10 (10.0)	2/11 (18.2)	3/21 (14.3)
		8	5/10 (50.0)	3/11 (27.3)	8/21 (38.1)
		16	1/10 (10.0)	1/11 (9.1)	2/21 (9.5)
		32	0/10 (0.0)	1/11 (9.1)	1/21 (4.8)
		64	1/10 (10.0)	0/11 (0.0)	1/21 (4.8)
		128	0/10 (0.0)	2/11 (18.2)	2/21 (9.5)
		256	0/10 (0.0)	0/11 (0.0)	0/21 (0.0)
		512	0/10 (0.0)	0/11 (0.0)	0/21 (0.0)
EOT	ADA	Positive	9/72 (12.5)	6/83 (7.2)	15/155 (9.7)
		1	1/9 (11.1)	0/6 (0.0)	1/15 (6.7)
		2	0/9 (0.0)	0/6 (0.0)	0/15 (0.0)
		4	3/9 (33.3)	2/6 (33.3)	5/15 (33.3)
		8	1/9 (11.1)	0/6 (0.0)	1/15 (6.7)
		16	0/9 (0.0)	3/6 (50.0)	3/15 (20.0)
		32	1/9 (11.1)	0/6 (0.0)	1/15 (6.7)
		64	1/9 (11.1)	1/6 (16.7)	2/15 (13.3)
		128	0/9 (0.0)	0/6 (0.0)	0/15 (0.0)
		256	1/9 (11.1)	0/6 (0.0)	1/15 (6.7)
		512	1/9 (11.1)	0/6 (0.0)	1/15 (6.7)

ADA = anti-drug antibody; EOT = End of Treatment
N= number of patients in the pharmacokinetic (PK) population; n = number of patients with event of interest; n' = number of patients with available assessment results at each time point Percentages were based on n'.
Results of titer for ADA positive reported as '< 1' were converted to '1' for summary.
Result of titer for ADA positive reported as 'Indeterminate' was treated as missing.

The number and percentage of patients with ADAs for the PK population of the Phase III study were presented by treatment group at each cycle as well as the overall ADA results up to Cycle 7 and EOT . The number of patients with an overall ADA-positive result up to Cycle 7 was 24 (16.1%) patients in the SB8 treatment group and 17 (10.6%) patients in the EU Avastin treatment group. The number of patients with an overall ADA-positive result up to EOT was 28 (18.8%) patients in the SB8 treatment group and 18 (11.2%) patients in the EU Avastin treatment group. There was no statistically significant difference (p-value > 0.05) for ADA formation at each cycle, but the study was not powered to detect any differences. The incidence of ADA formation in the PK subgroup with SB8 was higher at all cycles (1,3,5,7) and at EOT, but the percentage differences were generally low with highest difference at EOT with 5.3%. For cycles 1-7, the highest percentage difference in ADA formation was at cycle 3 with 3.5%.

Summary statistics of PK parameters (C_{trough} and C_{max}) by overall ADA results up to Cycle 7 for the PK population were provided. In the Avastin treatment group, the mean C_{trough} at all cycles in the ADA-positive subgroup was lower than the corresponding values in the ADA-negative subgroup, whereas the mean C_{trough} of SB8 were sometimes higher or lower in the ADA-positive subgroup compared to the ADA-negative subgroup. Mean C_{max} of both SB8 and Avastin at all cycles in the ADA-positive subgroup was higher than in the ADA-negative subgroup.

Taken together, the percentage of ADA-positive patients per cycle in the PK population are overall comparable between the SB8 and EU Avastin treatment groups and the influence on PK values is considered minimal. The difference in mean PK outcomes does not seem to be associated with the difference in ADA formation, i.e. higher differences in the number of ADA positive patients does not lead to higher differences in mean concentration outcomes between treatment groups comparing all cycles (comparing Table 11 to Table 63).

Impact of ADAs on efficacy:

Best ORR was separately presented for ADA positive and ADA negative patients. Slightly more responders in the SB8 treatment arm were ADA positive by cycle 7: 13.5% vs 10.1% subjects with SB8 and Avastin, respectively. The influence of ADA formation on ORR was quite different: whereas with SB8 best ORR rate was lower in ADA positive patients compared to ADA negative patients, response incidence was higher in the ADA positive patients compared to ADA negative patients in the

Avastin treatment arm. The difference [95% CI] in best ORR among subjects with an overall negative ADA result was 6.9% [-1.6%, 15.5%] and in positive ADA result -9.3% [-31.6%, 13.0%] for the PPS, with the lower bound of the CI lying much below the non-inferiority margin. A direct comparison to the primary analysis is not possible, as efficacy outcomes for ADA were presented by cycle 7 compared to best ORR by w24 for the primary endpoint.

Additional analyses of ORR by w24 with imputation of values for patients who discontinue the study were also presented.

Table 64: Subgroup analysis of difference in best overall response rate during the induction treatment period by 24 weeks by overall ADA result up to cycle 7 (Per-protocol set, study SB8-G31-NSCLC) (Ad-hoc analysis)

Parameter	SB8 N=337	EU Avastin® N=328
ADA positive subject, N'	45	33
Best ORR: CR+PR [n (%)]	18 (40.6%)	17 (51.2%)
95% CI within treatment group	[26.2%, 56.2%]	[33.3%, 69.0%]
Difference of Best ORR: SB8 – Avastin	−10.7%	
95% CI	[−33.0%, 11.6%]	
ADA negative subject, N'	259	261
Best ORR: CR+PR [n (%)]	130 (50.3%)	118 (45.2%)
95% CI within treatment group	[44.0%, 56.5%]	[39.1%, 51.5%]
Difference of Best ORR: SB8 – Avastin	5.0%	
95% CI	[−3.5%, 13.6%]	
ADA inconclusive subject, N'	9	8
Best ORR: CR+PR [n (%)]	5 (58.8%)	4 (50.0%)
95% CI within treatment group	[23.8%, 88.1%]	[15.7%, 84.3%]
Difference of Best ORR: SB8 – Avastin	8.8%	
95% CI	[−38.4%, 55.9%]	

ADA = Anti-Drug Antibody; CI = confidence interval
The best ORR was defined as the proportion of subjects whose best overall response was either complete response (CR) or partial response (PR) according to RECIST v1.1 during the induction treatment period by 24 weeks.
Missing data from patients who withdrew the study due to death and disease progression without any tumor assessment were considered as non-responder.
Missing data from patients who withdrew the study with reasons other than death and disease progression without any tumor assessment were imputed using multiple imputation method.
Difference and 95% CI were estimated by the binomial regression model with treatment group as an explanatory variable.

Table 65: Overall response rate at each cycle by overall ADA status up to cycle 7 during the induction period (Per-protocol set, study SB8-G31-NSCLC) (Ad-hoc analysis)

	Overall ADA Positive		Overall ADA Negative	
	SB8 (N = 45)	EU Avastin® (N = 33)	SB8 (N=259)	EU Avastin® (N = 261)
Timepoint	n (%)	n (%)	n (%)	n (%)
Cycle 2	9 (20.0%)	12 (36.4%)	80 (31.0%)	73 (28.0%)
Cycle 4	18 (40.4%)	15 (45.5%)	119 (45.8%)	109 (41.8%)
Cycle 6	13 (29.3%)	8 (25.0%)	109 (42.2%)	94 (36.0%)

ADA = anti-drug antibody; N= number of patients determined with overall ADA positive or negative' n = number of patients whose overall response either complete response or partial response at each cycle
Missing data from patients who withdrew the study with reasons other than death and disease progression without any tumor assessment were imputed using multiple imputation method.
Missing data from patients who withdrew the study due to death and disease progression without any tumor assessment were considered as non-responder.

The response was higher in ADA positive patients compared to ADA negative patients in the Avastin treatment arm. In contrast, response was lower in ADA positive patients compared to ADA negative patients with SB8. Comparison of PFS and DOR shows no relevant effect of ADA development on these efficacy endpoints in both treatment groups.

The applicant further investigated influencing factors on ORR by ADA subgroup, as baseline or disease characteristics. Some unfavourable prognostic factors (e.g. higher proportion of patients in age ≥ 65 years and ≥ 70 years, males, non-Asian, cancer type of other than adenocarcinoma, ECOG PS of 1 rather than 0, and formal and current smoker) were detected in the ADA positive patients treated with SB8 compared to Avastin.

Impact of ADAs on safety:

Subgroup safety analysis by overall ADA results up to EOT was performed on the SAF. Overall, in ADA positive patients, more patients experienced TEAEs with SB8 compared to EU Avastin: 53 vs. 35 patients until EOT, respectively. A total of 4126 TEAEs were reported for 519 patients (252 in the SB8 and 267 in the EU Avastin treatment groups) with an overall negative ADA result until EOT. The most commonly reported TEAEs at the system organ class (SOC) level was skin and subcutaneous tissue disorders in both ADA positive and ADA negative subgroups.

As a follow-up, the Applicant investigated the ADA status at the time of start date of TEAEs among overall ADA-positive patients who discontinued the study due to TEAEs in both treatment groups along with the assessments for IP and non-IP relatedness and the severity of TEAEs to explore the association of TEAEs and ADA results. There was a numerically higher incidence of TEAEs leading to discontinuation in patients with overall ADAs up to EOT in the SB8 treatment group. When considering the causal relationship of the TEAEs with immunogenicity, only 2 events (one patient with anaphylaxis reaction and one with hypersensitivity) appeared to be related to immunogenicity.

ADAs at EOT represents the incidence of ADA positive results at EOT timepoint without consideration of 'treatment induced ADA' or 'treatment-boosted ADA', 'transient' and 'inconclusive'. Twenty-one (14%) patients in the SB8 and 9 (5.6%) patients in the EU Avastin group had ADAs at EOT and 55 (16.1%) patients in the SB8 and 37 (11%) patients in the EU Avastin group had overall ADAs up to EOT. Twenty-eight (7.4%) patients in the SB8 and 26 (6.8%) patients in the EU Avastin group had nAbs at EOT and 26 (6.9%) patients in the SB8 and 23 (6.1%) patients in the EU Avastin group had nAbs up to EOT. Up to Cycle 7, 19 (5%) patients in the SB8 and 20 (5.3%) patients in the EU Avastin group had nAbs.

Safety related to drug-drug interactions and other interactions

No drug-drug interactions studies were submitted.

Discontinuation due to adverse events

Phase I Study SB8-G11-NHV

No subjects discontinued due to a TEAE.

Phase III Study SB8-G31-NSCLC

- **TEAEs leading to IP or Non-IP Discontinuation**

A summary of TEAEs leading to IP or non-IP discontinuation is presented in Table 66.

The most frequently reported TEAEs considered related to IP discontinuation were asthenia, dyspnoea, and pulmonary embolism (Table 67).

The most frequently reported TEAEs considered related to paclitaxel discontinuation were anaemia, thrombocytopenia, and neutropenia.

The most frequently reported TEAEs considered related to carboplatin discontinuation were thrombocytopenia, neutropenia, and anaemia.

Table 66: Summary of adverse events leading to investigational product or non-investigational product discontinuation (safety set)

Number of subjects experiencing	SB8 N = 378 n (%) E	Avastin® N = 380 n (%) E	Total N = 758 n (%) E
TEAEs leading to IP discontinuation	50 (13.2) 58	36 (9.5) 43	86 (11.3) 101
Drug related TEAE leading to IP discontinuation	4 (1.1) 4	1 (0.3) 1	5 (0.7) 5
TEAEs leading to Paclitaxel discontinuation	43 (11.4) 49	42 (11.1) 50	85 (11.2) 99
Drug related TEAE leading to Paclitaxel discontinuation	2 (0.5) 2	2 (0.5) 2	4 (0.5) 4
TEAEs leading to Carboplatin discontinuation	44 (11.6) 50	37 (9.7) 45	81 (10.7) 95
Drug related TEAE leading to Carboplatin discontinuation	2 (0.5) 2	0 (0.0) 0	2 (0.3) 2

IP = Investigational product; TEAE = treatment-emergent adverse event; N = number of subjects in the Safety set; n = number of subjects with TEAEs; E = frequency of the adverse events.
Source: Table 14.3.1-1.1

A summary of TEAEs by SOC and PT leading to IP discontinuation is provided in the below table.

The most common reasons by SOC for IP discontinuation were respiratory, thoracic and mediastinal disorders (2.6% of patients in the SB8 treatment group and 3.2% in the Avastin treatment group).

In the SB8 treatment group, the most frequently reported TEAEs at the PT level were asthenia (5 [1.3%] patients) and dyspnoea (4 [1.1%] patients). In the Avastin treatment group, the most frequently reported TEAEs at the PT level were pulmonary embolism (7 [1.8%] patients) and asthenia (6 [1.6%] patients).

Table 67: Summary of treatment-emergent adverse events by system organ class and preferred term leading to investigational product discontinuation during the overall study period (safety set)

System organ class Preferred term	SB8 N = 378 n (%) E	Avastin® N = 380 n (%) E	Total N = 758 n (%) E
Any TEAE leading to discontinuation of IP	50 (13.2) 58	36 (9.5) 43	86 (11.3) 101
Blood and lymphatic system disorders	**2 (0.5) 2**	**1 (0.3) 1**	**3 (0.4) 3**
Anaemia	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Thrombocytopenia	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Febrile neutropenia	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Cardiac disorders	**2 (0.5) 2**	**1 (0.3) 1**	**3 (0.4) 3**
Acute myocardial infarction	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Myocardial ischaemia	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Myocardial infarction	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Endocrine disorders	**0 (0.0) 0**	**1 (0.3) 1**	**1 (0.1) 1**
Hypothyroidism	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Eye disorders	**1 (0.3) 1**	**0 (0.0) 0**	**1 (0.1) 1**
Optic atrophy	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Gastrointestinal disorders	**2 (0.5) 2**	**3 (0.8) 3**	**5 (0.7) 5**
Gastritis	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Small intestinal perforation	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Duodenal ulcer	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Gastric ulcer	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Gastric ulcer haemorrhage	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
General disorders and administration site conditions	**7 (1.9) 7**	**10 (2.6) 10**	**17 (2.2) 17**
Asthenia	5 (1.3) 5	6 (1.6) 6	11 (1.5) 11
Fatigue	2 (0.5) 2	4 (1.1) 4	6 (0.8) 6
Immune system disorders	**4 (1.1) 4**	**0 (0.0) 0**	**4 (0.5) 4**
Hypersensitivity	2 (0.5) 2	0 (0.0) 0	2 (0.3) 2
Anaphylactic reaction	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Anaphylactic shock	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Infections and infestations	**7 (1.9) 7**	**2 (0.5) 2**	**9 (1.2) 9**
Pneumonia	3 (0.8) 3	0 (0.0) 0	3 (0.4) 3
Cellulitis	2 (0.5) 2	1 (0.3) 1	3 (0.4) 3
Atypical pneumonia	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Infectious pleural effusion	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1

System organ class Preferred term	SB8 N = 378 n (%) E	Avastin® N = 380 n (%) E	Total N = 758 n (%) E
Lung abscess	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Injury, poisoning and procedural complications	**1 (0.3) 1**	**0 (0.0) 0**	**1 (0.1) 1**
Post procedural fistula	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Investigations	**2 (0.5) 4**	**1 (0.3) 3**	**3 (0.4) 7**
Alanine aminotransferase increased	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Aspartate aminotransferase increased	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Blood creatinine increased	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Creatinine renal clearance decreased	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Blood bilirubin increased	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Metabolism and nutrition disorders	**1 (0.3) 1**	**1 (0.3) 1**	**2 (0.3) 2**
Decreased appetite	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Tumour lysis syndrome	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Musculoskeletal and connective tissue disorders	**1 (0.3) 1**	**0 (0.0) 0**	**1 (0.1) 1**
Muscular weakness	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Nervous system disorders	**5 (1.3) 5**	**2 (0.5) 2**	**7 (0.9) 7**
Cerebral ischaemia	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Encephalopathy	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Ischaemic stroke	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Neuropathy peripheral	1 (0.3) 1	2 (0.5) 2	3 (0.4) 3
Transient ischaemic attack	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Renal and urinary disorders	**3 (0.8) 3**	**1 (0.3) 1**	**4 (0.5) 4**
Proteinuria	3 (0.8) 3	0 (0.0) 0	3 (0.4) 3
Cystitis glandularis	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Respiratory, thoracic and mediastinal disorders	**10 (2.6) 10**	**12 (3.2) 12**	**22 (2.9) 22**
Dyspnoea	4 (1.1) 4	2 (0.5) 2	6 (0.8) 6
Haemoptysis	3 (0.8) 3	1 (0.3) 1	4 (0.5) 4
Pulmonary embolism	3 (0.8) 3	7 (1.8) 7	10 (1.3) 10
Dyspnoea exertional	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Pulmonary thrombosis	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Skin and subcutaneous tissue disorders	**1 (0.3) 1**	**2 (0.5) 4**	**3 (0.4) 5**
Skin ulcer	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Decubitus ulcer	0 (0.0) 0	1 (0.3) 3	1 (0.1) 3
Rash	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1
Vascular disorders	**6 (1.6) 7**	**2 (0.5) 2**	**8 (1.1) 9**
Embolism arterial	2 (0.5) 2	0 (0.0) 0	2 (0.3) 2
Hypertensive crisis	2 (0.5) 2	1 (0.3) 1	3 (0.4) 3
Jugular vein thrombosis	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Peripheral artery thrombosis	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Superior vena cava syndrome	1 (0.3) 1	0 (0.0) 0	1 (0.1) 1
Hypertension	0 (0.0) 0	1 (0.3) 1	1 (0.1) 1

IP = investigational product; TEAE = treatment-emergent adverse event; N = number of subjects in the Safety set; n = number of subjects with TEAEs; E = frequency of the adverse events.
Adverse events were coded to system organ class (SOC) and preferred term (PT) using the MedDRA version 20.0 coding dictionary. SOCs are presented alphabetically. PTs are sorted within the SOC in descending order of subject frequency in the SB8 treatment group. If the frequencies of the PTs are the same, the PTs are sorted alphabetically.
Source: Table 14.3.1-1.11

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The Applicant has provided safety data from Phase I single-dose PK clinical trial in healthy male volunteers (Study SB8-G11-NHV), and one Phase III clinical trial in adult NSCLC patients (Study SB8-G31-NSCLC).

In the pivotal PK study, the safety population consisted of 119 healthy male subjects aged 18 to 59 years who were randomised to one of three treatment arms and exposed to a single dose of 3mg/kg bevacizumab i.v. (SB8: 40 subjects; EU sourced Avastin: 40 subjects; US sourced Avastin: 39 subjects). In the Phase III trial, the safety population consisted of all NSCLC patients who received bevacizumab (either SB8 or EU Avastin) at a dose of 15 mg/kg i.v. at least once. Hence, a total of 758 out of the 763 randomized patients were included in the SAF (SB8 group: 378 patients [99.7%]; EU Avastin group: 380 patients [99%]). The overall safety population is considered sufficient to capture relevant safety signals in this comparability exercise.

In the efficacy study, NSCLC patients were randomized in a 1:1 ratio to receive either an IV dose of 15 mg/kg of SB8 or EU Avastin plus paclitaxel and carboplatin (every three weeks) for at least 4 and no more than 6 cycles (induction treatment phase). Patients who responded to treatment continued with bevacizumab as monotherapy in the maintenance treatment phase until evidence of disease progression (PD), unacceptable toxicity, death, or 12 months from the randomization of the last patient (End of Study [EOS]), whichever occurred first.

Due to the heterogeneity of the study populations and the different treatment schemes used in both studies, no pooled safety analysis of the two clinical trials was applicable.

A similar extent of exposure was observed between the two treatment arms in the efficacy study with regard to the mean cumulative actual doses during the induction and maintenance treatment period, the mean duration of exposure (SB8 34.26 weeks, range: 3 to 105.4 weeks; EU-Avastin 35.26 weeks, range: 3 to 101.3 weeks) and mean number of cycles received (4.8 cycles in both treatment groups during the induction treatment; 9.3 cycles in the SB8 group and 9.1 cycles in the EU-Avastin group during the maintenance treatment period). The number of patients who received bevacizumab decreased constantly throughout the study duration and to a similar extent in both groups.

The overall extent of exposure to paclitaxel and carboplatin was also similar between the two groups and dose reduction of paclitaxel and carboplatin due to mainly AEs, were necessary in a similar proportion of patients in both groups.

The proportion of patients who experienced at least one dose delay of bevacizumab during the induction or maintenance treatment phase was comparable between both treatment groups. The main reasons were AEs (17.5% in the SB8 group and 14.5% in the EU Avastin group). Upon request, the Applicant provided data in relation to dose delay of bevacizumab during the induction or maintenance treatment phase. The difference in dose delay due to adverse events in the maintenance phase was minimal, whereas in the induction phase 66 patients had 100 AEs leading to dose delay in the SB8 group compared to 55 patients and 87 events in the Avastin group. The differences were mainly observed in Blood and lymphatic system disorders and other laboratory blood parameters (SOC "Investigations"). Hematologic TEAE leading to dose delays were further investigated by SOC, PT and CTCAE grade in induction period for patients with at least one dose delay. Beside a difference in `anaemia' (8 [2.1%] patients in the SB8 treatment group and 3 [0.8%] patients in the EU Avastin treatment group) there was no specific trend in other events indicating more events in the SB8 treatment group in comparison to Avastin treatment group (Data not shown).

The number of patients that completed the induction treatment period was comparable between the SB8 and EU Avastin treatment groups (68.1% in the SB8 treatment group and 72.1% in the Avastin treatment group). A similar proportion of patients discontinued during the maintenance treatment period in both groups (58.8% in the SB8 group; 62.2% in the EU Avastin group). The main reasons for discontinuation in the induction and maintenance treatment period in both groups were disease progression, AEs or death in both groups. Thus, at the time of EOS, the proportion of subjects who were ongoing in the maintenance treatment period was very low in both groups, 9.2% in the SB8 treatment group and 9.9% in the EU Avastin treatment group, respectively.

In the pivotal PK trial (Study SB8-G11-NHV) the proportion of subjects who experienced a TEAE was lower in the EU Avastin group (37.5%) as compared to the SB8 (50%) and US-Avastin group (53.8%) groups. All of the TEAEs were however, grade 1 (mild) in severity, with the exception of one TEAE being grade 3 in the SB8 group (a severe perirectal abscess, considered to be serious) and one TEAE being grade 3 in the US-Avastin group (severe syncope; not considered to be serious). The Applicant considered the two TEAEs to be unlikely related to the IP based on the late onset of the AEs (53 days and 71 days, respectively). In the case of the perirectal access, this argumentation cannot be followed, since an abscess does not originate spontaneously. The Applicant further stated that upon retrospective review of all cases grouped under the same primary SOCs as those two events, no particular safety risk was identified. This is acknowledged but it should be noted that the sample size (N=119) is too small to draw firm conclusions on differences in these AEs based on the results obtained in Study SB8-G11-NHV. No TEAES of Grade 4 (life threatening) or 5 (death) in severity and no discontinuations due to TEAEs or other safety issues occurred during the study in any of the groups. No infusion related reactions were reported in this study.

The most frequently affected SOCs among the treatment groups in Study SB8-G11-NHV were infections and infestations and gastrointestinal disorders. A higher incidence of gastro-intestinal disorders was noticed however, in the SB8 group (22.5%) when compared with the EU- (5.0%) or US-Avastin groups (5.1%). According to the Applicant, only 1 of the 16 TEAEs in SOC "GI disorders" was assessed as "related to IP". The number of subjects experiencing TEAEs related to IP was similarly low between the three treatment groups.

In the efficacy trial (Study SB8-G31-NSCLC), the majority of patients (91.6%) experienced at least one causality TEAE (92.1% in the SB8 group; 91.1% in the EU Avastin group), most of the TEAEs being grade 1 and grade 2 in severity in both treatment groups. In general, across both treatment arms, the incidence, type and severity of TEAEs seem similar and the distribution is in line with the safety profile for bevacizumab (SmPC Avastin). No new safety signals were identified during the induction period, 70 IP-related Grade 3 TEAEs occurred in 32 (8.5%) patients in the SB8 treatment group and 44 events occurred in 20 (5.3%) patients in the EU Avastin treatment group. Thus, the majority of TEAEs causing the imbalance in the incidence rate of Grade 3 TEAEs occurred during the induction period where the IP was administered concurrently with chemotherapy. Although this kind of TEAEs is also known for the chemotherapy, this does not explain the imbalance between the two groups. All in all, the numbers of patients and events of leukopenia in the induction period were consistently higher in the SB8 group compared to the Avastin group. The Applicant clarified that the difference of events reported by PT 'leukopenia' between treatment groups during the induction treatment period was due to a higher incidence of Grade 1 leukopenia in the SB8 treatment group (18 (4.8%) patients with 23 events in the SB8 group versus 8 (2.1%) patients with 9 events in the EU Avastin group). The numerically higher incidence of Grade 1 'leukopenia' is considered clinically negligible based on similar characteristics of reported events between the treatment groups and on the comparable results between the SB8 and EU

Avastin treatment groups obtained from an extended analysis of related PTs grouped under the AESI of neutropenia.

Among the AESIs (all Grades) occurring in ≥ 0.5% of patients, the overall AESIs showing ≥ 1% difference between treatments were ATE, hypertension, cardiac disorders (excluding CHF and ATE) (higher in the SB8 treatment group), and pulmonary haemorrhage, pulmonary hypertension and peripheral sensory neuropathy (higher in the EU Avastin treatment group). The absolute incidence of all these events in both treatment groups were within the expected range of the incidence of similar events previously described for bevacizumab.

The reported TEAEs for hypertension and proteinuria grade ≥ 3 were found to be within the expected incidences for the reference product Avastin (see Avastin EPAR) and considered comparable between the two treatment arms. It is noticed however, that a slightly higher number of patients exhibited "hypertension grade ≥ 3" in the SB8 group (7.7% of the patients; EU Avastin: 4.2%). An ad-hoc analysis of the number and proportion of patients who experienced hypertension (PT) with Grade ≥ 3 using the Wald's method resulted in a difference of 2.66% [95% CI: -0.44%, 5.77%]. Thus, there was no statistical difference in the incidence of hypertension (PT) Grade ≥ 3. Furthermore, an ad-hoc analysis for the AESI hypertension based only on the blood pressure measurements demonstrated comparable results between the SB8 and Avastin treatment groups. It was concluded that based on the comparable incidence of hypertension by objective blood pressure assessment results, the numerical difference in the incidence of hypertension Grade ≥ 3 is deemed clinically negligible. No grade 4 hypertension or proteinuria have been reported in any of the groups (data not shown).

Infusion-related reactions were observed in a slightly higher number of patients of the SB8 group (20/378 patients; 5.3%) compared to the EU Avastin group (11/380 patients; 2.9%). It is further noted, that in the SB8 group slightly more patients exhibited hypersensitivity or anaphylactic reactions after infusions of bevacizumab than in the EU Avastin group and up to a higher number of cycles for each IP and Non-IP. In addition, four patients in the SB8 group (none in the EU Avastin group) experienced immune system disorders leading to IP discontinuation.

The Applicant provided further data on the incidences in hypersensitivity and anaphylactic reactions observed in study SB8-G31-NSCLC (data not shown). Overall, these data seem comparable to historical data with the reference product as described in the Avastin SmPC.

The incidence and type of the SAEs reported in the efficacy study SB8-G31-NSCLC were in line with the known safety profile of bevacizumab and generally comparable between the groups and no clinically meaningful differences were noted. Altogether, 20.6% of the patients experienced SAEs, all of which were treatment-emergent (i.e. serious TEAEs). A summary of the outcomes and further action taken in patients experiencing serious adverse events (SAEs) in the Safety Set (SAF) in the clinical Phase III study (SB8-G31-NSCLC) together with a summary of SAEs separately for the induction treatment period and maintenance treatment period were provided (data not shown).. All SAEs including serious TEAEs, serious TEAEs leading to IP/non-IP discontinuation and death were comparable between treatments during induction and maintenance treatment period.

SAEs leading to death occurred in a total of 49 patients: in 22 patients (5.8%) of the SB8 group, and in 27 (7.1%) patients of the EU Avastin group. The most commonly reported TEAEs leading to death were similar between both groups including respiratory, thoracic and mediastinal disorders (1.3% in the SB8 and 2.9% in the Avastin treatment groups), general disorders and administration site conditions (1.3% and 1.6%, respectively), and nervous system disorders (0.8% and 1.1%, respectively). There were two patients who died due to cerebrovascular accidents (strokes), one in each treatment group for which detailed case reports were provided. According to these narratives, there were no autopsy nor CNS imaging (CT or MRI) performed in any case. Causal relationship between the fatal cerebrovascular accident AE and the IP (SB8) treatment could not be ruled out, according to the Sponsor; whereas, relationship between the fatal cerebrovascular AE and the IP (Avastin) treatment could not be determined due to the too many confounding factors, including the patient's underlying ankylosing spondylitis (AS), which might result in an elevated risk for haemorrhagic stroke compared to non-AS patients.

A tabulated overview of fatal AEs of haemorrhagic origin for both treatment groups (SB8 and Avastin) showed that the number and incidence of fatal haemorrhage AEs associated with SB8 was comparable to and numerically lower than that of EU Avastin (data not shown).

There was no evidence of clinically relevant differences in any laboratory parameter between the three treatment groups over time in the pivotal PK study and between the two treatment arms in the efficacy study. The laboratory findings along with shifts from normal values for both clinical studies were presented and did not show clinically relevant differences between the treatment groups.

Based on the validation of the assay, the biosimilar drug product and reference product appear similar and the validated single-assay approach can be utilized for the measurement of both anti-SB8 and anti-Avastin antibodies. Antigenic equivalence could be shown for the nAb assay validated for the Phase III study in NSCLC patients justifying the use of the single-assay approach applied by the applicant. The specification criteria set in the validation protocol were met for both of the applied nAb assays.

The evaluation of immunogenicity in the pivotal PK study in healthy volunteers, revealed only one patient positive for ADA development with SB8, with occurrence at d85 (EOS). No subject was tested ADA positive at baseline. Also with EU sourced and US sourced Avastin, ADA formation was very low and transient. No subject developed NAbs and results are considered comparable. In the efficacy trial, antidrug antibodies against bevacizumab seem to be transient. Pre-existing antibody was shown in 30 out of 741 treatment-naïve pre-dose samples (4.0%). Literature on the overall prevalence of pre-existing antibodies by assay also suggests a rate of 4.2% in disease population (Xue L and Rup B, 2013). ADA formation was similar at each time point, being 13.5% vs. 10.1% with SB8 and EU Avastin by cycle 7, respectively. At EOT the difference was more pronounced: 14% of patients were tested ADA positive with SB8 compared to 5.6% with EU sourced Avastin, with statistically significant association between treatments and the ADA status at EOT (p=0.0121). Overall, in ADA positive patients, numerically more subject experienced TEAEs with SB8 compared to EU Avastin: 53 vs. 35 subjects, respectively. The Applicant investigated the ADA status at the time of start date of TEAEs among overall ADA-positive patients who discontinued the study due to TEAEs in both treatment groups along with the assessments for IP and non-IP relatedness and the severity of TEAEs to explore the association of TEAEs and ADA results. There was a numerically higher incidence of TEAEs leading to discontinuation in patients with overall ADAs up to EOT in the SB8 treatment group. When considering the causal relationship of the TEAEs with immunogenicity, only 2 events (one patient with anaphylaxis reaction and one with hypersensitivity) appeared to be related to immunogenicity. This is not considered to affect the comparability of the two IPs.

Overall 16.1% vs. 11.0 % of subjects with SB8 and EU Avastin, respectively, had ADA formation up to EOT. The higher difference in overall ADA results is due to more different patients per cycle being affected in the SB8 compared to the EU Avastin group. For ADA formation at EOT it has to be considered that this happened at different time points for each patient. A significant proportion of ADA positive patients also tested positive for neutralizing antibodies (up to 42.9% of ADA positive patients with SB8 compared to 55.6% of ADA positive patients with EU Avastin at EOT). Distribution of high and low titres were comparable at each cycle except for EOT, where one patient had a titre of 128, 256, 512 with SB8 compared to none with EU Avastin. No difference in the rates of nAbs could be observed between the SB8 and the Avastin treatment group. Up to Cycle 7, 19 (5%) patients in the SB8 and 20 (5.3.%) patients in the EU Avastin group had nAbs. Twenty eight (7.4%) patients in the SB8 and 26

(6.8%) patients in the EU Avastin group had nAbs at EOT and 26 (6.9%) patients in the SB8 and 23 (6.1%) patients in the EU Avastin group had nAbs up to EOT. For the PK subpopulation, no remarkable difference could be seen between treatments in the proportion of ADA-positive patients with higher titre (≥64) which was generally quite low. The distribution of ADA titers are comparable between the two treatment groups for each cycle and higher titer levels are not generally observed for one of the treatments.

Although the Applicant's line of arguments to compare the overall ADA incidences up to EOT between the two treatment groups, which are 'treatment-induced' and 'treatment-boosted ADAs' up to EOT, can be followed, the number of ADAs at EOT was higher in the SB8 group. The number of patients who discontinued due to progressive disease (PD), adverse events (AE) and death between the two treatment groups among the patients by overall ADA status up to EOT was investigated to discuss clinical relevance of differences in ADAs and nAbs between the treatment groups. Only the rate of AEs was higher in the SB8 treatment group, but this does not influence comparability between the treatment groups.

2.6.2. Conclusions on the clinical safety

The incidence, type and severity of TEAEs of the data presented are comparable between SB8 and EU Avastin and are in line with the safety profile for bevacizumab (SmPC Avastin). No new safety signals were identified and the immunogenicity results do not indicate relevant differences to the reference product. Nevertheless, the presence of C-terminal AA sequence variants at low levels in the batches used in the clinical studies, were scrutinised in terms of potential effects on the safety profile of SB8. In addition to safety and immunogenicity data from both clinical Phase I (SB8-G11-NHV) and Phase III (SB8-G31- NSCLC) studies, the C-terminal amino acid (AA) sequence variants of SB8 from structural aspect were discussed and its potential risk of immunogenicity was presented. An impact on immunogenicity and potential related consequences are clinically negligible as the sequence variants are unlikely to activate immunogenicity.

2.7. Risk Management Plan

Safety concerns

Table 68: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Long-term effects of bevacizumab when used in the paediatric population

Pharmacovigilance plan

Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are identified for Aybintio.

Summary of additional PhV activities

There are no additional pharmacovigilance activities (categories 1-3 safety studies) planned for Aybintio.

Risk minimisation measures

The safety information in the proposed product information is aligned to the reference product.

Routine Risk Minimisation Measures

Table 69: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Missing information	
Long-term effects of bevacizumab when used in the paediatric population	Routine risk communication: EU SmPC section 4.2 and 4.8, PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 of the RMP are considered sufficient to manage the safety concerns of the medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Avastin. 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, Aybintio (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

Aybintio (SB8) is developed as a biosimilar to Avastin. The approval is sought for intravenous use in the same therapeutic indications as Avastin, with the exception of the treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel.

- Aybintio in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.
- Aybintio 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.
- Aybintio in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracyclinecontaining regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Aybintio in combination with capecitabine. For further information as to HER2 status.
- Aybintio, 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.

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

At quality level, a comprehensive and well-established biosimilarity exercise, which is in line with the relevant EMA guidelines has been conducted.

An extensive characterisation of the EU-sourced reference medicinal product Avastin including a total of up to 46 EU-sourced lots of Avastin has been provided. The subsequent side-by-side comparison included pilot, clinical and process performance qualification active substance batches as well as clinical and process performance qualification batches of the finished product (for both presentations) and a subset of lots of Avastin.

A broad panel of standard and state-of-the-art methods covering relevant physicochemical as well as biological quality attributes has been used. In particular, the quantity, the primary structure, purity and impurities, charged variants, hydrophobic variants, carbohydrate structure, and higher order structure have been addressed. Regarding the biological characteristics, cell-based potency assays, binding assays, Fc related activities, and additional assays for further characterisation have been used.

In summary, the used panel of methods for characterisation and comparison of SB8 with its reference medicinal product is considered sufficient and no additional tests have been requested.

In terms of non-clinical aspects, two *in vivo* xenograft mouse studies were provided: biosimilarity between SB8 and EU Avastin was studied in a non-small cell lung cancer xenograft model (Study No. E0303-U1501), and between SB8 and US Avastin in a colorectal carcinoma xenograft model (Study No. E0303-U1502). Additionally, biosimilarity between SB8 and US Avastin was studied in 4 weeks repeated dose toxicity study in cynomolgus monkeys (Study No. 000080642).

In general, the clinical development program followed EMA guidelines and prior CHMP advice, and consisted of

- a pivotal three-arm PK study (SB8-G11-NHV), comparing SB8 to EU-sourced and US-sourced Avastin in 119 healthy male subjects, investigating PK, safety and immunogenicity

- a multi-center parallel group efficacy/safety study (>12 months) (SB8-G31-NSCLC) in 763 patients with metastatic or recurrent non-squamous NSCLC to comparatively investigate efficacy, safety, immunogenicity and PK (in a subset of patients).

3.2. *Results supporting biosimilarity*

Quality results

A comprehensive and robust biosimilarity exercise demonstrates similarity of the biosimilar candidate with its reference medicinal product. In particular, the various assays addressing the biological functions of bevacizumab showed a highly similar profile of SB8 with its reference medicinal product. At the physicochemical level, some differences have been observed. These differences have been sufficiently justified to have no impact on the clinical performance of Aybintio and its biosimilarity to the reference medicinal product.

Non-clinical results

Non-clinical studies supported biosimilarity between SB8 and Avastin. The biological functions of SB8 and EU-sourced Avastin assessed in vitro, i.e. VEGF-A binding, VEGF-A neutralization, inhibition of HUVEC proliferation and migration as well as Fc-related activities, have been demonstrated to be similar. The anti-tumour activity of SB8 and EU Avastin was generally comparable in the non-small cell lung cancer mouse xenograft model (Study No. E0303-U1501), and the toxicological and toxicokinetic profile of SB8 and US Avastin was similar in the 4 weeks repeated dose toxicity study (Study *No.* 000080642).

Clinical results

Pharmacokinetics: In the pivotal PK study SB8-G11-NHV, the primary PK analysis demonstrated PK comparability of SB8 with its reference product EU-Avastin as the 90% confidence intervals for the ratios of the primary ($AUC_{0\text{-}inf}$) and key secondary parameters (AUC_{last}, C_{max}) were well contained within the standard bioequivalence interval of 0.80–1.25. The geometric LSMean ratios (90% CI) for SB8 and EU Avastin in AUC_{inf}, AUC_{last}, and C_{max} were 0.880 (0.8154 to 0.9498), 0.886 (0.8258 to 0.9516) and 0.996 (0.9333 to 1.0628), respectively. Similar results were obtained when comparing SB8 and US-Avastin.

The secondary parameters (T_{max}, V_z, $t_{1/2}$, CL) were also found to be generally comparable between SB8 and EU/US-Avastin, indicating however a higher clearance and thus a lower bioavailability of SB8 compared to its reference products (see Section 3.3 below).

PK was further evaluated in a subset of 341/763 patients in the clinical Phase III Study SB8-G31-NSCLC comparing SB8 (161 patients; 42.5%)) with EU-Avastin (180 patients; 46.9%). The C_{trough} and C_{max} levels of SB8 and EU-Avastin (measured at cycles 1, 3, 5, and 7) were considered largely comparable between both treatment groups. The C_{trough} and C_{max} values appear to increase steadily in both treatment groups, converging to a steady state at Cycle 3.

Efficacy:

The primary endpoint best ORR by w24 indicated a difference in the PPS of 5.3%, [95% CI: -2.2%, 12.9%], with the upper limit of the 95% CI slightly exceeding the pre-defined comparability margin of [-12.5%, 12.5%]. In the sensitivity analysis performed with the FAS, the difference was 4.8%, the 95% CI being within the comparability margin. The risk ratio of best ORR including 90% CI was also within the predefined comparability margin of [0.737, 1.357] in both, the FAS and PPS.

The secondary endpoints and further analyses are largely in support of biosimilarity. The median PFS was 8.5 months [95% CI: 7.20, 9.70] vs. 7.9 months [95% CI: 7.30, 9.40] for SB8 and Avastin, respectively, with a HR of 1.02. The median OS was 14.80 [95% CI: 13.00, 17.00] vs. 15.80 [95% CI: 13.80, 17.70] for SB8 and Avastin, respectively and a HR of 1.08. The PFS and OS rates of 6-month, 12 month (and 18 month in case of OS) were comparable. The difference in DOR was 0.48 months in favour of EU Avastin.

Best ORR by w11 and w17 were similar, the 95% CI of the difference being within a ±12.5% margin.

Further post hoc analyses were presented due to the observed difference in the primary endpoint:

- ORR at cycle 2 and cycle 4 were comparable. Analyses of PFS and OS using a Cox regression model showed similar results as the initial analysis, in support of biosimilarity. In addition, the maximum change in tumor burden from baseline was investigated post-hoc, showing similar results between treatments: The mean of the maximum percentage change from baseline in tumor burden by 24 weeks of chemotherapy was −27.8% for SB8 and −27.3% for EU-sourced Avastin. The difference between the two treatment groups was 0.6% [95% CI of −4.18%, 2.99%]. Results were comparable by w11 and w17 with a difference of 0.5% and 0.7%, respectively. The ad-hoc sensitivity analysis of the difference in best ORR adjusted by the subcategory of distant metastasis showed an adjusted difference of 4.7%, with the two-sided 95%CI of [−2.9%, 12.2%], which was entirely contained within the pre-defined equivalence margin of [−12.5%, 12.5%].
- The requested MMRM analysis of the difference in change from baseline in tumour burden showed no significant difference (sum of the diameters of the target lesions) during the induction period, even with negative point estimate.
- In the forest plot of demographic subgroup analyses for best ORR at cycle 6 the point estimates for the difference in best ORR during induction period lie within the equivalence margins (except for the Russian subgroup, which is very likely a chance finding beside very slight differences between prognostic baseline characteristics), but mostly show a higher efficacy of SB8 compared to Avastin.
- The Kaplan-Meier (K-M) curve of the time to study discontinuation for all randomized patients were comparable.
- A more conservative imputation method including all patients without tumour assessment was presented upon request for the primary endpoint best ORR by w24 of the induction period, for ORR at cycle 6 of the induction period, and multiple other analyses. As the difference of ORR still very slightly crossed the upper bound of the predefined comparability range, these results are discussed in the uncertainties section. In order to classify the clinical relevance of this slight difference, a WLS regression analysis based on the dataset of 6 observations (four historical studies with Avastin and Study SB8-G31-NSCLC) was performed: a best ORR difference of 12.5% vs. 13% would correspond to 2.47-month and 2.63-month PFS, respectively. The 95% bootstrap CI for the difference in median PFS between the SB8 and EU Avastin treatment groups was calculated as [−1.5, 2.0] months.Further supportive in terms of biosimilarity is the analysis for the difference in ORR at Cycle 6 regardless of study period, which can be interpreted as a treatment policy estimand and better reflect the outcome in clinical practice after 6 cycles. The difference in ORR at Cycle 6 regardless of study period resulted in 4.8% [95% CI: –2.8%, 12.3%] for the PPS and in 4.9% [95% CI: –2.0%, 11.9%] for the FAS, which was entirely within a comparability range of ±12.5%.The analyses for ORR at cycle 2 and 4 with data imputed for patients without tumour assessment showed only slight difference in ORR, which is similar to the initially presented results.

Safety:

In healthy volunteers in the pivotal PK study SB8-G11-NHV no TEAES of Grade 4 (life threatening) or 5 (death) in severity and no discontinuations due to TEAEs or other safety issues occurred during the study in any of the groups. No infusion related reactions were reported in this study.

In patients the overall extent of exposure to IP and Non-IP seemed to be comparable between both treatment groups, nevertheless further analyses are requested as potential differences are considered to impact efficacy outcome. The incidences, types and severities of TEAEs and SAEs seem also comparable between SB8 and EU Avastin and are in line with the safety profile for bevacizumab (SmPC Avastin). No new safety signals were identified.

SAEs leading to death occurred in a comparable number of patients in both groups: in 22 patients (5.8%) of the SB8 group, and in 27 (7.1%) patients of the EU Avastin group. The most commonly reported TEAEs leading to death were similar between both groups and were respiratory, thoracic and mediastinal disorders (1.3% in the SB8 and 2.9% in the Avastin treatment groups), general disorders and administration site conditions (1.3% and 1.6%, respectively), and nervous system disorders (0.8% and 1.1%, respectively).

The number of patients completing the induction treatment period was comparable between the SB8 and EU Avastin treatment group (68.1% in the SB8 treatment group and 72.1% in the Avastin treatment group). A similar amount of patients discontinued during the maintenance treatment period in both groups (58.8% in the SB8 group; 62.2% in the EU Avastin group). The main reasons for discontinuation in the induction and maintenance treatment period in both groups were disease progression, AEs or death in both groups. Thus, at the time of EOS the proportion of subjects who were ongoing in the maintenance treatment period was very low and similar in both groups, 9.2% in the SB8 treatment group and 9.9% in the EU Avastin treatment group, respectively.

Immunogenicity was comparable in healthy volunteers. In the efficacy/safety study, ADA formation by cycle 7 was 13.5% vs. 10.1% with SB8 and EU Avastin, respectively. The distribution of high and low titres was comparable at each cycle except for EOT, where one patient each had a titre of 128, 256, 512 with SB8 compared to none with EU Avastin. A respectable proportion of ADA positive patients also tested positive for neutralizing antibodies (up to 42.9% of ADA positive patients with SB8 compared to 55.6 with EU Avastin at EOT). Any potential impact of ADAs on PK, efficacy and safety was thoroughly investigated and found not to be clinically relevant.

3.3. Uncertainties and limitations about biosimilarity

Quality uncertainties and limitations:

The presence of additional C- and N-terminal sequence variants at low levels, observed in SB8 but not in EU Avastin, was a matter of discussion during the procedure. The question emerged whether biosimilarity between two recombinant proteins, in this case between two IgG monoclonal antibodies, can be considered demonstrated despite certain differences in the amino acid sequence, since the concept of biosimilarity of recombinant proteins requires sequence identity. However, it should be highlighted that these sequence variants are extensions at the ends of the amino acid chain, and not amino acid insertions within the protein. The above-mentioned identity refers to the main component of the active substances and minor variants are conceived as product-related substances. The heavy chain C-terminal lysine heterogeneity is well known, and additional N-terminal residues from the signal peptides are not uncommon either. In summary, these sequence variants are considered as product-related impurities which need to be strictly controlled by an appropriate control system.

Since a potential impact of these sequence variants on safety/immunogenicity – although not observed in the clinical efficacy and safety comparability study – could not be completely ruled out, the Applicant strengthened the control strategy initially proposed. In addition, the Applicant is recommended to a) consider a further tightening of the limit when a number of batch results sufficient for statistical analysis is available, and b) to implement a more direct control dedicated to control C-terminal sequence variants present in Aybintio post-marketing.

Clinical Uncertainties and limitations:

Pharmacokinetics:

Even though in the pivotal PK study, the primary endpoint (AUC_{inf}) and the main secondary endpoints (AUC_{last}, C_{max}) with their 90% CIs were entirely within the predefined acceptance range of 80-125% indicating biosimilarity between the test and reference product, the upper limit of the 90% CIs for AUC_{inf} and AUC_{last} did not include 1 implying a statistical significant difference between the two treatments. Clearance was slightly higher with SB8 compared to Avastin which might be caused by differences in the glycovariant profile in particular the difference in the content of high mannose. The impact of ADA formation on PK was investigated and it was considered that the slight difference in ADA formation has no causal relationship to the observed lower exposure. Overall, the clinical relevance of the observed differences between SB8 and EU-Avastin in certain PK parameters is considered negligible.

Efficacy:

In the initial analysis the primary endpoints best ORR by w24 failed to show equivalence with the upper limit of the 95% CI slightly exceeding the pre-defined comparability margin of [-12.5%, 12.5%] in the PPS. With the primary endpoint "best ORR by 24 weeks of the induction period" very different response patterns can lead to the same outcome making the treatment arms more similar. The applicant argued, that best ORR by 24 weeks (induction period) represents a more clinically relevant endpoint and therefore can detect any potential clinically meaningful difference between two products. It is agreed that achieving response at any time point within the induction period may be more clinically relevant, but for showing equivalence in efficacy a more sensitive endpoint is preferred. Although the applicant included results for ORR at specific time points in the initial dossier for the PPS at Cycle 2, Cycle 4 and Cycle 6 of the induction period, it was unclear if and how missing data due to discontinuation was imputed. Several imputation methods were presented by the applicant. Finally, a more conservative estimate of the effect difference between Aybintio and Avastin and corresponding 95% CI was presented upon request to investigate how large the difference could become for a sensitive and a clinically relevant endpoint, using a more conservative imputation method on all patients without tumor assessment for both, best ORR by w24 of the induction period and for ORR at w24/cycle 6 (further analyses were also presented for ORR at several timepoints.

- In the most appropriate analysis the difference in best ORR (SB8 – EU Avastin) is 5.3% with a 95% CI of [−2.2%, 12.7%] for PPS and 6.0% with 95% CI of [−0.9%, 12.9%] for the FAS. The imputation therefore revealed a lower difference between treatment arms compared to the initial analysis, which is reassuring. Nevertheless, the 95% CI still crosses the predefined comparability margin of ±12.5%. The response rate-time curves showed that the difference in response favours SB8 and is highest between w20 and w30 and then slightly decreases till w40. With other imputation methods presented (which were not considered most appropriate), the difference in best ORR would be completely within a comparability range of ±12.5%.
- Due to the variability of tumour measurement time points, it was not possible to calculate ORR at Week 24. The analysis of ORR at Cycle 6 in the induction showed a difference (SB08 – EU

Avastin) of 5.6% [95% CI: -1.8%, 13.0%] for PPS and 6.2% [95% CI: −0.6%, 13.1%] for the FAS. Results for PPS and FAS were similar and indicated no statistically significant difference between the two treatment groups. Also in this analysis the difference was smaller than in the analysis without missing data imputation.

3.4. Discussion on biosimilarity

From a quality point of view, a comprehensive and robust biosimilarity exercise demonstrates similarity of the biosimilar candidate with its reference medicinal product. Differences observed at the physicochemical level have been sufficiently justified to have no impact on the clinical performance of Aybintio and its biosimilarity to the reference medicinal product. In particular, the observed sequence variants, considered as product-related impurities, are adequately controlled at the level of the active substance release specifications. The Applicant agreed to the Recommendations to consider further tightening of the corresponding acceptance limit when a number of batch results sufficient for statistical analysis is available and to submit an improved validated analytical method for their control.

No clinically relevant difference in immunogenicity to EU Avastin is expected from these product-related substances and demonstration of biosimilarity is not questioned.

Three non-clinical in vivo studies were submitted that strived to demonstrate biosimilarity between SB8 and EU or US Avastin. These studies were not required for filing a biosimilar MAA in the European Union, which was communicated to the Applicant within an EMA scientific advice procedure. As two of these studies were conducted with US Avastin as comparator, their results are not unambiguously representative for demonstrating biosimilarity between SB8 and EU Avastin.

The pivotal Phase I PK study demonstrated similarity, as results were within the comparability margin. It seems that SB8 exhibits a slightly higher clearance, which is most likely due to a higher D-mannose content observed with SB8. However this did not translate into lower efficacy of SB8 or have any impact on safety.

The primary efficacy analysis failed to show equivalence with the upper limit of the 95% CI slightly exceeding the pre-defined comparability margin of [-12.5%, 12.5%].

With the additionally requested more conservative imputation methods, the difference in best ORR by w24 of the induction period was smaller in the per protocol set, but still crossed slightly the upper margin. Difference in best ORR (SB8 – EU Avastin) is 5.3% with a 95% CI of [−2.2%, 12.7%] for PPS. The difference in (best) ORR seems to favour SB8 with an upper bound of the 95% CI around 13% in the induction period.

Nevertheless, the analysis for the difference in ORR at Cycle 6 regardless of study period for the PPS resulted in an upper bound of 12.3%. This endpoint could be interpreted as a treatment policy estimand and better reflect the outcome in clinical practice after 6 cycles. This estimand ignores a change of the treatment period (induction/maintenance) within the observation period of the primary endpoint of 24 weeks, i.e. if concurrent chemotherapy was still applied. As patients will change to the maintenance period prior to 24 weeks also in clinical practice, it reflects the comparison described in the ICH E9 Glossary (under Intention to Treat Principle) as the effect of a treatment policy. Moreover, further efficacy endpoints as PFS, OS, duration of response and change in tumour burden were similar. Further analyses evaluating the robustness of the study data were performed, including ad-hoc sensitivity analyses after adjusting the covariates (e.g. tumour burden or number of Cycles for IP and non-IP), best ORR based on the data from Investigator's review or different assessment time points and ORR at Cycle 2, Cycle 4 and Cycle 6 (regardless of study period). All of these analyses results showed that the treatment effect of SB8 and EU Avastin was largely comparable.

In the efficacy/safety study, at EOT the difference in ADA formation was more pronounced: 14% of patients were tested ADA positive with SB8 compared to 5.6% with EU sourced Avastin, with statistically significant association between treatments and the ADA status at EOT (p=0.0121). Overall ADA incidences up to EOT should also be counted for comparison of the ADA incidences between SB8 and EU Avastin treatment, as ADAs at EOT represent the incidence of ADA positive results at EOT timepoint without consideration of 'treatment induced ADA' or 'treatment-boosted ADA', 'transient' and 'inconclusive'. Samples from the patients at EOT are determined as ADA positive, regardless of ADA positiveness at the baseline. Up to EOT 55 (16.1%) patients in the SB8 and 37 (11%) patients in the EU Avastin group had overall ADAs. The clinical influence of potential differences in ADAs between the treatment groups on PK, efficacy and safety was investigated and revealed that the impact is negligible. ORR at each cycle showed no consistent trend in both subgroups. Comparison of PFS and DOR revealed no relevant effect of ADA development on these efficacy endpoints in both treatment groups. In the PK substudy of the Phase III trial SB8-G31-NSCLC, ADA formation was transient and showed no clear trend throughout all cycles, i.e. the incidence was not higher with SB8 in every cycle. In contrast, with Avastin, slightly more titer observations were observed with higher values, which should have a positive effect on the clearance for Avastin compared to SB8. Nevertheless, lower C_{trough} levels with SB8 were observed throughout all cycles. Furthermore also in the ADA negative subgroup, exposure was lower with SB8, also arguing against an effect of ADAs on the PK profile.

The safety profiles of SB8 and EU Avastin seem largely comparable. No new safety signals were identified. In ADA positive patients, the number of patients discontinuing due to TEAEs was higher in SB8 with 10 patients (18.2%) compared to Avastin with 4 patients (10.8%) whereas discontinuations due to death and progressive disease were slightly higher with Avastin. When considering the causal relationship of these TEAEs with immunogenicity, only 2 events (anaphylaxis reaction and hypersensitivity) appeared to be related to immunogenicity, therefore this does not appear to preclude biosimilarity.

Based on provided data it seems that the slight difference in ADA formation has no causal relationship to the observed lower exposure and an impact on immunogenicity and potential related consequences are clinically irrelevant.

3.5. Extrapolation of safety and efficacy

The primary mechanism of action of bevacizumab is the inhibition of tumour vessel growth by blocking VEGF. The mode of action of bevacizumab is considered to be the same across all approved cancer indications. Extensive state-of-the-art characterisation studies using orthogonal physicochemical and biological methods were performed to demonstrate the analytical similarity between SB8 and EU Avastin. Furthermore, SB8 and EU Avastin showed similar biological properties. Various cell based and binding assays demonstrated the similarity in the key features of the MoA of bevacizumab such as VEGF binding and neutralization as well as anti-proliferative effects. Extrapolation to other cancer indications of the reference product than advanced NSCLC is considered acceptable on the basis that similarity of Aybintio/SB8 to the bevacizumab reference product (EU-Avastin) has been convincingly demonstrated.

3.6. Additional considerations

Not applicable

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Aybintio 25 mg/ml concentrate for solution for infusion is considered biosimilar to Avastin 25 mg/ml concentrate for solution for infusion. 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 Aybintio 25 mg/ml is not similar to Zejula within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

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

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

Aybintio 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.

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

Aybintio, 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.

Aybintio, 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.

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

Aybintio, 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.

Aybintio, 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.

Aybintio, in combination with 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.

Aybintio, 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.