



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Bevacizumab

Proprietary Product Name: Abevmy

Sponsor: Alphapharm Pty Ltd

January 2022

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- 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 (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

About AusPARs

- An 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.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the plasma concentration time curve
Bmab-100	Product code for an earlier and alternative formulation of a related bevacizumab biosimilar
CI	Confidence interval
C _{max}	Maximum plasma concentration
C _{min}	Minimum plasma concentration
CPD	Certified Product Details
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States of America)
IgG1	Immunoglobulin G1
MedDRA	Medical Dictionary for Regulatory Activities
MYL-14020	Product code for Abevmy formulation intended for marketing in Australia
Nab	Neutralising antibody
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival

Abbreviation	Meaning
PFS	Progression free survival
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
SAE	Serious adverse event
SMQ	Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ)
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
US(A)	United States (of America)
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biosimilar medicine
<i>Product names:</i>	Abevmy/Trucleva; ¹
<i>Active ingredient:</i>	Bevacizumab
<i>Decision:</i>	Approved
<i>Date of decision:</i>	10 May 2021
<i>Date of entry onto ARTG:</i>	6 September 2021
<i>ARTG numbers:</i>	334814 and 334816; ¹
<i>, Black Triangle Scheme:²</i>	No
<i>Sponsor's name and address:</i>	Alphapharm Pty Ltd Level 1, 30 The Bond, 30 - 34 Hickson Road Millers Point NSW 2000
<i>Dose form:</i>	Concentrate for solution for infusion
<i>Strengths:</i>	25 mg/mL (100 mg/4 mL and 400 mg/16 mL)
<i>Container:</i>	Vial
<i>Pack size:</i>	One
<i>Approved therapeutic use:</i>	<p><i>Metastatic colorectal cancer</i></p> <p><i>Abevmy (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.</i></p> <p><i>Locally recurrent or metastatic breast cancer</i></p> <p><i>Abevmy (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 Pharmacodynamic properties, clinical trials).</i></p> <p><i>Advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC)</i></p>

¹ Trucleva has been approved by the TGA on 10 May 2021. Trucleva is not listed on the Australian Register of Therapeutic Goods (ARTG).

² The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

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

Advanced and/or metastatic renal cell cancer

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

Grade IV glioma

Abevmy (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

Abevmy (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for firstline 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

Abevmy (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.

Abevmy (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

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

Route of administration: Intravenous infusion

Dosage: Dosage of Abevmy is based on multiple factors, including the condition being treated, the body weight of the patient and whether the medicine is used as first or second line treatment.
For further information regarding dosage, 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. This 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 application by Alphapharm Pty Ltd (the sponsor) to register Abevmy/Trucleva (bevacizumab) 100 mg/4 mL and 400 mg/16 mL, concentrate for solution for infusion for the following proposed indications:

Metastatic colorectal cancer

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

Locally recurrent or metastatic breast cancer

Abevmy (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 Pharmacodynamic properties, clinical trials).

Advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC)

Abevmy (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

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

Grade IV glioma

Abevmy (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

Abevmy (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

Abevmy (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.

Abevmy (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

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

Colorectal cancer is the third most common cancer in men (663,000 cases, 10.0% of the total cancers) and the second in women (570,000 cases, 9.4% of the total cases) worldwide.³ Bevacizumab is part of the current standard of care first line treatment for patients with metastatic colorectal cancer. Adding bevacizumab to chemotherapy prolongs survival in advanced colorectal cancer patients. Folfox or Xelox (capecitabine and oxaliplatin) is considered as a convenient first line treatment option for metastatic colorectal cancer patients. Combining doublet chemotherapy regimens with bevacizumab has been shown to improve progression free survival (PFS) and overall survival (OS) in the treatment of patients with metastatic colorectal cancer in both the first and second line settings.

Lung cancer is the most common cause of cancer mortality worldwide for both men and women. For patients with non-small cell lung cancer (NSCLC), initial management is largely determined by the stage of disease. For patients with early stage disease, surgical resection offers the best opportunity for cure, while concurrent chemoradiotherapy is preferred for those with more extensive intrathoracic disease. In contrast, patients with advanced disease are managed palliatively with systemic therapy and/or local palliative modalities.⁴

In the treatment of cancers including colorectal cancer, the drug cost is growing faster than any other component of health care expenditure. There is an unmet need of similar biologic medicines and to improve affordable access to these medicines.

Bevacizumab is an immunoglobulin G1 humanised monoclonal antibody which selectively binds with high affinity to vascular endothelial growth factor (VEGF). Once it is bound to VEGF, it neutralises VEGF's biologic activity by sterically hindering the binding of VEGF to its receptors (vascular endothelial growth factor receptor (VEGFR)-1 and VEGFR-2) on the surface of endothelial cells, thus inhibiting endothelial cell proliferation, angiogenesis, and VEGF induced vascular permeability. VEGF is an endogenously expressed protein that stimulates new blood vessel formation. Bevacizumab reduces solid tumour growth by neutralising the proangiogenic activity of VEGF, thereby reducing the amount of new blood vessel formation in the tumour, and facilitating the activity of concomitant chemotherapy.

³ Bhattacharya et al. Colorectal Cancer: a Study of Risk Factors in a Tertiary Care Hospital of North Bengal, *J Clin Diagn Res*, 2014; 8(11): FC08–FC10.

⁴ Midthun, D. E. Overview of the Initial Treatment and Prognosis of Lung Cancer, In: UpToDate (Accessed on 18 August 2020).

Abevmy has been developed as a biosimilar medicine to the biological medicine Avastin;⁵ (bevacizumab). Avastin is approved in Australia for a number of indications. Dosage varies with the indication. The proposed dose regimens for Abevmy are the same as those approved for Avastin. Dosages vary from 5 mg/kg of body weight given once every 2 weeks to 15 mg/kg given every 3 weeks, until progression of disease. The exception to this duration is in the first line treatment of epithelial ovarian, fallopian tube or primary peritoneal cancer, where treatment is recommended to continue for a total of 15 months therapy or until disease progression, whichever occurs earlier.

In the pivotal studies, the sponsor selected subject populations and clinical endpoints sensitive to detect any clinically meaningful differences between MYL-14020 (product code for Abevmy formulation intended for marketing in Australia) and Avastin, if such differences existed.

Regulatory status

Abevmy (bevacizumab) is considered a new biosimilar medicine for Australian regulatory purposes. Abevmy has been developed as biosimilar medicine to Avastin (bevacizumab) that was first approved by the TGA and received registration on the Australian Register of Therapeutic Goods (ARTG) in February 2005.

At the time the TGA considered this application, similar applications were under consideration in the European Union (EU) (submitted on 27 February 2020), the United States of America (USA) (submitted on 27 December 2019), Canada (submitted on 5 June 2020), New Zealand (submitted on 17 June 2020) and Switzerland (submitted on 4 December 2020).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2020-01736-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	2 June 2020
First round evaluation completed	2 November 2020
Sponsor provides responses on questions raised in first round evaluation	4 January 2021
Second round evaluation completed	17 February 2021

⁵ Avastin was first registered on the ARTG on 24 February 2005 (ARTG number: 99755 and 99757).

Description	Date
Delegate's Overall benefit-risk assessment	4 May 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	10 May 2021
Completion of administrative activities and registration on the ARTG	6 September 2021
Number of working days from submission dossier acceptance to registration decision*	193

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- European Medicines Evaluation Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products, CHMP/437/04, 30 October 2005.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products, CHMP/437/04 Rev 1, 23 October 2014.
- European Medicines Evaluation Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues, EMA/CHMP/BWP/49348/2005, 22 February 2006.
- European Medicines Evaluation Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues, EMA/CHMP/BMWP/42832/2005, 22 February 2006.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues, EMA/CHMP/BMWP/42832/2005 Rev1, 18 December 2014.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies - Non-clinical and Clinical Issues, EMA/CHMP/BMWP/403543/2010, 30 May 2012.

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Immunogenicity Assessment of Therapeutic Proteins, EMEA/CHMP/BMWP/14327/2006 Rev 1, 18 May 2017.
- The FDA's biosimilars guidance, available at: <https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/biosimilars-guidances>

Quality

Bevacizumab is a recombinant humanised immunoglobulin G1 (IgG1) monoclonal antibody expressed in Chinese hamster ovary cell line. It consists of 1334 amino acids and contains two identical heavy chains and two identical light chains.

Bevacizumab as a drug substance has been assessed by the TGA previously, and is described in the approved Australian PI for Avastin, the originator (reference) drug product.⁶ Similarities between Abevmy and the reference product Avastin were investigated in a comprehensive comparability testing program, which covered physicochemical and biological characterisation of the MYL-14020 (bevacizumab) drug substance and the Abevmy drug product. The excipients in Abevmy are:

- α,α -trehalose dihydrate
- monobasic sodium phosphate dihydrate
- dibasic sodium phosphate
- polysorbate 20
- water for injections.

Abevmy is a clear to slightly opalescent, colourless to pale brown, sterile and preservative free solution. Both strengths (100 mg/4 mL and 400 mg/16 mL) of Abevmy come presented in Type I clear glass vials and each pack contains one vial of either 100 mg/4 mL or 400 mg/16 mL bevacizumab.

The TGA made a full evaluation of the chemical, pharmaceutical and biological aspects of the sponsor submitted dossier, including manufacturing and sterility considerations. After the quality evaluation was completed, there were no outstanding concerns from a quality perspective regarding the registration of this product.

Nonclinical

The key findings of the nonclinical evaluation included:

- The sponsor's proposed indications and dosing regimen/route for Abevmy match those of the originator product Avastin.
- The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics, single and repeat dose toxicity. The scope of the nonclinical program is adequate. The studies were conducted using the US and/or EU sourced Avastin as the reference product. No data were provided in nonclinical to verify the comparability of the US or EU sourced and Australian sourced Avastin.
- No meaningful differences between Abevmy and Avastin were observed in the comparative pharmacology, pharmacokinetic and toxicity studies.

⁶ The Approved Australian Product Information for Avastin (bevacizumab). Available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04263-3&d=202104261016933>.

- The ability of the nonclinical studies to support comparability of Abevmy to Australian sourced Avastin depends on the conclusion of the quality evaluator regarding the identity and comparability of Avastin products across jurisdictions. There are no nonclinical objections to the registration of Abevmy, provided that the US and EU sourced Avastin is considered to be identical or highly comparable to the Australian Avastin.

Clinical

Study designs

The clinical dossier submitted in support of Abevmy included three clinical studies (listed in Table 2), all of which have now been completed.

Two main formulations of bevacizumab were studied across the three clinical studies:

- Abevmy/MYL-14020: this formulation was used in the global development program (the Phase I Study MYL-14020-1002, and Phase III Study MYL-14020-3001) and is the formulation to-be-marketed in Australia as Abevmy.
- Bmab-100: this earlier and alternative formulation was used in a randomised clinical study (Study BM100-CC-03-1-01) conducted by a development partner of the study sponsor for the two studies listed for the formulation above) to obtain marketing authorisation in the country of origin (India).

Table 2: Listing of clinical studies included in the submission

Study ID	Objectives	Design	Treatments	Population	Duration of treatment
Study MYL-14020-1002	Primary: compare PK of MYL-14020, US-Avastin and EU-Avastin Secondary: safety, tolerability, immunogenicity	Single centre, randomised, double blind, 3 parallel arm Phase I study	Single dose (1 mg/kg 90 min IV infusion) of MYL-14020, EU-Avastin or US-Avastin.	Healthy male volunteers ITT=111 MYL-14020=37 EU-Avastin=37 US-Avastin=37	Single dose. 90 days follow up
Study MYL-14020-3001	Primary: ORR of MYL-10420 versus EU-Avastin, in combination with carboplatin-paclitaxel chemotherapy for 18 weeks then continued as monotherapy. Secondary: safety, other efficacy endpoints, immunogenicity	Multicentre, double blind, randomised, parallel group	15 mg/kg IV infusion every 21 days of MYL-14020 or EU-Avastin, given in combination with standard carboplatin-paclitaxel chemotherapy for the first 18 of 42 weeks	Patients with stage IV non-squamous NSCLC (nsNSCLC) ITT=671 MYL-14020=337 EU-Avastin=334	42 weeks

Study ID	Objectives	Design	Treatments	Population	Duration of treatment
Study BM100-CC-03-I-01	<p>Part 1</p> <p>Safety of Bmab-100 in combination with capecitabine and oxaliplatin</p> <p>Part 2</p> <p>Primary: single dose PK bioequivalence of Bmab-100 and EU-Avastin.</p> <p>Secondary: efficacy, multiple dose PK equivalence, safety and immunogenicity</p>	Multicentre, double-blind, randomised, parallel group	7.5 mg/kg IV infusion every 21 days of Bmab-100 or EU-Avastin, for up to six cycles, given in combination with capecitabine and oxaliplatin	<p>Patients with metastatic colorectal cancer</p> <p>Part 1 ITT=10 (all Bmab-100)</p> <p>Part2 ITT=136</p> <p>Bmab-100=68</p> <p>EU-Avastin=68</p>	18 weeks

Bmab-100 = product code for an earlier and alternative formulation of a related bevacizumab biosimilar; EU-Avastin = Avastin sourced from the European Union, ITT = intention-to-treat;⁷ IV = intravenous; MYL-14020 = product code for Abevmy formulation intended for marketing in Australia; NSCLC = non-small cell lung cancer, nsNSCLC = non-squamous non-small cell lung cancer; ORR = objective response rate; PK = pharmacokinetic(s), US-Avastin = Avastin sourced from the United States of America.

Population characteristics

Study MYL-14020-1002 (healthy male volunteers)

The mean age of the subjects was 30, 33 and 31 years, and mean body mass index was 24.0, 24.7 and 24.5 kg/m² for the MYL-14020 (Abevmy), US-Avastin and EU-Avastin treatments, respectively. Most subjects (93%) were White.

Study MYL-14020-3001 (patients with metastatic non-squamous non-small cell lung cancer)

The baseline demographics and disease characteristics of the enrolled population were reasonably balanced between arms, with both arms having a mean age of 59 years, 63% were male, around 70% were Caucasian and 30% were Asian race, and by Eastern Cooperative Oncology Group (ECOG) performance status, around a quarter had an ECOG performance status of 0;⁸ and the remainder had ECOG performance status of 1, and

⁷ Randomised clinical trials analysed by the **intent-to-treat (ITT)** approach provide the unbiased comparisons among the treatment groups. In the ITT population, none of the patients are excluded and the patients are analysed according to the randomisation scheme.

⁸ ECOG Performance Status: The **Eastern Cooperative Oncology Group (ECOG)** has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

- 0 - Fully active, able to carry on all pre-disease performance without restriction
- 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

around 50% were smokers. The majority had metastatic disease at diagnosis (approximate 90%) and had adenocarcinoma histology (approximate 95%) with multiple metastatic sites (approximate 60%).

Study BM100-CC-03-1-01 (patients with metastatic colorectal cancer)

The baseline demographics and disease characteristics of the enrolled population were reasonably balanced between arms. The mean age of patients in the Bmab-100 arm was 51 years, and in the EU-Avastin arm was 52 years. All patients were of Asian race, around 30% had an ECOG performance status of 0 and 70% had an ECOG performance status of 1. The majority had metastatic disease at diagnosis (approximate 90%) and had adenocarcinoma histology (approximate 95%) with multiple metastatic sites (approximate 60%).

Results

Pharmacokinetics

Study MYL-14020-1002

At a single centre, healthy volunteer male subjects were randomised into three arms (n = 37 each), and each received a single 1 mg/kg dose (intravenously over 90 minutes) of either MYL-14020 (Abevmy), US-Avastin or EU-Avastin. Dense pharmacokinetics (PK) sampling was undertaken from Day 1 through Day 99 (28 samples per person). The lower limit of quantification of the analytical assay was 160 µg/mL.

The observed bevacizumab PK parameters are shown in Table 3 and a comparison of the Least squares mean ratios and 90% confidence intervals for area under the plasma concentration time curve (AUC) and C_{max} between the groups is shown in Table 4.

Table 3: Study MYL-14020-1002 Summary of bevacizumab pharmacokinetic parameters

Parameter	MYL-14020 (n=37)	US-Avastin (n=37)	EU-Avastin (n=36)
AUC _{0-inf} (µg*hr/mL)	7663.6 (11.7%)	7904.2 (13.7%)	8186.4 (15.1%)
AUC _{0-t} (µg*hr/mL)	7526.5 (11.8%)	7764.8 (13.6%)	8031.3 (14.8%)
C_{max} (µg/mL)	24.41 (11.5%)	25.97 (13.0%)	27.50 (18.7%)
k_{el} (hr ⁻¹)	0.0019 (11.0%)	0.0020 (13.3%)	0.0019 (15.2%)
$t_{1/2}$ (hr)	374.1 (11.3%)	356.2 (14.0%)	369.1 (15.0%)
t_{max} (hr)	2.533 (31.1%)	2.798 (31.6%)	2.338 (26.9%)

AUC_{0-inf} = area under the plasma concentration time curve from time zero to infinity; AUC_{0-t} = area under concentration time curve from time zero to last measurable concentration; C_{max} = maximum plasma concentration; EU-Avastin = Avastin sourced from the European Union; k_{el} = elimination rate constant; MYL-14020 = product code for Abevmy formulation intended for marketing in Australia; n = sample size; $t_{1/2}$ = terminal drug half life; t_{max} = the time after administration of a drug when the maximum plasma concentration is reached; US-Avastin = Avastin sourced from the United States of America.

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 - Dead

Table 4: Study MYL-14020-1002 Least squares mean ratios and 90% confidence intervals comparing the three arms

Parameter	MYL-14020/ US-Avastin [®]	MYL-14020/ EU-Avastin [®]	EU-Avastin [®] / US-Avastin [®]
LNAUC _{0-inf} (µg*hr/mL)	0.97 (92.32% - 102.33%)	0.94 (89.23% - 98.98%)	1.03 (98.20% - 108.93%)
LNAUC _{0-t} (µg*hr/mL)	0.97 (92.30% - 102.25%)	0.94 (89.31% - 99.01%)	1.03 (98.12% - 108.77%)
LNC _{max} (µg/mL)	0.94 (89.21% - 99.24%)	0.90 (84.90% - 94.52%)	1.05 (99.55% - 110.83%)

EU-Avastin = Avastin sourced from the European Union; LNAUC_{0-inf} = log transformed area under the plasma concentration time curve from time zero to infinity; LNAUC_{0-t} = log transformed area under concentration time curve from time zero to last measurable concentration; LNC_{max} = log transformed maximum plasma concentration; MYL-14020 = product code for Abevmy formulation intended for marketing in Australia; US-Avastin = Avastin sourced from the United States of America.

This study showed bioequivalence of MYL-14020 (Abevmy) with both EU-Avastin and US-Avastin. The pharmacokinetics of bevacizumab are linear from doses of 1 mg/kg to 10 mg/kg (the approved dose regimen for bevacizumab includes doses up to 15 mg/kg).

Study MYL-14020-3001

Each patient received a bevacizumab dose of 15 mg/kg intravenous over 90 minutes every 3 weeks, and PK sampling was undertaken at Cycles 1, 2, 4 and 6, as well as some additional sparse sampling. The lower limit of quantification of the analytical assay was 320 µg/mL.

Pharmacokinetic results from this study were incorporated with those of Study MYL-14020-1002 in the population pharmacokinetic (popPK) analysis described below.

Study BM100-CC-03-1-01

This study did not contribute significantly to the TGA assessment of Abevmy PK as it used a different formulation (Bmab-100) and the PK was adequately characterised in the other two clinical studies.

Population pharmacokinetics

A popPK analysis was performed to assess the linearity of PK characteristics and potential significant covariates across dose levels from 1 mg/kg to 15 mg/kg, and the similarity of MYL-14020 (Abevmy) to Avastin. The analysis used pooled PK data from:

- Study MYL-14020-1002
- Study MYL-14020-3001

The model describing the PK of MYL-14020 (Abevmy) versus Avastin was considered robust. Exposure parameters (AUC, half-life, maximum plasma concentration (C_{max}), and maximum plasma concentration (C_{min})), predicted based on the final model for all Phase III patients in steady state, are summarised in Table 5. The popPK profile of MYL-14020 (Abevmy) was not different to that for EU-Avastin in patients with non-squamous non-small cell lung cancer (NSCLC). The final model supported linearity or approximate linearity of bevacizumab doses of 15 mg/kg when given in 21 day cycles. No clinically meaningful covariates were identified.

Table 5: Study MYL-14020-3001 Bayesian parameter based exposure estimates for patient at steady state (final model) stratified by treatment

Subject Characteristic	Statistic	Treatment	
		MYLAN-14020	EU-Avastin
AUC ₀₋₂₁ in steady-state (mcg x day/mL)	Mean (StdDev)	3881.591 (1289.571)	4035.769 (1364.511)
	Median	3752.200	3874.700
	Min, Max	866.85, 9793.10	878.52, 10641.00
	n	333	327
C _{max} (mcg/mL)	Mean (StdDev)	389.274 (111.376)	395.161 (104.605)
	Median	373.650	387.120
	Min, Max	113.83, 1090.60	136.16, 830.57
	n	333	327
C _{min} (mcg/mL)	Mean (StdDev)	107.603 (47.783)	112.747 (50.947)
	Median	102.730	105.800
	Min, Max	14.05, 354.58	10.78, 393.48
	n	333	327
Half-life (days)	Mean (StdDev)	20.611 (4.681)	21.078 (4.891)
	Median	20.267	20.601
	Min, Max	9.86, 43.87	8.56, 46.48
	n	333	327

AUC₀₋₂₁ = area under the plasma concentration time curve from time zero to Day 21; EU-Avastin = Avastin sourced from the European Union; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; MYL-14020 = product code for Abevmy formulation intended for marketing in Australia; StdDev = standard deviation; US-Avastin = Avastin sourced from the United States of America.

Pharmacodynamics

Summary of immunogenicity

Immunogenicity was assessed in all three submitted clinical studies.

The immunogenicity assays used across studies included a homogeneous bridging electrochemiluminescence assay validated for testing of anti-MYL-14020 (Abevmy) / anti-Avastin antibodies (anti-drug antibodies (ADAs)) in normal and disease state serum, and a non-cell based assay to determine neutralising antibodies (Nab) in NSCLC serum.

Baseline ADA positivity in a small proportion of patients has been observed in other bevacizumab studies and may be due to cross reactivity with pre-existing antibodies.^{9,10,11}

The immunogenicity data summarised below from the three clinical trials indicates that there was no appreciable difference between immunogenicity of MYL-14020 (c) and Avastin. They also indicated no appreciable effect of ADAs on safety or efficacy. Maximum observed ADA titres were below the minimum sensitivity level (100 ng/mL) recommended by the US Food and Drug Administration (FDA) for assays for

⁹ Reinmuth, N. et al. PF-06439535 (a Bevacizumab Biosimilar) Compared with Reference Bevacizumab (Avastin), Both Plus Paclitaxel and Carboplatin, as First-Line Treatment for Advanced Non-squamous Non-small-cell Lung Cancer: A Randomized, Double-blind Study, *BioDrugs*, 2019; 33, 555–570.

¹⁰ Food and Drug Administration (FDA), Center for Drug Evaluation and Research, Clinical Pharmacology and Biopharmaceutics Review(s), ABP215, 100 or 400 mg solution, for intravenous infusion. Available from the FDA website.

¹¹ European Medicines Agency (EMA), European Public Assessment Report (EPAR), Aybintio (bevacizumab), EMA/349890/2020, 2 September 2020. Available from the EMA website.

immunogenicity, at which level an association with clinical events has been previously described.¹²

A high incidence of low titre ADA positivity was seen in Study MYL-14020-1002 and Study BM100-CC-03-1-01 (colorectal cancer), compared to the Phase III Study MYL-14020-3001 (NSCLC). This is not in keeping with the historically reported ADA positivity rate for Avastin, and is considered likely to be false positivity due to assay sensitivity to endogenous VEGF. As explained by the sponsor in their response to the European Medicines Agency (EMA)'s Day 120 list of questions.¹³

Thus, the ADA assay methodology used in Study MYL-14020-3001 (NSCLC) had a higher VEGF tolerance target (2 µg/mL) than did the methodology used in Study-BM100-CC-03-1-01 (colorectal cancer) (15 ng/mL) or Study MYL-14020-1002 (400 pg/mL).

Study MYL-14020-1002

In the PK Study MYL-14020-1002, blood samples were taken at Baseline and at four visits post exposure for the presence of ADAs. The results of the ADA testing are summarised in Table 6. Post dosing, none of the baseline positive subjects showed a significant increase in titre with time. The highest post dose ADA titres obtained were:

- 20.9 ng/mL in the MYL-14020 arm (on Day 99; no subsequent measurements taken, as Day 99 was the final study visit)
- 16.3 ng/mL (on Day 71; titre returned to 3.0 ng/mL by next test on Day 99)
- 14.7 ng/mL (on Day 15; titre negative by next test on Day 43)

The percentage of ADA positive subjects at each timepoint, though higher than expected (see explanation above) was comparable across treatments.

Neutralising activity was not assessed in this study.

Table 6: Study MYL-14020-1002 Incidence of anti-drug antibodies by visit and treatment

Visit	MYL-14020 (N=37)		EU-Avastin (N=37)		US-Avastin (N=37)	
	n'	n (%)	n'	n (%)	n'	n (%)
Baseline	37	1 (3)	37	1 (3)	37	2 (5)
Day 15	37	35 (95)	37	37 (100)	37	33 (89)
Day 43	37	28 (76)	37	28 (76)	37	31 (84)
Day 71	37	8 (22)	36	12 (33)	37	12 (32)
Day 99	37	2 (5)	37	6 (16)	37	4 (11)

EU-Avastin = Avastin sourced from the European Union; MYL-14020 = product code for Abevmy formulation intended for marketing in Australia; N = number of subjects exposed to treatment; n =

¹² Food and Drug Administration (FDA), U.S. Department of Health and Human Services. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER), Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection Guidance for Industry, January 2019. Available from the FDA website.

¹³ Inclusion of this information is beyond the scope of the AusPAR.

number of subjects with positive anti-drug antibody results; n' = number of subjects with available anti-drug antibody results; US-Avastin = Avastin sourced from the United States of America.

Study MYL-14020-3001

Results of ADA testing in Phase III Study MYL-14020-3001 are summarised in Table 7 and Table 8. Post-Baseline, ADA and NAb were infrequent, declined over time and were comparable between both treatment arms.

Most ADA were transient, occurring at one or two timepoints. One patient in the Avastin arm had treatment boosted ADA at 3 timepoints.

Table 7: Study MYL-14020-3001 Incidence of anti-drug antibodies by visit and treatment (safety set)

Visit	Results	MYL-14020 (N=335) n (%)		Avastin (N=329) n (%)	
		ADA	NAb	ADA	NAb
Baseline	Positive	12 (4)	2 (0.6)	16 (5)	4 (1.2)
	Negative	318 (96)	328 (99.4)	307 (95)	319 (98.8)
	Missing	1	1	0	0
Period 1/ Week 4	Positive	12 (4)	1 (0.3)	11 (4)	2 (0.6)
	Negative	291 (96)	302 (99.7)	300 (96)	309 (99.4)
	Missing	1	1	0	0
Period 1/ Week 10	Positive	10 (4)	0	10 (4)	2 (0.8)
	Negative	243 (96)	253 (100)	246 (96)	254 (99.2)
	Missing	0	0	1	1
Period 1/ Week 16	Positive	3 (1)	0	8 (4)	4 (1.4)
	Negative	219 (99)	222 (100)	207 (96)	212 (98.6)
	Missing	0	0	0	0
End of treatment	Positive	1 (2)	0	1 (2)	1 (2.1)
	Negative	43 (98)	44 (100)	46 (98)	46 (97.9)
	Missing	0	0	0	0
Safety follow-up	Positive	1 (3)	0	2 (4)	0
	Negative	36 (97)	37 (100)	43 (96)	45 (100)
	Missing	0	0	0	0

ADA = anti-drug antibodies; MYL-14020 = product code for Abevmy formulation intended for marketing in Australia; N=number of patients exposed; Nab = neutralising antibodies; Missing = attended the visit but no ADA sample collected.

Percentages are based on number of patients in safety set at corresponding visit.

Table 8: Study MYL-14020-3001 Overall rates of anti-drug antibodies (safety set)

Visit	MYL-14020 (N=335)			Avastin (N=329)		
	n	M	n/m, %	n	m	n/m, %
Any post-Baseline positive ADA result	22	310	7.1	21	316	6.6
Binding ADA	1	310	0.3	8	316	2.5
Neutralising ADA						
Treatment-induced ADAs	18	306	5.9	11	309	3.6
Treatment-boosted ADAs	0	306	0	2	309	0.6
Overall incidence (induced plus boosted)	18	306	5.9	13	309	4.2

m=number of patients with evaluable ADA results (Baseline and at least one post-Baseline); MYL-14020 = product code for Abevmy formulation intended for marketing in Australia; N=number of patients exposed; n=number of patients with positive ADA results; treatment-induced = no Baseline and any post-Baseline; treatment-boosted = baseline positive and post-Baseline 4-fold higher at any timepoint.

Study BM100-CC-03-1-01

Results of ADA testing in Study BM100-CC-03-1-01 are summarised in Table 9, below. The incidences of ADA positivity at each timepoint and ADA titres were comparable across treatments. The highest individual post-dose ADA titres obtained in the Bmab-100 and EU-Avastin arms were 9.0 ng/mL and 7.0 ng/mL respectively.

Similarly to Study MYL-14020-1002, the high incidence of ADA positivity in this study is attributed to confounding by endogenous epidermal growth factor receptor (EGFR).

Neutralising activity was not assessed in this study.

Table 9: Study BM100-CC-03-1-01 Overall rates of anti-drug antibodies (safety set)

Visit	Bmab-100 (N=68)			EU-Avastin (N=67)		
	n	m	n/m, %	N	m	n/m, %
Baseline	68	5	7	67	2	3
Visit 4	52	45	87	55	48	87
End of study	51	46	90	52	47	90

Bmab-100 = product code for an earlier and alternative formulation of a related bevacizumab biosimilar; EU-Avastin = Avastin sourced from the European Union; m=number of patients with positive anti-drug antibody results; N=number of patients exposed; n=number of patients with evaluable anti-drug antibody results (Baseline and at least one post-Baseline).

Efficacy**Study MYL-14020-3001**

The primary endpoint in Study MYL-14020-3001 was the objective response rate (ORR) of MYL-14020 (Abevmy) compared to EU-Avastin in the first line treatment of non-squamous NSCLC during the first 18 weeks of treatment, in combination with carboplatin and paclitaxel. After the first 18 weeks, bevacizumab was continued as monotherapy (in patients without disease progression) for a total of 42 weeks.

Secondary efficacy endpoints were not formally tested or alpha controlled, and included disease control rate (DCR), duration of response (DOR), PFS, and OS.

The sample size was calculated based on an assumed ORR of 41.6% in both arms, with a pre-specified equivalence margin of +/- 15% based on a fixed effect meta-analysis of five published studies. The primary endpoint was tested using two different statistical approaches (due to differences in the EMA and FDA requirements for equivalence testing).

The main results of Study MYL-14020-3001 are summarised in Table 10.

Table 10: Study MYL-14020-3001 Results for Week 18 objective response rate (intent-to-treat set)⁷

	MYL-14020 (N=337)	EU-Avastin (N=334)
Best overall response, ¹ n (%)		
Complete response (CR)	2 (0.6)	3 (0.9)
Partial response (PR)	138 (40.9)	141 (42.2)
Stable disease (SD)	134 (39.8)	144 (43.1)
Non-CR/Non-PD	2 (0.6)	1 (0.3)
Progressive disease (PD)	22 (6.5)	14 (4.2)
Not evaluable (NE)	0	0
Not done (ND)	39 (11.6)	31 (9.3)
Objective response rate (ORR)		
Responders, n (%)	140 (41.5)	144 (43.1)
95% CI for ORR (%)	(36.3, 46.8)	(37.8, 48.4)
DIFF in ORR and 95% CI (%) ²	-1.6 (-9.0, 5.9)	
Ratio of ORR and 90% CI ³	0.96 (0.83, 1.12)	

CI = confidence interval; CR = complete response; EU-Avastin = Avastin sourced from the European Union; MYL-14020 = product code for Abevmy formulation intended for marketing in Australia; N = population size; ND = no post-Baseline lesion assessment; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

1 Responses assessed by blinded independent review using the Response Evaluation Criteria in Solid Tumours (RECIST);¹⁴ v1.1

2 As required by the European Medicines Agency: $DIFF = ORR_{MYL-14020} \text{ minus } ORR_{Avastin}$; asymptotic 2-sided 95% CI per Wald; equivalence region (-12.5%, 12.5%).

3 As required by Food and Drug Administration (United States of America): ratio = $ORR_{MYL-14020}/ORR_{Avastin}$; 2-sided 90% CI per logarithmic transformation; equivalence region (0.73, 1.36).

Disease control rate (DCR) at Week 18 was 81.3% in the MYL-14020 arm and 86.2% in the Avastin arm. The ratio of DCR was 0.94 (90% confidence interval (CI): 0.89, 1.00) and the difference in DCR was -4.9 (95% CI: -10.5, 0.6).

Study BM100-CC-03-I-01

The efficacy results of Study BM100-CC-03-I-01 have limited relevance because the study was not designed to demonstrate equivalent efficacy for Bmab-100 and EU-Avastin, and the formulation studied (Bmab-100) is not the formulation proposed for registration (MYL-14020/Abevmy).

The primary objectives of this study were infusion-related toxicities (Part 1, n = 10, single arm) and PK bioequivalence between Bmab-100 and EU-Avastin (Part 2, n = 136, randomised 1:1).

Efficacy endpoints were included amongst the secondary objectives of Part 2, with results for Bmab-100 versus EU-Avastin as follows:

- objective response rate (ORR): 91% (n = 62) versus 88% (n = 60)
- progression free survival (PFS) rate at 18 weeks: 62% versus 60%
- disease control rate (DCR) at 18 weeks: 91% versus 88%

The results are not incompatible with similar efficacy for Bmab-100 and EU-Avastin.

Safety

Study MYL-14020-1002

Interpretation of the safety data from Study MYL-14020-1002 is limited due to the nature and design of the study (early phase; single dose; healthy volunteer population; small size).

The most frequently reported treatment emergent adverse events (TEAEs) across the three treatment groups were headache (20%), nasopharyngitis (12%), diarrhoea (8%) and back pain (8%). No serious adverse events (SAEs), TEAEs of Grade 3 or higher, or unexpected TEAEs were reported.

Study MYL-14020-3001

Exposure to carboplatin, paclitaxel and bevacizumab was similar between the MYL-14020 (Abevmy) arm and the EU-Avastin arm.

In general, the incidence of TEAEs was comparable between the two treatment arms. The most common TEAEs in both arms were alopecia, anaemia and thrombocytopenia.

¹⁴ The **Response Evaluation Criteria In Solid Tumours (RECIST)** is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

Differences of > 5% between the two treatment arms were observed in the following TEAEs, but are not considered likely to be significant:

- Alopecia (MYL-14020, 148 (44%) versus EU-Avastin, 168 (51%))
- Thrombocytopenia (MYL-14020, 108 (32%) versus EU-Avastin, 86 (26%))
- Asthenia (MYL-14020, 53 (16%) versus EU-Avastin, 33 (10%))
- Vomiting (MYL-14020, 56 (16.7%) versus EU-Avastin, 38 (11.6%))

Treatment emergent adverse events led to permanent discontinuation of treatment in 11% of the MYL-14020 arm and 9% of the EU-Avastin arm, and were fatal in 25 patients (7.5%) in the MYL-12040 arm and 14 patients (4.3%) in the EU-Avastin arm.

Fatal TEAEs that were considered treatment related by the investigator occurred in 8 (2.4%) patients in the MYL-14020 arm (pulmonary embolism (n = 2); pulmonary haemorrhage (n = 2); cardiorespiratory arrest; acute coronary syndrome; gastric perforation; cerebrovascular accident) and 5 (1.5%) patients in the EU-Avastin arm (sepsis (n = 2); febrile neutropenia; acute respiratory distress syndrome; pulmonary haemorrhage).

Adverse events of interest were nominated based on the known toxicity profile of bevacizumab, and were similar between arms as demonstrated by standardised Medical Dictionary for Regulatory Activities (MedDRA)¹⁵ Query (SMQ)¹⁶ grouping (Table 11).

¹⁵ The **Medical Dictionary for Regulatory Activities (MedDRA)** is a single standardised international medical terminology, developed as a project of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use. As a result, MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle (that is, from clinical trials to post-marketing surveillance). Furthermore, MedDRA supports ICH electronic communication within the ICH's Electronic Common Technical Document (eCTD) and the E2B Individual Case Safety Report.

¹⁶ **Standardised MedDRA Queries (SMQs)** are groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification.

Table 11: Study MYL-14020-3001 Adverse events of interest that occurred in at least 2 patients in either arm (safety set, data through Week 42)

Standard Medical Query (SMQ) Preferred Term	MYL-14020 (N=335) n (%)	Avastin (N=329) n (%)
Number of Patients with at Least One Event	71 (21.2)	81 (24.6)
Haemorrhage Terms (Excl Laboratory Terms) (SMQ)	17 (5.1)	33 (10.0)
Epistaxis	6 (1.8)	17 (5.2)
Haemoptysis	4 (1.2)	7 (2.1)
Pulmonary Haemorrhage	4 (1.2)	3 (0.9)
Haematuria	0	3 (0.9)
Hypertension (SMQ)	22 (6.6)	17 (5.2)
Hypertension	19 (5.7)	17 (5.2)
Essential Hypertension	2 (0.6)	0
Hypertensive Crisis	2 (0.6)	0
Proteinuria (SMQ)	11 (3.3)	17 (5.2)
Proteinuria	11 (3.3)	17 (5.2)
Embolic and Thrombotic Events, Venous (SMQ)	8 (2.4)	11 (3.3)
Pulmonary Embolism	5 (1.5)	6 (1.8)
Deep Vein Thrombosis	3 (0.9)	3 (0.9)
Venous Thrombosis	0	2 (0.6)
Hypersensitivity (SMQ)	9 (2.7)	6 (1.8)
Dermatitis Allergic	5 (1.5)	2 (0.6)
Drug Hypersensitivity	2 (0.6)	0
Osteonecrosis (SMQ)	3 (0.9)	6 (1.8)
Bone Pain	3 (0.9)	5 (1.5)
Cardiac Failure (SMQ)	5 (1.5)	2 (0.6)
Oedema Peripheral	3 (0.9)	1 (0.3)
Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous (SMQ)	6 (1.8)	1 (0.3)
Cerebrovascular Accident	2 (0.6)	1 (0.3)
Gastrointestinal Perforation (SMQ)	2 (0.6)	2 (0.6)
Peritonitis	0	2 (0.6)

MYL-14020 = product code for Abevmy formulation intended for marketing in Australia; N = population size; n = sample size; SMQ = standard medical query.

Study BM100-CC-03-1-01

Interpretation of the safety data from this study is limited by the small study size, short duration (18 weeks) and the use of a different formulation (Bmab-100) to the one intended for Australian marketing (MYL-14020).

The main objective of Part 1 (n = 10) was to assess infusion reactions with first dose of Bmab-100. No infusion related reactions occurred. The most frequent TEAE was palmar-planter erythrodysesthesia syndrome (6 events): a toxicity known to be associated with capecitabine treatment.¹⁷

In Part 2, the safety population comprised 68 patients treated with Bmab-100 and 67 patients treated with EU-Avastin. Bevacizumab exposure was similar between arms, and the observed safety profile was in keeping with the known toxicity profile of bevacizumab plus capecitabine in context of metastatic colorectal carcinoma.^{17,6} Palmar-

¹⁷ The Approved Australian Product Information for Xelocitabine (capecitabine). Available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-01416-1>.

planter erythrodysesthesia syndrome and diarrhoea were the most common TEAEs, in keeping with the co-administration of capecitabine.¹⁷

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.¹⁸

Risk-benefit analysis

Delegate's considerations

Assessment of the appropriateness of extrapolation to the other indications registered for the reference biological medicine is structured here around the summary of key principles outlined by Weise et al (2014).¹⁹ In biosimilar development, the objective of the data package is to show similarity between test and reference product, rather than to re-establish the safety and efficacy of the reference product for the approved indications.

Being a monoclonal antibody, bevacizumab has a single, specific target (VEGF) and well-studied mechanism of action (attenuation of activation of downstream signalling pathways). The target receptor and mechanism of action are the same across all indications that are approved for the reference biological medicine.

The route of administration is the same across all indications. Dosages vary across indications from 5 mg/kg of body weight given once every 2 weeks to 15 mg/kg given every 3 weeks, however, the high similarity between the pharmacokinetics of Abevmy and Avastin supports extrapolation of the supporting efficacy and safety comparability data for Abevmy to the doses used in all registered bevacizumab indications.

Avastin data shows low immunogenicity across indications, and the submitted trials provide adequate data to demonstrate that Abevmy has similar immunogenicity, in settings associated with both immunocompetency (with a single dose in healthy volunteers) and immunocompromise (metastatic NSCLC). This data can accordingly be extrapolated to the other clinical settings in which bevacizumab is registered (breast cancer, renal cell carcinoma, glioma, epithelial ovarian, fallopian tube or primary peritoneal cancer, and cervical cancer) settings.

The safety profile of Abevmy was not meaningfully different to Avastin in any of the submitted studies. The data from Study MYL-14020-3001 provide the strongest support for this conclusion, due to study design. The follow-up duration of 42 weeks is considered adequate. Extensive safety information has been previously generated for Avastin, and indicates that significant differences in attributable toxicities should not be expected between indications.

Extrapolation of data from the Abevmy biosimilarity studies to the other registered indications for Avastin is therefore reasonable.

Proposed action

The totality of evidence for the Abevmy product demonstrates it to be highly similar to the reference biological medicine, Avastin.

¹⁸ The sponsor must still comply with routine product vigilance and risk minimisation requirements.

¹⁹ Weise, M. et al. Biosimilars: the science of extrapolation, *Blood*, 2014; 124(22): 3191-3196.

Extensive physicochemical and biological analysis supports this conclusion. Data from toxicology studies and from three clinical studies provides adequate additional support to the analytical assessment of biosimilarity, and indicates Abevmy does not demonstrate clinically meaningful differences from, and is therapeutically equivalent to, the reference biological medicine Avastin.

The proposed indications are identical to those for the reference biological medicine. Although there were no studies conducted for the MYL-14020 formulation of Abevmy in clinical settings other than non-squamous NSCLC, extrapolation to all other indications currently approved in Australia for Avastin is supported.

Advisory Committee considerations²⁰

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Abevmy/Trucleva (bevacizumab) 100 mg/4 mL and 400 mg/16 mL, concentrate for solution for infusion, vial, indicated for:

Metastatic colorectal cancer

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

Locally recurrent or metastatic breast cancer

Abevmy (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 Pharmacodynamic properties, clinical trials).

Advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC)

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

Advanced and/or metastatic renal cell cancer

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

Grade IV glioma

Abevmy (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

²⁰ The ACM provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: <https://www.tga.gov.au/committee/advisory-committee-medicines-acm>.

Abevmy (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for firstline 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

Abevmy (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.

Abevmy (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

Abevmy (bevacizumab) in combination with paclitaxel and cisplatin is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix. Abevmy (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

- This approval does not impose any requirement for the submission of periodic safety update reports (PSURs). The sponsor should note that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.
- Laboratory testing and compliance with Certified Product Details (CPD)
 - All batches of Abevmy (bevacizumab) 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) (<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>), 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.

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Abevmy approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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