Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for ONBEVZI

Active ingredient: Bevacizumab

Sponsor: Samsung Bioepis AU Pty Ltd

April 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AUC	Area under the curve
AUC_{inf}	Area under the curve from time 0 extrapolated to infinite time
CI	Confidence intervals
C_{max}	The maximum concentration that a drug achieves in a specified compartment.
CMI	Consumer Medicines Information
C_{trough}	The concentration reached by a drug immediately before the next dose is administered
DLP	Data lock point
EU	European Union
FAS	Full analysis set
LSMean	Least squares mean.
mAb	monoclonal antibody
mBC	Metastatic breast cancer
mCRC	Metastatic carcinoma of the colon or rectum
mRCC	Advanced and/or metastatic renal cell cancer
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
PPS	Per protocol set
PSUR	Periodic safety update report
RMP	Risk management plan
TGA	Therapeutic Goods Administration
VEGF	Vascular endothelial growth factor

Product submission

Submission details

Type of submission:	New biosimilar medicine
Product name:	ONBEVZI
Active ingredient:	Bevacizumab
Decision:	Approved
Date of decision:	9 January 2024
Date of entry onto ARTG:	24 January 2024
ARTG numbers:	431837, 431838
, *Black Triangle Scheme*	No
Sponsor's name and address:	SAMSUNG BIOEPIS AU PTY LTD Suite 1, Level 11, 66 Goulburn Street, Sydney NSW 2000, Australia
Dose form:	Solution for infusion
Strength(s):	100 mg/4 mL and 400 mg/16 mL
Container:	Vial
Pack size:	1
Approved therapeutic use for the current submission:	**Metastatic Colorectal Cancer** ONBEVZI (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer. **Locally recurrent or metastatic Breast Cancer** ONBEVZI (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated. **Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC)** ONBEVZI (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer. **Advanced and/or metastatic Renal Cell Cancer** ONBEVZI (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer. **Grade IV Glioma** ONBEVZI (bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or

	disease progression after standard therapy, including chemotherapy. **Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer** ONBEVZI (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. **Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer** ONBEVZI (bevacizumab), in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, is indicated for the treatment of patients with first recurrence of platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior bevacizumab or other VEGF-targeted angiogenesis inhibitors. ONBEVZI (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens and have not received any prior anti-angiogenic therapy including bevacizumab. **Cervical Cancer** ONBEVZI (bevacizumab) in combination with paclitaxel and cisplatin is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix. ONBEVZI (bevacizumab) in combination with paclitaxel and topotecan is an acceptable alternative where cisplatin is not tolerated or not indicated.
Route(s) of administration:	Intravenous Infusion
Dosage:	**Metastatic Colorectal Cancer** The recommended dose of ONBEVZI, administered as an IV infusion, is as follows: First-line treatment: 5 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg of body weight given once every 3 weeks. Second-line treatment: 10 mg/kg of body weight given every 2 weeks or 15 mg/kg of body weight given once every 3 weeks. It is recommended that ONBEVZI treatment be continued until progression of the underlying disease. **Locally recurrent or metastatic Breast Cancer** The recommended dose of ONBEVZI is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

It is recommended that ONBEVZI treatment be continued until progression of the underlying disease.

Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer

The recommended dose of ONBEVZI in combination with carboplatin and paclitaxel is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

ONBEVZI is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by ONBEVZI as a single agent until disease progression.

Advanced and/or Metastatic Renal Cell Cancer

The recommended dose of ONBEVZI is 10 mg/kg given once every 2 weeks as an IV infusion. It is recommended that ONBEVZI treatment be continued until progression of the underlying disease.

ONBEVZI should be given in combination with IFN alfa-2a (Roferon-A). The recommended IFN alfa-2a dose is 9 MIU three times a week, however, if 9 MIU is not tolerated, the dosage may be reduced to 6 MIU and further to 3 MIU three times a week.

Please also refer to the Roferon-A Product Information.

Grade IV Glioma

The recommended dose of ONBEVZI is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

It is recommended that ONBEVZI treatment be continued until progression of the underlying disease.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

The recommended dose of ONBEVZI administered as an IV infusion is as follows:

First line treatment: 15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles of treatment, followed by continued use of ONBEVZI as single agent.

It is recommended that ONBEVZI treatment be continued for a total of 15 months therapy or until disease progression, whichever occurs earlier.

Treatment of recurrent disease:

Platinum sensitive

15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and paclitaxel for 6 cycles (up to

8 cycles) followed by continued use of ONBEVZI as a single agent until disease progression.

Alternatively, 15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and gemcitabine for 6 cycles (up to 10 cycles), followed by continued use of ONBEVZI as single agent until disease progression.

Platinum resistant

10 mg/kg body weight given once every 2 weeks when administered in combination with one of the following agents – paclitaxel or topotecan (given weekly) or pegylated liposomal doxorubicin. Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks.

It is recommended that treatment be continued until disease progression.

Cervical Cancer

ONBEVZI is administered in combination with paclitaxel and cisplatin or, if cisplatin is not tolerated or not indicated, paclitaxel and topotecan.

The recommended dose of ONBEVZI is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

It is recommended that ONBEVZI treatment be continued until progression of the underlying disease.

For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.

Pregnancy category: D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Samsung Bioepis AU Pty Ltd (the sponsor) to register ONBEVZI (bevacizumab), 100 mg/4 mL and 400 mg/16 mL, solution for infusion, single dose vial.

The disease/condition

Bevacizumab was initially authorised in the EU for treatment of metastatic colorectal cancer, as an improvement in survival was demonstrated in colorectal patients receiving bevacizumab treatment in combination with chemotherapy. Since the initial approval, it has been approved for use in combination with other chemotherapy to treat certain types of cancers as follows: metastatic breast cancer; non-small cell lung cancer (NSCLC); advanced and/or metastatic renal cell cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancer; and cervical cancer.

Current treatment options

The sponsor has developed ONBEVZI as a similar biological medicinal product (biosimilar) to AVASTIN. AVASTIN was approved in Australia in 2005. There are currently five bevacizumab biosimilar products approved in Australia – ABEVMY (Alphapharm), BEVACIP (Cipla Australia), MVASI (Amgen Australia), VEGZELMA (Celltrion Healthcare Australia) and ZIRABEV (Pfizer Australia).

Clinical rationale

Bevacizumab (rhuMAb VEGF, anti-VEGF) is a recombinant humanised monoclonal antibody (mAb) that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab belongs to the pharmacotherapeutic group “monoclonal antibodies” (ATC code L01XC07). The human framework region consists of a human immunoglobulin gamma (IgG1) constant region, and the murine heavy and light chain complementarity determining region (CDR) sequences of the antibody that selectively binds to VEGF with high affinity. Bevacizumab was generated by the humanisation of the murine parent antibody A4.6.1. The mechanism of action of bevacizumab is to bind to VEGF and inhibits the interaction of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells thereby inhibiting the tumour angiogenesis and tumour growth.

The mechanism of action for bevacizumab is independent of tumour site, and its effect on tumour growth inhibition has conferred substantial clinical benefit in the treatment of solid tumours. Bevacizumab was initially authorised in the EU for treatment of metastatic colorectal cancer, as a significant improvement in survival was demonstrated in colorectal patients receiving bevacizumab treatment in combination with chemotherapy. Since the initial approval, it has been approved for use in combination with other chemotherapy to treat certain types of the following cancers: metastatic carcinoma of the colon or rectum; metastatic breast cancer; non-small cell lung cancer (NSCLC); advanced and/or metastatic renal cell cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancer; cervical cancer.

The applicant has requested the same therapeutic indications for ONBEVZI as granted for AVASTIN.

Regulatory status

Australian regulatory status

This product is considered a new biosimilar medicine for Australian regulatory purposes.

Foreign regulatory status

Table 1: International regulatory status at the time of product registration.

Region	Submission date	Status	Approved indications
EU - Centralised Procedure	Jun 2019	Approved 19 Aug 2020 11 Jan 2021	Metastatic carcinoma of the colon or rectum (mCRC) Metastatic breast cancer (mBC) Non-small cell lung cancer (NSCLC) Advanced and/or metastatic renal cell cancer (mRCC) Epithelial ovarian, fallopian tube and primary peritoneal cancer Cervical cancer
Republic of Korea	May 2020	Approved Mar 2021	Metastatic carcinoma of the colon or rectum (mCRC) Metastatic breast cancer (mBC) Non-small cell lung cancer (NSCLC) Advanced and/or metastatic renal cell cancer (mRCC) Epithelial ovarian, fallopian tube and primary peritoneal cancer Cervical cancer Malignant Glioma (WHO Grade IV) - Glioblastoma

Region	Submission date	Status	Approved indications
UK	Baseline submission of EU dossier: Apr 2021	Approval is effective from 1 Jan 2021 based on Brexit guidance	Metastatic carcinoma of the colon or rectum (mCRC) Metastatic breast cancer (mBC) Non-small cell lung cancer (NSCLC) Advanced and/or metastatic renal cell cancer (mRCC) Epithelial ovarian, fallopian tube and primary peritoneal cancer Cervical Cancer
Canada	Dec 2020	Approved Nov 2021	Metastatic Colorectal Cancer (mCRC) Locally advanced, metastatic or recurrent non- small cell lung cancer (NSCLC) Platinum-sensitive recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer Platinum-resistant recurrent epithelial ovarian, fallopian tube and primary peritoneal Malignant Glioma (WHO Grade IV) - Glioblastoma

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2021-04826-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	30 November 2021
First round evaluation completed	3 May 2022
Second round evaluation completed	11 August 2022
Advisory Committee meeting	6 October 2022
Registration decision (Outcome)	9 January 2024

Description	Date
Administrative activities and registration in the ARTG completed	24 January 2024
Number of working days from submission dossier acceptance to registration decision*	222

* Statutory timeframe for standard submissions is 255 working days

* The COR-A process has a 120 working day evaluation and decision timeframe.

* The COR-B process has a 175 working day evaluation and decision timeframe.

Submission overview and risk/benefit assessment

Quality

The quality evaluator concluded that ONBEVZI (bevacizumab) is comparable to AVASTIN in terms of structure, species, function and degradation profile (i.e. physicochemically and biologically). Extensive characterisation studies involving comparison of primary, secondary and tertiary structures, physicochemical properties, degradation profile and biological activities showed that ONBEVZI and EU/US AVASTIN are sufficiently similar.

There are no objections on quality grounds to the approval of ONBEVZI / bevacizumab.

Nonclinical

The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat-dose toxicity. The scope of the nonclinical program is adequate under the relevant EU guideline. These studies were conducted using EU/ and US-sourced AVASTIN as the reference product. Bridging data between EU-sourced and Australia (AU)-sourced AVASTIN were provided in the quality evaluation report.

Two nonclinical pharmacology studies in xenograft animal models using either EU- or US-AVASTIN were submitted. Similar anti-tumour activity was seen between ONBEVZI and EU-AVASTIN in mice grafted with Non-Small Cell Lung Cancer (NSCLC) cells. However, in colorectal cancer xenograft models, the decrease in tumour weight was significantly superior with US-AVASTIN regarding ONBEVZI, while the reduction in tumour volume was similar between the forms of bevacizumab. While no clear reason was evident for these differences, taken together, sufficient comparability was noted between ONBEVZI and EU-AVASTIN based on other studies, and the discrepancy in activity in the colorectal cancer model could at least in part be accounted by experimental variability inherent to xenograft models.

Comparable serum kinetic profiles after IV administration were evident for ONBEVZI and US-AVASTIN from toxicokinetic data obtained in cynomolgus monkeys.

No meaningful differences between ONBEVZI and US-AVASTIN were observed in the comparative toxicity studies in monkeys.

Provided that EU-sourced and US-sourced AVASTIN used in the nonclinical investigations are found to be to be highly comparable to the Australia-sourced AVASTIN, and that the ONBEVZI

batch in the toxicity study is found to be comparable to the batch to be marketed, by the quality or clinical evaluators, there are no nonclinical objections to the registration of ONBEVZI.

Clinical

Summary of clinical studies

The dossier included one pivotal PK study and population PK analysis, and a Phase III randomised study (for efficacy/safety), in addition to one PSUR (periodic safety update report) and two integrated immunogenicity analyses. SB8 refers to the sponsor's code for ONBEVZI / bevacizumab.

- PK studies:
  - SB8-G11-NHV – general PK study of single dose in healthy adults
  - SB8-G31-NSCLC – PK of multi-dose in target population
  - SB8-PopPK-01 – population PK analyses in healthy subjects and target population
- One Phase III randomised study (SB8-G31-NSCLC) comparing the efficacy, safety, pharmacokinetics and immunogenicity between SB8 and AVASTIN in subjects with metastatic or recurrent non-squamous NSCLC.

No pharmacodynamic studies were included in the submission. There is currently no validated PD biomarker for bevacizumab efficacy. Therefore, the PD properties of SB8 were assessed only through the clinical efficacy and safety outcomes in Study SB8-G31-NSCLC.

Pharmacokinetics

Study SB8-G11-NHV (pivotal study)

This was a Phase I, randomised, double blind, three arm, parallel group, single dose study in 114 healthy male subjects in which SB8 was compared to EU sourced AVASTIN and US sourced AVASTIN. In line with TGA-adopted EMA guidelines (see EMA/CHMP/BMWP/403543/2010), pharmacokinetic characteristics of ONBEVZI were compared with reference medicinal product in a single dose parallel group study; although a single dose cross-over study is preferable, a parallel group study was considered acceptable, given the long-half-life of bevacizumab (approximately 20 days), also allowing an adequate period to assess the potential influence of immunogenicity.

The study was limited to only male subjects due to the documented gender differences observed with the PK profile of bevacizumab and the risk of ovarian failure associated with the product. As there is no therapeutic dose of bevacizumab in healthy subjects, the sponsor chose a dose of 3 mg/kg for IV infusion as this dose minimised the safety risk to the healthy subjects but provided adequate serum concentrations of bevacizumab during the entire PK sampling period. This dose was agreed during meetings by both the US FDA and the EMA.

For the similarity assessment, the PK parameters were compared between SB8 and EU AVASTIN using a pre-defined acceptance interval of 0.80 to 1.25, which was the same for the bioequivalence acceptance criteria. PK results are shown in Table 3.

Table 3. Study SB8-G11-NHV: 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
Vz (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	n	38	38	38

PK Parameter	Statistics	SB8 N=38	EU AVASTIN N=38	US AVASTIN N=38
(mL/h)	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
t½ (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

In the PK population, the 90% CIs for the geometric LSMean ratio of SB8 and EU AVASTIN for AUC_{inf}, AUC_{last}, and C_{max} all were within the predefined acceptance interval of 0.8 to 1.25.

Table 4. Study SB8-G11-NHV: Statistical comparison of primary PK parameters between SB8 and EU 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 sourced Avastin®.
LSMean = least squares mean; CI = confidence interval; N = number of subjects in PK population; n = number of subjects who contributed to the analysis.
Source: Module 2.5 Table 6 (Study SB8-G11-NHV CSR Table 11-4, Table 14.2-2.1. Table 14.2-2.2 and Table 14.2-2.3)

SB8 and EU AVASTIN therefore exhibit equivalent PK profiles.

In the PK population, the 90% CIs for the geometric LSMean ratio of SB8 and US AVASTIN for AUCinf, AUClast, and Cmax all were within the predefined acceptance interval of 0.8 to 1.25.

Table 5. Study SB8-G11-NHV: 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; 0.9566
	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		

N = number of subjects in PK population; n = number of subjects with an available assessment; LSMean = least squares mean; A = SB8; B = US sourced AVASTIN; CI = confidence interval.

SB8 and US AVASTIN therefore exhibit equivalent PK profiles.

Study SB8-G31-NSCLC (main efficacy study)

Study **SB8-G31-NSCLC** also evaluated PK by means of serum trough and maximum concentrations (C_{trough}, C_{max}) in a subset of enrolled patients. This was a randomised, double blind, parallel group, multicentre study to evaluate the efficacy, safety and immunogenicity of SB8 compared with EU AVASTIN in patients with recurrent or metastatic non-squamous NSCLC.

Patients were randomised 1:1 to received either SB8 or EU sourced AVASTIN via IV infusion on Day 1 of every 3 week cycle concurrently with paclitaxel (200 mg/m^2) and carboplatin (AUC 6) for 4 to 6 cycles of the induction treatment period. Patients responding to treatment after completion of the induction treatment period continued to receive SB8 or EU AVASTIN maintenance monotherapy as per randomisation until PD, unacceptable toxicity, death, or 12 months from randomisation of the last patient, whichever occurred first.

The PK population consisted of 341 patients (161 in the SB8 treatment group and 180 in the EU AVASTIN treatment group. Blood sampling for PK assessments was collected at pre-dose and post-dose of Cycle 1, 3, 5, and 7 in approximately 50% of patients in the study.

The overall mean C_{trough} and C_{max} values of SB8 and EU AVASTIN were comparable for all time points measured from Cycle 1 to Cycle 7:

C_{trough}

- SB8 treatment group - ranging from 0.0000 to 121.7382 ± 62.62150 [SD] µg/mL from Cycle 1 to Cycle 7
- EU Avastin® treatment groups - ranging from 0.0000 to 133.7669 ± 58.84136 [SD] µg/mL from Cycle 1 to Cycle 7

C_{max}

- SB8 treatment group - ranging from 306.0352 ± 98.71872 [SD] to 397.5435 ± 120.74092 [SD] µg/mL from Cycle 1 to Cycle 7
- EU Avastin® treatment groups - ranging from 302.6362 ± 87.10467 [SD] to 426.1350 ± 144.24538 [SD] µg/mL from Cycle 1 to Cycle 7

Variability in the C_{trough} and C_{max} and the range of individual C_{trough} and C_{max} values were also comparable between the SB8 and EU AVASTIN treatment groups. The concentrations of both SB8 and EU AVASTIN appeared to have reached a steady state around Cycle 3.

PopPK

The population PK analysis (Report SB8-PopPK-01) was conducted using a non-linear mixed effects model and compared simulated trough and peak serum concentrations and exposure of

SB8 and AVASTIN at steady state in healthy male subjects (from Study SB8-G11-NHV) and patients with recurrent or metastatic non-squamous NSCLC (from Study SB8-G31-NSCLC). A total of 3,718 quantifiable bevacizumab concentrations from 459 subjects (118 healthy subjects and 341 patients with recurrent or metastatic non-squamous NSCLC) were used to support the population PK analysis.

The model-predicted average bevacizumab exposure ($AUC_{0-\tau,ss}$) ratio of SB8 to EU AVASTIN was 0.91 [90% Prediction Interval: 0.86, 0.96] in patients with recurrent or metastatic non-squamous NSCLC and 0.90 [90% PI: 0.85, 0.96] in healthy subjects. The $AUC_{0-\tau,ss}$ ratio of SB8 to US AVASTIN was 0.91 [90% PI: 0.85, 0.96] in healthy subjects. The $AUC_{0-\tau,ss}$ ratio of US AVASTIN to EU AVASTIN was 1.00 [90% PI: 0.96, 1.05] in healthy subjects. These pairwise comparisons of exposure between treatments were consistent with the results of the PK comparison of SB8, EU AVASTIN, and US AVASTIN in Study SB8-G11-NHV) and the C_{max} and C_{trough} profiles of SB8 and EU AVASTIN in Study SB8-G31-NSCLC.

Summary of PK

The pivotal Study SB8-G11-NHV in healthy subjects demonstrated bioequivalence between SB8 and EU-sourced AVASTIN and US-sourced AVASTIN. The 90% CIs of the geometric LSMeans for the AUC_{inf}, AUC_{last} and C_{max} were contained entirely within the pre-defined acceptance interval (0.80 – 1.25) for each of the comparisons i.e., between SB8 and EU AVASTIN, SB8 and US AVASTIN and between EU AVASTIN and US AVASTIN. In addition, in the patient study SB8-G31-NSCLC, comparable C_{trough} and C_{max} profiles were documented for SB8 and EU AVASTIN with comparable inter-patient variability.

The PK profile of ONBEVZI and AVASTIN are therefore considered comparable.

Efficacy

Study SB8-G31-NSCLC (main efficacy study)

This was 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.

An overview of Study SB8-G31-NSCLC is shown in as follows:

Table 6. Study SB8-G31-NSCLC overview

Study SB8-G31-NSCLC	
Study objectives	Primary objective: To demonstrate equivalence of SB8 to AVASTIN in terms of best ORR by 24 weeks of chemotherapy in subjects with metastatic or recurrent non-squamous NSCLC. Secondary objective: To evaluate the efficacy by PFS, OS and DOR; safety and tolerability; PK and immunogenicity of SB8 compared to AVASTIN. Exploratory objective: best ORR by weeks 11 and 17
Study design and duration	Randomised, double-blinded Phase III study. 763 patients with metastatic or recurrent non-squamous NSCLC Randomised 1:1 to SB8 + paclitaxel and carboplatin (n=379) or EU AVASTIN + paclitaxel and carboplatin (n=384) Two treatment periods: induction treatment period (chemotherapy in combination with bevacizumab), followed by maintenance treatment period (bevacizumab maintenance monotherapy).
Efficacy outcomes	Primary efficacy outcome: Best ORR* by 24 weeks (per RECIST v1.1 during induction treatment period) Secondary efficacy outcomes: PFS OS DOR

	*For EMA review, equivalence was declared when the two-sided 95% CI for the difference in best ORR between treatments is entirely contained within the equivalence margin of [−12.5%, 12.5%], as estimated in the Per Protocol Set (*For FDA review, equivalence was declared when the two-sided 90% CI for the ratio of best ORR between treatments is entirely contained within the equivalence margin of [0.737, 1.357], as estimated in the Full Analysis Set (FAS), where patients with missing tumour assessments were imputed using a multiple imputation method To support each primary efficacy result, the analysis for the difference in best ORR was repeated in the FAS, and the analysis for the ratio of best ORR was repeated in the PPS.
Key inclusion criteria	Patients ≥ 18 years of age Histologically and/or cytologically confirmed metastatic or recurrent non-squamous NSCLC or NSCLC NOS ECOG 0-1 Measurable disease by RECIST v1.1 Adequate organ function
Key exclusion criteria	Small cell carcinoma of lung, or squamous cell carcinoma of lung EGFR mutation or ALK rearrangement Evidence of tumour invasion into blood vessels or close to large vessels that may have risk of bleeding. Previous systemic anti-cancer therapy for metastatic or recurrent NSCLC Any systemic anti-cancer therapy including neoadjuvant or adjuvant chemotherapy administered for NSCLC and completed within 12 months prior to randomisation Treatment with anticoagulant therapy within 10 days to randomisation Uncontrolled hypertension Major cardiovascular event within 6 months of screening.
Study treatment	Test product: SB8 15mg/kg IV Day 1 of every 3 week cycle, concurrently with paclitaxel (200mg/m^2) and carboplatin (AUC 6), for at least 4 cycles and up to 6 cycles (induction treatment period) Reference product: EU AVASTIN 15mg/kg IV Day 1 of every 3 week cycle, concurrently with paclitaxel (200mg/m^2) and carboplatin (AUC 6), for at least 4 cycles and up to 6 cycles (induction treatment period)

The choice of study design, population, inclusion and exclusion criteria, and study treatments is considered to be appropriate. The choice of efficacy outcomes and equivalence margin is acceptable, as per CHMP guidance.

The total number of subjects in the analysis sets are shown in Table 7.

Table 7. Study SB-G31-NSCLC: Data Sets Analysed (Randomised Set)

	SB8 n (%)	EU Avastin n (%)	Total n (%)
Randomised 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 randomised patients.
Source: Module 2.7.3 Table 2 (Study SB8-G31-NSCLC CSR Table 11-1, Table 14.1-2.1)

Sample size & statistical methods:
The ORR for AVASTIN and chemotherapy was reviewed in the published literature and the overall ratio of best ORR, and the 70% CI were calculated to be 1.87 [1.7143, 2.0400] using fixed-effect method from meta-analysis. Retaining the 50% of the effect of AVASTIN over the placebo in the lower margin, the equivalence margin of [0.737, 1.357] was used for the primary analysis with the ratio of the best ORR by 24 weeks.
For the primary analysis with the difference of the best ORR by 24 weeks, the equivalence margin of [-12.5%, 12.5%] was used due to the similar derivation. The overall difference in the best ORR and its 95% CI were calculated to be 18.12% [13.66%, 22.58%] using the fixed-effect method from meta-analysis, or for 80% CI to be [15.32%, 21.15%]. The equivalence margin of [-12.5%, 12.5%]

ensured the superiority of SB8 over placebo with a small safety margin retaining around 10% for 95% CI and 20% for 80% CI of the effect over the placebo in the difference of best ORR.

With 305 completers 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 AVASTIN and SB8 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 subjects (339 subjects per treatment group) were to be randomised.

For USA Food and Drug Administration (FDA) or other regulatory agency submissions for those who were in favour of risk ratio, the primary efficacy analysis was performed in the FAS for the ratio of best ORR (best ORR of SB8/best ORR of AVASTIN) by 24 weeks, and the equivalence was declared if the 90% Confidence Interval (CI) of the ratio in the best ORR was contained within the pre-defined equivalence margin of [0.737, 1.357]. The similar analysis was performed for the PPS to support the primary analysis.

For EMA, Ministry of Food and Drug Safety (MFDS, Korea) or other regulatory agency submissions for those who were in favour of risk difference, the primary efficacy analysis was performed in the 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 was declared if the 95% CI of the difference in the best ORR was entirely contained within the pre-defined equivalence margin of [-12.5%, 12.5%]. The similar analysis was performed for the FAS to support the primary analysis.

Participant flow:

Both treatment arms are considered to be balanced with respect to patient demographics and disease characteristics (see p35-36 of Clinical Evaluation Report for details on participant flow and baseline data).

Results – primary efficacy outcome:

The primary efficacy outcome was the best ORR (per RECIST v1.1 during the induction treatment period) by 24 weeks; overall the proportion of subjects with CR, PR, SD, and PD was comparable in the SB8 and AVASTIN treatment groups.

Table 8 Study SB8-G31-NSCLC: Summary of best Overall Response (Full Analysis Set)

Parameter	SB8 N=379 n (%)	Avastin N=383 n (%)
Best Overall Response		
Complete Response (CR)	0	1 (0.3)
Partial Response (PR)	172 (45.4)	151 (39.4)
Stable Disease	136 (35.9)	151 (39.4)
Progressive Disease (PD)	27 (7.1)	21 (5.5)
Not Evaluable (NE)	43 (11.3)	58 (15.1)

CR = complete response; NE = not evaluable; PR = partial response; PD = progressive disease; N = number of subjects in the Full analysis set; n = number of subjects.
Source: Study SB8-G31-NSCLC CSR Table 11-4 (Table 14.2-1.3)

The analysis of the best ORR was different in the requirements of the EU and US.

The EU required the analysis of the difference, and the US required the analysis of the ratio, between SB8 and the comparator. The two agencies also required the analysis to be done on different populations, the difference on the PPS and the ratio on the FAS.

Primary analysis of ratio in best ORR:

Table 9. Study SB8-G31-NSCLC: Primary analysis of ratio in best Overall Response Rate during induction treatment period by 24 Weeks (Full analysis set)

Parameter	SB8 N=379 n (%)	AVASTIN N=383 n (%)
Best Overall Response Rate (Best ORR) CR+PR	181 (47.6)	164 (42.8)
Ratio of Best ORR Ratio (SB8/Avastin) 90% CI	1.11 [0.975, 1.269]	

In the FAS, the ratio of best ORR (best ORR of SB8/best ORR of AVASTIN) was 1.11, and the 90% CI of the ratio of the best ORR between SB8 and AVASTIN was [0.975, 1.269], which was contained within the pre-defined equivalence margin of [0.737, 1.357].

Primary analysis of difference in best ORR

Table 10. Study SB8-G31-NSCLC: 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) 95% CI	5.3% [-2.2%, 12.9%]	

In the PPS, the difference of best ORR (best ORR of SB8-best ORR of AVASTIN) was 5.3%, and the 95% CI of the difference of the best ORR between SB8 and AVASTIN was [-2.2%, 12.9%], which was not contained within the pre-defined equivalence margin of [-12.5%, 12.5%].

To support the robustness of each primary efficacy result, the sensitivity analyses were performed using the log-binomial regression model and binomial regression model, with the covariates of age group (< 70, $\geq$ 70 years), sex (male, female), region (EU, non-EU), and treatment group.

Table 11. Study SB8-G31-NSCLC: Sensitivity analysis of ratio and difference 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)		
Analysis Set	**Treatment**	**n**	**(%)**	**Difference**	**95% CI**
FAS	SB8 (N=379)	181	(47.6)	4.8%	[-2.2%, 11.9%][b]
	Avastin (N=383)	164	(42.8)		
PPS	SB8 (N=337)	169	(50.1)	5.4%	[-2.2%, 12.9%]
	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].
b. Represent the confidence interval was fully within the equivalence margin [-12.5%, 12.5%]
Source: Study SB8-G31-NSCLC Table 11-8 and 11-9 (Table 14.2-2.3.1 and 14.2-2.3.2 and 14.2-2.4.1 and 14.2-2.4.2)

For the ratio, the sensitivity analysis gave similar results for the PPS as the FAS with both results within the comparability margin (0.737, 1.357).

For the difference, the sensitivity analysis performed with the FAS found that the difference was 4.8% *which was within the comparability margin* compared with a difference of 5.4% for the PPS which was not within the comparability margin (-12.5, 12.5).

Results - Secondary outcomes:

The secondary efficacy variables, PFS, OS, and DOR were comparable between the SB8 and AVASTIN treatment groups in the PPS. Best ORR by Week 11 and Week 17 were similar with the 95%CI of the difference being within the ± 12.5 equivalence margin.

Table 12. Study SB8-G31-NSCLC: Summary of results of other efficacy outcomes per protocol set.

Outcome	SB8	EU Avastin
% patients experiencing disease progression or death	230 (68.2%)	223 (68.0%)
Median PFS [95%CI]	8.5 [7.20, 9.70]	7.90 [7.30, 9.40]
6 month PFS rates*	73% [68%, 78%]	76% [71%, 80%]
12 month PFS rates*	34% [28%, 39%]	30% [24%, 35%]
6 month OS*	85% [80%, 88%]	89% [85%, 92%]
12 month OS*	61% [55%, 66%]	63% [57%, 68%]
18 month OS*	43% [36%, 50%]	43% [36%, 50%]

*Calculated using the Kaplan-Meier method

Safety and immunogenicity

Safety data was provided for studies SB8-G11-NHV and SB8-G31-NSCLC; these datasets were relatively small, consisting of 119 healthy male subjects in the Phase I study (SB8-G11-NHV) and 758 patients with NSCLC in the Phase III efficacy study (SB8-G31-NSCLC).

Study SB8-G11-NHV

In SB8-G11-NHV, the proportion of subjects who experienced AEs was similar between the SB8, EU AVASTIN and US AVASTIN and the AEs were consistent with the known AEs for bevacizumab.

A total of 85 TEAEs were reported in 56 (47.1%) subjects: 32 TEAEs were reported from 20 (50.0%) subjects following infusion of SB8, 17 TEAEs were reported in 15 (37.5%) subjects after infusion of EU AVASTIN, and 36 TEAEs were reported from 21 (53.8%) subjects after infusion of US AVASTIN. The most frequently reported AEs were nasopharyngitis and headache. There were no marked differences in the incidence of these events between the treatment groups (see Table 23, page 50 of clinical evaluation report). The proportion of subjects with TEAEs suspected to be treatment related was comparable across the 3 treatment groups. There were no infusion related reactions reported during the study.

Immunogenicity

The overall incidence of post dose ADA positive results was similar in the treatment groups - 1 (2.6%), 4 (10.3%) and 1 (2.6%) subjects in the SB8, EU AVASTIN, and US AVASTIN treatment groups, respectively. No subject in any treatment group was positive for NAbs.

Study SB8-G31-NSCLC

In the Phase III efficacy study (SB8-G31-NSCLC), the duration of exposure to the study drugs was 34.26 weeks for the SB8 group and 35.26 weeks for the EU AVASTIN group with similar number of cycles received (11.2 cycles for the SB8 group and 11.5 cycles for the EU AVASTIN group) in both groups.

There were similar numbers of patients who reported TEAEs (91.6%) between SB8 (92.1%) and EU AVASTIN (91.1%). The incidence and severity of the reported AEs were generally comparable between the two groups; see Table 22, page 51 of clinical evaluation report for "Study SB8-G31-NSCLC: TEAEs by System Organ Class and Preferred Term (≥5% in any treatment group) during the overall study period".

The most frequently occurring TEAEs were alopecia (48.7% in the SB8 group and 48.2% in the EU AVASTIN group), anaemia (24.3% and 23.7%, respectively), and nausea (19.6% and 21.1%, respectively), all of which are known expected AEs in patients receiving chemotherapy.

628 TEAEs related to study drug in 160 (42.3%) patients of the SB8 treatment group and 651 TEAEs in 177 (46.6%) patients were reported to be related to study drug in the EU AVASTIN treatment group.

A total of 31 (4.1%) patients reported 47 TEAEs associated with infusion-related reactions. In the SB8 treatment group, 23 TEAEs associated with infusion-related reactions were reported in 20 (5.3%) patients. In the EU AVASTIN treatment group, 24 TEAEs associated with infusion-related reactions were reported in 11 (2.9%) patients. The most common symptoms of infusion-related reactions reported at PT level were dyspnoea, hypersensitivity, and drug hypersensitivity. The incidence of common symptoms of infusion-related reactions was balanced between the two treatment groups.

It is noted that there was one event of anaphylactic reaction occurred in SB8 treatment group and two events of anaphylactic shock occurred in one patient each in each treatment group.

Immunogenicity

The immunogenicity profile was similar between the treatment groups with similar low ADA and NAb incidences:

- At Cycle 7, the number and proportion of patients with an overall ADA positive result were 46 (13.5%) patients in the SB8 treatment group and 34 (10.1%) patients in the EU AVASTIN treatment group.

- At EOT, the number and proportion of patients with an overall ADA positive result were 55 (16.1%) patients in the SB8 treatment group and 37 (11.0%) patients in the EU AVASTIN treatment group.
- In the ADA positive patients, the proportion of patients with NAb was also comparable between the two treatment groups.

Summary of safety and immunogenicity

Overall, the safety profile of ONBEVZI appeared comparable to EU AVASTIN, and the immunogenicity profile was similar between the treatment groups with similar low ADA and NAb incidences.

Risk-benefit analysis

Delegate's considerations

The proposed indication for ONBEVZI is the same as for the reference product (AVASTIN). The comparability exercise is based on Quality data, non-clinical evaluation and clinical data from PK studies (SB8-G11-NHV, SB8-G31-NSCLC, SB8-PopPK-01) and one supportive efficacy/safety study (SB8-G31-NSCLC) in patients with metastatic or recurrent non-squamous NSCLC.

Quality & Manufacturing evaluation:

It has been determined that ONBEVZI (bevacizumab) is comparable to AVASTIN in terms of structure, species, function and degradation profile (that is, physicochemically and biologically).

- SB8 and AVASTIN (EU/US/KR) are shown to be similar from two studies.
- EU and AU AVASTIN are highly similar.
- SB8 and AVASTIN lots are within the quality ranges of the EU-AVASTIN and thereby bridge EU-Approved AVASTIN lots to the AU Approved AVASTIN.

There are no objections on quality grounds to the approval of ONBEVZI / bevacizumab.

Non-clinical evaluation:

Data from comparative studies on pharmacology, pharmacokinetics and repeat-dose toxicity were considered by the non-clinical evaluator. There are no nonclinical objections to the registration of ONBEVZI.

Clinical evaluation:

The pivotal PK study SB8-G11-NHV, and study SB8-G31-NSCLC demonstrate comparable PK characteristics between ONBEVZI and AVASTIN (EU sourced and US sourced); comparability between ONBEVZI, EU AVASTIN and AU AVASTIN as per bridging studies has been confirmed by the quality evaluation.

- In study SB8-G11-NHV, the 90% CIs of the geometric LS Means for the AUC_{inf}, AUC_{last} and C_{max} were contained entirely within the pre-defined acceptance interval (0.80 – 1.25) for each of the comparisons i.e., between SB8 and EU AVASTIN, SB8 and US AVASTIN and between EU AVASTIN and US AVASTIN.
- In study SB8-G31-NSCLC, comparable C_{trough} and C_{max} profiles were documented for SB8 and EU AVASTIN with comparable inter-patient variability.

The efficacy profile is similar, considering results of the extensive post hoc analyses, despite the primary efficacy outcome according to the EU requirement having not been met (see *Uncertainties* below).

Overall, ONBEVZI demonstrates a similar safety and immunogenicity profile to the reference product (per AVASTIN Product Information).

The clinical evaluator therefore concluded that:

- The PK profile of SB8 is bioequivalent to AVASTIN.
- The slight difference in clinical efficacy is unlikely to be clinically meaningful and so the products can be considered equivalent.
- The safety profiles and immunogenicity appear similar.

Uncertainties

The objective of the supportive comparability study (SB8-G31-NSCLC) was to demonstrate equivalence between SB8 and the reference product AVASTIN, using the primary efficacy outcome of best ORR at week 24. To achieve this objective, the study required 305 completed subjects in each treatment group to achieve a two-sided 90% CI of the best ORR ratio to lie within [0.737, 1.357] with approximately 80% power, and a two-sided 95% CI of the best ORR difference between AVASTIN and SB8 to lie within [-12.5%, 12.5%] with 80% power when the expected best ORR was assumed to be 35%. The study enrolled 965 subjects and 535 (70%) completed induction treatment period. There were 762 patients assessable in the FAS and 665 in the PPS.

The study met the primary outcome per FDA requirements; the results for the ratio were contained within the pre-defined equivalence margin, i.e., ratio of best ORR=1.11, 90% CI 0.975 – 1.269 (predefined equivalence ratio 0.737 – 1.357).

However, the primary efficacy outcome according to the EU requirement was not met, as the results for the difference were not contained within the pre-defined equivalence margin, i.e., the upper limit in the study was 12.9% slightly above the required limit of 12.5%. The sensitivity analysis performed with the FAS found that the difference was 4.8% *which was within the comparability margin* compared with a difference of 5.4% for the PPS which was not within the comparability margin (-12.5, 12.5).

As described in the clinical evaluation report, the sponsor undertook a number of additional analyses to try to explain whether there was a clinically meaningful difference in the ORR. No contributing factor to the primary efficacy result was identified from the pre-specified subgroup analyses. An additional ad hoc sensitivity analysis was performed to try to identify prognostic factors significant to survival and assess the impact on the primary efficacy results. The analysis of the difference in best ORR adjusted by the subcategory of distant metastasis (M0: no distant metastasis; M1a: separate tumour nodule(s) in a contralateral lobe or tumour with pleural nodules or malignant pleural or pericardial effusion; M1b: distant metastasis) showed the 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 sponsor concluded that the observed difference in best ORR is at least in part explained by the distant metastasis subcategory.

As no other contributing factors were further identified, the sponsor performed additional post hoc analyses to evaluate the clinical relevance of the observed difference and concluded that there are no clinically meaningful differences between the two products based on the following results:

- The overall changes in tumour burden during the induction treatment period were comparable between the SB8 and EU AVASTIN treatment groups, as shown in waterfall plots. 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 the EU AVASTIN treatment group. The difference [95% CI] between the two treatment groups was 0.6% [−4.18%, 2.99%], indicating no difference in the treatment effect of SB8 and EU AVASTIN.

Analysis of the overall responses at specific time points (Cycle 2, Cycle 4, and Cycle 6) of the induction treatment period showed that the proportion of the responders (complete response [CR] + partial response [PR]) were comparable between the two treatment groups. The 95% CI for the difference in best ORR between SB8 and EU AVASTIN at Cycle 2 and Cycle 4 was both within the predefined equivalence margin of [−12.5%, 12.5%]. A slightly higher response was observed in the SB8 treatment group compared to the EU AVASTIN treatment group at Cycle 6, likely due to a limited number of the patients in the analysis set.

The secondary efficacy variables, PFS, OS, and DOR were comparable between the SB8 and AVASTIN treatment groups in the PPS, and best ORR by Week 11 and Week 17 were similar with the 95%CI of the difference being within the ± 12.5 equivalence margin.

The sponsor concluded the following:

- Analyses of PFS and OS showed that the survival rates were comparable between the SB8 and EU AVASTIN treatment groups (hazard ratio (HR) of PFS: 1.01 [95% CI: 0.84, 1.22]; HR of OS: 1.08 [95% CI: 0.86, 1.35]). Comparable survival rates between the two treatment groups indicate that the observed difference in the best ORR was not clinically meaningful in terms of efficacy.
- A slight difference in best ORR between SB8 and EU AVASTIN in the PPS did not lead to an increase in the incidence of AEs or detection of new safety signals in the SB8 treatment group. The safety profiles of SB8 and EU AVASTIN were comparable during the study

Overall, the clinical evaluator noted that the EU has approved the product. Review of the initial evaluation by the EMA (*Aybintio EPAR, 2020*) indicates that the EMA considered that PK bioequivalence and the efficacy results including the extensive post hoc analyses established equivalence between SB8 and AVASTIN.

The Delegate agrees with the conclusion of the clinical evaluator that despite the supporting comparability study (SB8-G31-NSCLC) not meeting the primary efficacy outcome according to the EU requirement, ONBEVZI appears to be comparable to EU AVASTIN based on overall results of efficacy analyses. The Delegate will seek ACM's opinion regarding the comparability of ONBEVZI with the reference product in relation to the primary efficacy outcome.

Proposed action

Following review of the submitted data, it is determined that ONBEVZI is considered biosimilar to AVASTIN, and therefore a benefit/risk balance comparable to the reference product can be concluded.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Does ACM support the use of ONBEVZI as a bevacizumab biosimilar, based on the findings of the comparability studies?

The ACM supports the registration of ONBEVZI as a bevacizumab biosimilar as the physicochemical and PK profiles are both similar to the reference product. There is also no evidence that the proposed biosimilar is less efficacious or has increased toxicity compared to the reference product.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the same indication as the innovator product (AVASTIN) in Australia:

> ONBEVZI (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.
>
> ONBEVZI (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline based therapy is contraindicated.
>
> ONBEVZI (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic, or recurrent, non-squamous, non-small cell lung cancer.
>
> ONBEVZI (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.
>
> ONBEVZI (bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.
>
> ONBEVZI (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.
>
> ONBEVZI (bevacizumab), in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, is indicated for the treatment of patients with first recurrence of platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior bevacizumab or other VEGF-targeted angiogenesis inhibitors.
>
> ONBEVZI (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens and have not received any prior anti-angiogenic therapy including bevacizumab.
>
> ONBEVZI (bevacizumab) in combination with paclitaxel and cisplatin is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix. ONBEVZI (bevacizumab) in combination with paclitaxel and topotecan is an acceptable alternative where cisplatin is not tolerated or not indicated.

Outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register ONBEVZI for:

Metastatic Colorectal Cancer

ONBEVZI (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.

Locally recurrent or metastatic Breast Cancer

ONBEVZI (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated (see Section 5.1 Clinical Trials).

Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC)

ONBEVZI (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.

Advanced and/or metastatic Renal Cell Cancer

ONBEVZI (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.

Grade IV Glioma

ONBEVZI (bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

ONBEVZI (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

ONBEVZI (bevacizumab), in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, is indicated for the treatment of patients with first recurrence of platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior bevacizumab or other VEGF-targeted angiogenesis inhibitors.

ONBEVZI (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens and have not received any prior anti-angiogenic therapy including bevacizumab.

Cervical Cancer

ONBEVZI (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated (bevacizumab) in combination with paclitaxel and cisplatin is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix. ONBEVZI (bevacizumab) in combination with paclitaxel and topotecan is an acceptable alternative where cisplatin is not tolerated or not indicated.

Specific conditions of registration applying to these goods

All batches of ONBEVZI supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Attachment 1. Product Information

The Product Information (PI) approved with the submission for ONBEVZI which is described in this AusPAR can be found as Attachment 1. It may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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Reference/Publication #