Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for Trastuzumab

Proprietary Product Name: Ogivri

Sponsor: Alphapharm Pty Ltd

**March 2020**

TGA Health Safety Regulation

# 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.

# Contents

# Common abbreviations

| Abbreviation | Meaning |
|---|---|
| ADA | Anti-drug antibody/antibodies |
| ADCC | Antibody-dependent cell-mediated cytotoxicity |
| AE | Adverse event |
| ARTG | Australian Register of Therapeutic Goods |
| AUC | Area under the curve or area under the serum concentration versus time curve |
| $AUC_{0-\infty}$ | Area under the curve or area under the serum concentration versus time curve from time 0 (dosing) extrapolated to infinity |
| $AUC_{0-last}$ | Area under the curve or area under the serum concentration versus time curve from time 0 (dosing) to last measured concentration |
| CHMP | Committee for Medicinal Products for Human Use (EU) |
| CI | Confidence interval |
| $C_{max}$ | Maximum observed serum concentration after IV infusion (just after end of infusion) |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency (EU) |
| ErbB-2 | Human epidermal growth factor receptor 2 (also known as HER2) |
| EU | European Union |
| FDA | Food and Drug Administration (US) |
| GMP | Good Manufacturing Practice |
| HER2 | Human epidermal growth factor receptor 2 |
| HFI | Hereditary fructose intolerance |
| ICH | International Conference on Harmonisation |
| IHC | Immunohistochemistry |
| IM | Intramuscular |
| ITT | Intention-to-treat |

| Abbreviation | Meaning |
|---|---|
| IV | Intravenous |
| LVEF | Left ventricular ejection fraction (via echocardiography) |
| MAA | Marketing Authorisation Application |
| mAbs | Monoclonal antibodies |
| ODAC | Oncologic Drugs Advisory Committee (US) |
| ORR | Objective response rate |
| OS | Overall survival |
| pCR | Pathological complete response |
| PD | Pharmacodynamic(s) |
| PE | Point estimate |
| PEG | Polymers of ethylene glycol |
| PFS | Progression free survival |
| PI | Product Information |
| PK | Pharmacokinetic(s) |
| popPK | Population pharmacokinetic(s) |
| PRAC | Pharmacovigilance Risk Assessment Committee (EU) |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RMP | Risk management plan |
| SAE | Serious adverse event |
| SmPC | Summary of Product Characteristics (EU) |
| TEAE | Treatment-emergent adverse event |
| TTP | Time to tumour progression |
| US(A) | United States (of America) |

# I. Introduction to product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | Biosimilar |
| *Decision*: | Approved |
| *Date of decision:* | 5 December 2018 |
| *Date of entry onto ARTG:* | 11 December 2018 |
| *ARTG numbers:* | 288222, 288223 |
| , *Black Triangle Scheme* | No |
| *Active ingredient:* | Trastuzumab |
| *Product name:* | Ogivri |
| *Sponsor's name and address:* | Alphapharm Pty Ltd<br>PO Box R1462<br>Royal Exchange<br>NSW 1225 |
| *Dose forms:* | Powder for injection 150 mg vial; and Powder for injection 440 mg vial with bacteriostatic water for injection vial |
| *Strength:* | 150 mg and 400 mg |
| *Container:* | Vial |
| *Pack size:* | 1 |
| *Approved therapeutic use:* | ***Early Breast Cancer***<br>*Ogivri is indicated for the treatment of HER2-positive early breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.*<br>***Locally Advanced Breast Cancer***<br>*Ogivri is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant OGIVRI.*<br>***Metastatic Breast Cancer***<br>*Ogivri is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:* |

*a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;*

*b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or*

*c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.*

***Advanced Gastric Cancer***

*Ogivri is indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.*

| | |
|---|---|
| *Routes of administration:* | Intravenous |
| *Dosage:* | The dosage is the same as for the innovator product Herceptin trastuzumab. |

## Product background

This AusPAR describes the application by Alphapharm Pty Ltd (the sponsor) to register Ogivri trastuzumab, 150 mg powder for injection vial, and, 440 mg powder for injection vial with bacteriostatic water for injection vial for the following indication:

*Early Breast Cancer*

*Ogivri is indicated for the treatment of HER2-positive early breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.*

*Locally Advanced Breast Cancer*

*Ogivri is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Ogivri.*

*Metastatic Breast Cancer*

*Ogivri is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:*

*a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;*

*b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or*

*c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.*

*Advanced Gastric Cancer*

*Ogivri is indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.*

The proposed product is a biosimilar product for the registered innovator product Herceptin trastuzumab. The proposed indications are as for the already registered product, Herceptin.

The rationale for the use of human epidermal growth factor receptor 2 (HER2)-directed therapy is well established in both HER2-positive breast cancer and HER2-positive gastric cancer.

The sponsor is seeking registration of a new vial size 440 mg, with potential to vary the diluent to allow repeat access and a longer storage time once reconstituted. Herceptin trastuzumab is available as 600 mg/ 5 mL vial for subcutaneous administration. The 150 mg size presentation is for single dose only.

The presentation also includes the introduction of sorbitol, a new excipient not in the reference product, Herceptin trastuzumab. Inclusion of sorbitol has introduced a new risk requiring a precaution warning against use in those with hereditary fructose intolerance (HFI).

No other biosimilar medicinal products for Herceptin trastuzumab have been registered in Australia, the United States of America (USA), European Union (EU) or Canada at the time of evaluation of this submission (30 October 2017).

### Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 11 December 2018.

At the time the TGA considered this application, a similar application was under consideration in the EU, 150 mg strength (centralised procedure; Submitted 26 July 2016); USA, 440 mg strength, (submitted 3 November 2016) and Canada 150 mg and 440 mg strengths (submitted 7 April 2017).

### 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 time line

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-2017-01084-1-4**

| Description | Date |
|---|---|
| Submission dossier accepted and first round evaluation commenced | 31 May 2017 |
| First round evaluation completed | 8 January 2018 |
| Sponsor provides responses on questions raised in first round evaluation | 5 February 2018 |

| Description | Date |
|---|---|
| Second round evaluation completed | 8 February 2018 |
| Delegate's Overall benefit-risk assessment | 18 September 2018 |
| Registration decision (Outcome) | 5 December 2018 |
| Completion of administrative activities and registration on the ARTG | 11 December 2018 |
| Number of working days from submission dossier acceptance to registration decision* | 217 |

*Statutory timeframe for standard applications is 255 working days

# III. Overall conclusion and risk/benefit assessment

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

## Introduction

### Documents used to prepare the Delegate's overview

- TGA biotechnology (Module 3), nonclinical (Module 4), and clinical (Module 5) evaluations.
- US Food and Drug Administration (FDA) briefing document to the Oncologic Drugs Advisory Committee (ODAC) dated 13 July2017, publicly available on the FDA web site.
- European Medicines Agency (EMA) Withdrawal Assessment Report, dated 18 May 2017, publicly available on the EMA web site.
- EMA Rapporteurs' Day 150 Joint Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) response assessment report, dated 28 August 2018.

### Regulatory status

#### *European Union*

- A Marketing Authorisation Application (MAA) for the 150 mg presentation was submitted to the EMA in July 2016.
- The evaluation was stopped (and the application withdrawn) in August 2017 following Good Manufacturing Practice (GMP) inspection of the Drug Product manufacturing site at Biocon Ltd (Bangalore, India). The EMA Withdrawal Assessment Report, dated 18 May 2017, is publicly available on the EMA website: http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2017/11/WC500239508.pdf

The following is from the Recommendations: The major objection precluding a recommendation of marketing authorisation, pertains to the following principal deficiencies: Quality: the lack of a valid GMP certificate for the Drug Product manufacturing site Biocon Ltd (India).

- The GMP follow-up inspection of the proposed drug product manufacturing site at Biocon Ltd (Bangalore, India) in March 2018 resulted in GMP compliance.
- On 10 Sep 2018, the sponsor provided the TGA with the Rapporteurs' Day 150 Joint CHMP and PRAC response assessment report, dated 28 August 2018, which recommended approval.
- The EMA decision is expected in the fourth quarter of 2018.

The reference biological medicine (Herceptin trastuzumab) is marketed in the EU as a 150 mg single-dose vial, only.

### *United States Food and Drug Administration*

- A dossier for the 440 mg presentation was submitted to the US FDA in November 2016.
- In July 2017, ODAC recommend approval.
- Ogivri was approved for marketing in the US in December 2017. All the indications approved for the reference biological medicine (Herceptin trastuzumab) were approved for Ogivri.

The FDA Briefing document to ODAC, dated 13 July 2017, is publicly available on the FDA web site.

### *Health Canada*

Health Canada received the application in April 2017 for both the 150 mg and 440 mg presentations.

### *Australia*

- The sponsor of Ogivri does not know whether EU-Herceptin or US-Herceptin is marketed in Australia.
- The pairwise-comparisons of Ogivri, US-Herceptin and EU-Herceptin (analytical, functional, and pharmacokinetic(s) (PK) established the scientific bridge among the three products. The clinical and non-clinical studies that used EU-Herceptin also established similarity to US-Herceptin and vice versa.

The reference biological medicine (Herceptin trastuzumab) is approved for marketing as 60 mg and 150 mg presentations in Australia.

The sponsor is proposing to market the 150 mg and 440 mg presentations of Ogivri.

## Regulatory framework

See, for example:

### *European Medicines Agency*

- Weise M, et al. Biosimilars: what clinicians should know. *Blood* 2012; 120: 5111-5117.
- Weise M, et al. Biosimilars: the science of extrapolation. *Blood* 2014; 214: 3191-3196.

### *United States Food and Drug Administration*

- Christl LA et al. Biosimilars: The US regulatory framework. *Ann Rev Med* 2017; 68: 243-254.

- Lemery SJ et al. FDA's approach to regulating biosimilars. *Clinical Cancer Res* 2017; 23: 1882-1885.

The typical development program for biosimilars is abbreviated (compared to a new active substance) and a stepwise approach is used:

- *In-vitro* (analytic) characterisation of the molecule:
  - physicochemical/structural; and
  - functional.
- Nonclinical (animal) studies.
- Clinical pharmacology; that is, bioequivalence (PK/ pharmacodynamic (PD))
- Supportive comparative clinical studies:
  - to check efficacy (especially if there is no PD endpoint);
  - to check safety; and
  - to assess immunogenicity.

If, based on the analytic characterisation of the molecule and the clinical pharmacology studies, there is no/little uncertainty about efficacy/safety, then a single-arm clinical study (duration of 12 months for example) might be sufficient to assess immunogenicity. For Ogivri, the sponsor conducted a comparative clinical study with contemporaneous controls.

- At each step, any residual uncertainty is identified and steps are taken to address that residual uncertainty.
- All the clinical studies for the reference biological medicine do not need to be repeated for the biosimilar. The aim is to establish similarity to the reference biological medicine, and then bridge to all the efficacy and safety studies that have already been done for the reference biological medicine. There is no need to independently establish the efficacy and safety of the biosimilar.
- The nature and extent of data required for regulatory approval are determined on a product-specific basis and depend on the level of evidence obtained in the preceding steps.
- Most of the evidence to support the marketing approval of a biosimilar comes from the *in-vitro* studies (analytic and functional). This is called the *'reverse pyramid'* approach; that is, it is the reverse of a new medicine, where most of the evidence to support marketing approval comes from the clinical development program; and, in particular, the Phase II and Phase III studies.
- There is no one pivotal study that establishes biosimilarity. The approach taken is *'totality of evidence'*, although, as above, most emphasis is put on the *in-vitro* characterisation.
- The comparative clinical study, if required, is the final step to reduce any remaining uncertainty.

The sponsor obtained endorsement for the development program for Ogivri from the FDA and EMA.

### Excipients

The formulation to be marketed in the EU, US, and Australia (and used in the clinical development program) has different excipients from EU-Herceptin and US-Herceptin.

Specifically, macrogol 3350 and sorbitol in Ogivri trastuzumab replace polysorbate 20 and trehalose dihydrate in Herceptin trastuzumab.

**Table 2: List of excipients in Herceptin trastuzumab and in Ogivri trastuzumab**

| | Ogivri 150 mg | Ogivri 440 mg | US-Herceptin 440 mg | EU-Herceptin 150 mg |
|---|---|---|---|---|
| Trehalose | -- | -- | 400 mg | 136.2 mg |
| Polysorbate 20 | -- | -- | 1.8 mg | 0.6 mg |
| Sorbitol | 115.2 mg | 337.9 mg | -- | -- |
| Macrogol 3350 | 33.6 mg | 98.6 mg | -- | -- |
| L-Histidine | 2.16 mg | 6.34 mg | 6.4 mg | 2.16 mg |
| L-Histidine HCl | 3.36 mg | 9.9 mg | 9.9 mg | 3.36 mg |

The sorbitol and macrogol comply with applicable European Pharmacopoeial standards and are used in other injectable dosage forms.

***Sorbitol***

The concern with sorbitol is HDI, which is rare; prevalence of about 1 in 15,000 to 1 in 30,000. It is an autosomal recessive inborn error of metabolism that results from a deficiency of fructose 1-phosphate aldolase in the liver, intestine and kidney.

Ingestion of fructose, sorbitol or sucrose causes abdominal pain, vomiting and symptomatic hypoglycaemia. It is typically diagnosed in the newborn at the time of weaning when food containing sucrose or fructose is given. Continued ingestion leads to poor feeding, growth retardation, and gradual liver and kidney failure. If large quantities of fructose are consumed, seizures and progressive coma can occur. Dietary exclusion results in normal growth and longevity.

The infusion of fructose or sorbitol containing solutions in patients with unsuspected disease can lead to potentially fatal hepato-renal failure. For example, more than 20 cases have been reported in Germany.

Sorbitol is used on many flavoured chewable tablets and oral suspensions, designed for paediatric use. It is also present in some parenteral medications (for example, filgrastim) and vaccines (such as certain influenza and meningococcal vaccines).

For parenteral medicines, hospital pharmacists would clear the use of the medicine on a case-by-case basis.

The following is from the sponsor of Ogivri:

> 'With the infusion of Ogivri the dose would be usually lower than 0.5 g since approved loading and maintenance dose of trastuzumab is not more than 8 mg/kg and 6 mg/kg, respectively. Taking into account this medicine is used in an adult metastatic breast cancer population with an average dose of sorbitol not usually larger than 0.5 g (approximately 50 times lower than reported in literature), and that most of the patients will be aware of their medical history of hereditary fructose intolerance by this age; chances of complication or any life-threatening consequences are quite small because the treating oncologist/physicians will be aware of the appropriate warning and precaution included in the product's label.'

***Macrogols***

Macrogols are polymers of ethylene glycol (PEG) that are widely used as osmotic laxatives (higher-weight variants) or as excipients in pharmaceutical products (lower-weight variants). Solid variants are used in cosmetics, ointments, and lubricants.

Some anti-neoplastic agents, which are given by intravenous (IV) infusion, contain macrogol; for example, various formulations of etoposide, docetaxel and temsirolimus.

Case-reports of therapy-related reactions, including anaphylaxis, have been linked to macrogol excipients; for example, intramuscular (IM) medroxyprogesterone, and bowel preparation for colonoscopy.

Monoclonal antibodies (mAbs) typically contain the excipient polysorbate, not macrogol. The function is mainly to prevent aggregation; important because aggregated proteins are immunogenic and can induce a patient's immune system to generate neutralising antibodies, reducing efficacy.

Infusion-related reactions and anaphylaxis have been reported for many mAbs. Of course, it can be difficult to determine which agent in the product is causing the reaction/ anaphylaxis: the excipient or the active agent.

Infusion reactions and anaphylaxis have been reported for a number of mAbs; rituximab, ofatumumab, obinutuzumab, trastuzumab, cetuximab, tocilizumab, infliximab, etanercept, adalimumab, abciximab, golimumab, certolizumab, brentuximab, bevacizumab, and omalizumab; all of which are formulated with polysorbate surfactants.

The UpToDate database lists trastuzumab, rituximab, and cetuximab as products that have been particularly associated with analphylaxis.[1]

***Polysorbates***

Polysorbates are also used in vaccines and small-molecules medicines and have also been linked to reactions and anaphylaxis for those products.

Most mAb formulations contain either polysorbate 20 (PS-20) or polysorbate 80 (PS-80). Polysorbate surfactants are one such family of excipients incorporated into many biotherapeutics to prevent protein aggregation and associated loss of efficacy.

In the Phase III comparative study (the HERITAGE trial) for Ogivri, the nature and severity of these infusion reactions were consistent with known trastuzumab and taxane infusion reactions.

Anaphylactic reaction events were reported in 2 patients in the Ogivri arm (none in the Herceptin arm). Both were reported as serious adverse events (SAEs) of Grade 3 intensity, and both resolved; 1 was considered related to Ogivri and resolved on the same day, the other event was unrelated to Ogivri but was considered related to concomitant medication (piperacillin/tazobactam).

## Quality

The biological medicines (quality) evaluator had no objections to approval.

Ogivri was compared to US-Herceptin and EU-Herceptin using a range of biochemical, biophysical, and functional assays, including assays that addressed each major potential mechanism of action. The analytical data submitted supported the conclusion that Ogivri is highly similar to US-Herceptin and EU-Herceptin. The amino acid sequences are identical. A comparison of the secondary and tertiary structures and the impurity profiles also support the conclusion that they are highly similar.

Critical functional assays, which reflect the primary mechanisms-of-action of trastuzumab (binding to human epidermal growth factor receptor 2 (HER2; also known as ErbB-2),

[1] LaCasce AS, et al. (2019) Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy. *UpToDate;* Available at: https://www.uptodate.com/contents/infusion-related-reactions-to-therapeutic-monoclonal-antibodies-used-for-cancer-therapy

inhibition of target cell proliferation, and antibody-dependent cellular cytotoxicity (ADCC) activity) also showed similarity.

## Nonclinical

The nonclinical evaluator had no objections to approval.

The submitted nonclinical studies were:

- a single dose comparative PK study in cynomolgus monkeys comparing the biosimilar to EU-Herceptin; and
- a 4-week, repeat-dose toxicity and toxicokinetic study in cynomolgus monkeys comparing the biosimilar to EU-Herceptin.

These studies did not identify any differences in the PK or toxicity profile of the proposed biosimilar compared to EU-Herceptin in cynomolgus monkeys.

## Clinical

Three clinical studies (2 clinical pharmacology studies and 1 comparative clinical study) were submitted to reduce residual uncertainties following the analytic studies (and nonclinical studies).

### Clinical pharmacology studies

- Study MYL-Her-1001 was a single centre, single dose, 2-period, randomised, double blind, crossover study in healthy male volunteers. The participants received either the Ogivri or EU-Herceptin in Period I and the reverse in Period II. The primary objective was to confirm bioequivalence between Ogivri and Herceptin administered at a dose of 8 mg/kg, administered as a single IV infusion over 90 minutes in healthy male volunteers
- Study MYL-Her-1002 was a single centre, single dose, randomised, double blind, 3-arm parallel-group study investigating the bioequivalence of Ogivri versus EU-Herceptin and US-Herceptin after 8 mg/kg as single dose administered as an IV infusion over 90 minutes in healthy male volunteers.

Healthy male volunteers were recruited to the studies because PK differences are more likely to be detected on this group.

### Comparative clinical study

- Study MYL-Her-3001 (also known as the HERITAGE trial) was a multicentre, double blind, randomised, parallel-group, pivotal confirmatory study to compare the efficacy and safety of Ogivri plus docetaxel or paclitaxel (that is, taxane) versus EU-Herceptin plus a taxane in patients with ErbB-2-positive metastatic breast cancer (MBC; documented by central laboratory results) with continuation (part 2 of the study) of single-agent Ogivri versus Herceptin for patients who had at least stable disease in order to evaluate continued safety and immunogenicity.

### Supportive studies

- The population pharmacokinetic (popPK) model showed good concordance between the Ogivri and Herceptin trastuzumab.

- Study BM200-CT3-001-11 (with the [information redacted]; Bmab-200) supported similarity to EU-Herceptin, based on PK parameters. It enrolled 135 women with metastatic breast cancer; dosed every 3weeks over 24 weeks (103 completed all 8 cycles). The 90% confidence interval (CI) for $C_{max}$ and AUC;[2] were within the acceptance interval of 80% to 125%. It was the main clinical study that supported the marketing approval of Bmab-200 in India in January 2014.

**Pharmacokinetics**

Tables 3 and 4 summarise the PKs results from the clinical pharmacology studies.

**Table 3: Study MYL-Her-1001 pharmacokinetic results**

| | Ogivri N=19 | EU-Herceptin N=19 | Ratio Point estimate (90% CI) |
|---|---|---|---|
| Cmax ug/mL | 165 | 178 | 92.2% (87.6%, 97.0%) |
| AUCinf ug.h/mL | 45486 | 48350 | 93.7% (88.7%, 98.9%) |
| Md(Tmax) range | 1.5 hrs (1.4, 9.0) | 1.5 hrs (1.3, 9.0) | |

**Table 4: Study MYL-Her-1002 pharmacokinetic results**

| | Ogivri N=42 | EU-Herceptin N=41 | Ratio Point estimate (90% CI) |
|---|---|---|---|
| Cmax ug/mL | 200.4 | 192.6 | 104.0% (99.0%, 109.8%) |
| AUCinf ug.h/mL | 48241 | 50075 | 97.0% (91.2%, 103.0%) |
| | | | |
| | | US-Herceptin N=37 | |
| Cmax ug/mL | 200.4 | 197.9 | 102.0 (96.4, 107.3) |
| AUCinf ug.h/mL | 48241 | 50181 | 96.0 (90.0, 101.9) |

EU-Herceptin versus US-Herceptin:

- $C_{max}$: 97.1 (92.2, 102.4)
- $AUC_{0-\infty}$:98.5 (92.4, 105.1).[3]

These studies establish the pairwise bioequivalence of Ogivri, US-Herceptin, EU-Herceptin: all the 90% CI are well within the acceptance interval of 80% to 125%.

The studies also checked the immunogenicity of Ogivri and Herceptin. There were no detectable anti-drug antibodies (ADAs), indicating no immunogenicity. This was expected given the known low immunogenicity of trastuzumab and the single doses in healthy volunteers.

**Pharmacodynamics**

- There are no established PD endpoints for trastuzumab.

[2] $C_{max}$ = Maximum observed serum concentration after IV infusion (just after end of infusion); AUC = Area under the curve or area under the serum concentration versus time curve over time periods
[3] $AUC_{0-\infty}$: Area under the serum concentration-time curve from time zero (dosing) extrapolated to infinity.

- In Study Myl-Her-1001, *ex vivo* serum samples and peripheral blood mononuclear cells were used for exploratory investigation.
- Because there is no validated PD marker (predictive of the efficacy for trastuzumab), the various PD endpoints that were investigated cannot be considered as definitive evidence in support of similarity. Nevertheless, the PD findings do not contradict the analytic, nonclinical and clinical data on similarity.

Note: Sections on the design, efficacy, and safety of the comparative clinical study (Study MYL-Her-3001/the HERITAGE trial) are long, but their length does not reflect the relative importance of this study in establishing biosimilarity. That is, the HERITAGE trial was the final step for a biosimilar that had already been shown to be highly similar to the reference biological medicine (Herceptin trastuzumab), based on analytic, functional, PK, and nonclinical (animal) studies.

### Design of the comparative Phase-III clinical study

Study MYL-Her-3001 (the HERITAGE trial)

The results of this study have been published.[4]

#### *Role of this study in establishing biosimilarity*

This study was designed to check efficacy and safety for Ogivri, which had already been shown to be structurally and functionally highly similar to a reference biological medicine (Herceptin). The earlier nonclinical (animal) studies were also supportive of similarity; and the clinical pharmacology studies established bioequivalence.

In other words, this comparative Phase III study was not the main/pivotal evidence in the claim of biosimilarity. It was the final step in development; a check of efficacy and safety; and an assessment of immunogenicity.

For example, the pre-specified primary endpoint objective response rate (ORR) was a short-term (24-week) surrogate endpoint. This would not typically be an acceptable endpoint in a confirmatory Phase III study of a new medicine for metastatic breast cancer.

#### *Metastatic versus neoadjuvant setting for the comparative clinical study*

The comparative Phase III study should be conducted in a homogeneous population and on a sensitive endpoint, so that the probability of identifying differences between the biosimilar and the reference biological medicine is maximised.

Some commentators have postulated that women with early breast cancer in the neoadjuvant setting are a more homogeneous group than women with metastatic breast cancer.[5]

A sensitive endpoint is one that can be reliably measured. In terms of sample size and statistical power, it is also helpful if it has an event rate of around 50% (maximises the statistical power to detect differences for a given sample size).

ORR has an event rate of 60% to 70% and so is arguably, as suitable for detecting differences between the biosimilar and the reference biological medicine as pathological complete response (pCR), which has an event rate of between 45% and 55%.

[4] Rugo HS et al. Effect of a proposed trastuzumab biosimilar compared with trastuzumab on overall response rate in patients with ERBB2 (HER2)-positive metastatic breast cancer: A Randomized Clinical Trial. *JAMA*. 2017; 317: 37-47

[5] Cortes J et al. Expert perspectives on biosimilar monoclonal antibodies in breast cancer. *Breast Cancer Res Treat* 2014; 144: 233-239

**Table 5: Comparison of objective response rate and pathological complete response for Herceptin biosimilars**

| Biosimilar | Sponsor | Setting | Endpoint | Clinicaltrials.gov |
|---|---|---|---|---|
| Ogivri | Biocon/Mylan/AlphaPharm | metastatic | ORR | NCT02472964 |
| CT-P6 | Celltrion | early | pCR | NCT02162667 |
| ABP 980 | Amgen/Allergen | early | pCR | NCT01901146 |
| SB3 | Samsung | early | pCR | NCT02149524 |
| PF-05280014 | Pfizer | early<br>metastatic | pCR<br>ORR | NCT02187744<br>NCT01989676 |
| BCD-022 | Biocad | metastatic | ORR | NCT01764022 |
| HLX02 | Shanghai Henlius | locally recurrent | ORR | NCT03084237 |

ORR = objective response rate; pCR = pathological complete response; NCT number refers to clinicaltrials.gov identifier. Table adapted from: Poplomata E et al. ABP 980: promising trastuzumab biosimilar for HER2-positive breast cancer. *Exp Op Biol Ther* 2018; 18: 335-341.

When asked about the metastatic setting, the sponsor replied:

- At the time the HERITAGE trial (NCT02472964);[6] was designed, neoadjuvant use of Herceptin, was considered off label in many of the countries, where the study was conducted.
- The choice of the metastatic setting was discussed and agreed on with the FDA and EMA as part of the global development program.

### *External validity*

The comparative clinical study was conducted in countries that have different health systems and different approaches to the treatment of early breast cancer than Australia. That is, the women with metastatic breast cancer, who were recruited to this study, might have had different prior treatment, in the early stages of their disease, compared to women in Australia. For example, only 10% of women had previous treatment (before identification of a metastasis) with trastuzumab.

In addition, for about 85% of women the taxane was docetaxel; not paclitaxel (the clinical evaluator has advised that paclitaxel is more commonly used in Australia).

Further, pertuzumab was not added to the regimen owing to the lack of worldwide availability of this antibody at the time of the study.

These differences in background treatment between the women in the Heritage study and women in Australia might arguably, be a deficiency in the evidence base for a new medicine; where such a Phase III study would provide the pivotal evidence for marketing approval.

However, for a biosimilar, which has already been shown to be highly similar in *in vitro* studies, the aim of the comparative clinical study (that is, the HERITAGE trial) was to identify differences and reduce any residual uncertainties.

### *Design*

Phase III study (Study MYL-Her-3001 (the HERITAGE trial); a randomised, double blind, parallel study.

[6] ClinicalTrials.gov Identifier NCT02472964, *Study of Efficacy and Safety of Myl1401O + Taxane vs Herceptin + Taxane for 1st Line, Met. Br. Ca. (HERiTAge);* National Library of Medicine (US), Bethesda (MD). 30 October 2018.

95 sites in Bulgaria, Chile, Czech Republic, Hungary, India, Latvia, Philippines, Poland, Romania, Russia, Serbia, Slovakia, South Africa, Thailand, and Ukraine.

Recruitment: December 2012, and August 2015. Last follow-up visit: January 2016.

### *Patients*

*Intention-to-treat (ITT)*

- Ogivri: n=230
- Herceptin: n=228

*Selected inclusion criteria*

- metastatic breast cancer
- no prior systemic treatment (that is, chemotherapy, trastuzumab) in the metastatic setting
- ErbB-2 positive (defined as central laboratory documentation of ErbB-2 positive overexpression by immunohistochemistry (IHC), that is, IHC3+, or IHC2+ with fluorescent in situ hybridization confirmation (ratio > 2))
- Eastern Cooperative Oncology Group (ECOG) Performance Status score: 0 or 1
- left ventricular ejection fraction (LVEF) within institutional range of normal
- at least 1 year since adjuvant therapy with trastuzumab
- any patients with central nervous system metastases had to be stable following treatment: (for example, radiotherapy, stereotactic radiosurgery)
- hormonal agents had to be discontinued before beginning study therapy.

*Selected exclusion criteria*

- abnormal LVEF
- unstable angina, heart failure, myocardial infarction within the last 12 months, other significant cardiac disease
- Grade 2+ peripheral neuropathy
- other significant medical illness.

### *Intervention*

Eight cycles (24 weeks) unless the participant experienced unacceptable adverse effects, had disease progression, or requested withdrawal from the study:

- An initial 8 mg/kg loading dose of Ogivri was administered over 90 minutes, followed by dosing every 3 weeks of 6mg/kg over 30 minutes.

Clinician's choice of taxane (paclitaxel, docetaxel):

- After 8 cycles (24 weeks), for patients who had at least stable disease, continuation of Ogivri every 3 weeks (to evaluate safety and immunogenicity) until disease progression, unacceptable adverse events (AEs). The taxane could be continued at the clinician's discretion.

### *Comparator*

EU-Herceptin; regimen as above.

### *Endpoint*

*Primary, 24 weeks*

- ORR (complete or partial response) by RECIST criteria (blinded reviewers).[7]

*Secondary, 48 weeks, exploratory: not adjusted for multiplicity*

- Time to tumour progression (TTP)
- Progression free survival (PFS)
- Overall survival (OS)

*Other end points, 24 and 48 weeks*

- adverse events,
- laboratory assessments,
- LVEF,
- immunogenicity
- pharmacokinetic end points: AUC, $C_{max}$, $C_{min}$.

*Stratification*

Patients were stratified at randomisation based on 3 factors:

- time from primary diagnosis to metastases (< 2 years, 2+ years)
- oestrogen receptor (ER)/progesterone receptor (PR) status (both negative, at least one positive)
- type of taxane (paclitaxel, docetaxel).

*Assessment*

Tumour assessments were conducted every 6 weeks. Computed tomography or magnetic resonance imaging of the chest and upper abdomen and, if clinically indicated, bone and/or brain imaging were performed to quantify disease burden.

A protocol amendment changed eligibility criteria after 42 patients were enrolled to exclude patients who had already received first-line therapy based on steering committee recommendations to include a homogeneous patient population.

These patients were excluded from the primary ITT analysis population.

### *Boundaries for equivalence for the primary endpoint of ORR*

FDA: 2-sided 90% CI for ratio of ORRs (equivalent to 2 one-sided 95% CIs); acceptance interval: 0.81 to 1.24.

EMA: 2-sided 95% CI for the difference of ORRs; acceptance interval: -15% to +15%.

The equivalence margins for ORR were derived based on meta-analysis from previous randomised trials that related ORR to PFS. The boundaries of the equivalence margins for ORR corresponded to a PFS of ± 1.9 months from a median PFS of 12 months.

### *Sample size*

Assumed ORR=64% for both Ogivri and Herceptin at 24 weeks.

410 patients required to confirm equivalence on ORR at 24 weeks, using either the FDA or EMA acceptance intervals, with 80% power.

[7] RECIST = Response Evaluation Criteria in Solid Tumours.

### *Baseline characteristics*

**Table 6: Study MYL-Her-3001 (HERITAGE trial) baseline characteristics**

| | Ogivri + taxane N=230 | Herceptin + taxane N=228 |
|---|---|---|
| Age, Md (range) | 55 (26, 79) | 54 (26, 82) |
| <50 years | 74 (32%) | 86 (38%) |
| 50+ years | 156 (68%) | 142 (62%) |
| Race | | |
| Asian | 70 (30%) | 72(32%) |
| Caucasian | 159 (69%) | 154(68%) |
| Previous treatment | | |
| Trastuzumab | 22(10%) | 16(7%) |
| Taxane | 46(20%) | 42(18%) |
| Taxane used with Ogivri/Herceptin | | |
| Docetaxel | 193(84%) | 192(84%) |
| Paclitaxel | 35(15%) | 32(14%) |
| Hormone receptor status | | |
| ER/PR negative | 128(56%) | 127(56%) |
| ER/PR: one or both positive | 102(44%) | 101(44%) |
| ECOG | | |
| 0 | 127(51%) | 107(44%) |
| 1 | 115(47%) | 132(54%) |
| LVEF%; Md (range) | 64(51, 82) | 63(51,84) |
| Time from 1st dx to mets | | |
| <2 years | 146(64%) | 153(67%) |
| 2+ years | 75(33%) | 71(31%) |
| No. metastatic sites | | |
| 1 | 58(25%) | 16(27%) |
| 2 | 87(38%) | 67(29%) |
| 3 | 44(19%) | 57(25%) |
| 4+ | 41(18%) | 43(19%) |
| Visceral mets | 172(75%) | 185(81%) |
| CNS as 1st met | 1(0.4%) | 2(0.9%) |

Md = median; ER = oestrogen receptor; PR = progesterone receptor; ECOG = Eastern Cooperative Oncology Group (Performance Status score); dx = diagnosis; mets = metastases; CNS = central nervous system

### *Efficacy results*

*Primary endpoint: objective response rate*

**Table 7: Study MYL-Her-3001 (HERITAGE trial) response rates**

| | Ogivri + taxane N=230 | Herceptin + taxane N=228 |
|---|---|---|
| Complete response | 3(1.3%) | -- |
| Partial response | 157(68.3%) | 146(64.0%) |
| Stable disease | 48(20.9%) | 49(21.5%) |
| Progressive disease | 5(3.9%) | 20(8.8%) |
| Not evaluable | 13(5.7%) | 13(5.7%) |

ORR = (complete response) + (partial response)

Ogivri versus Herceptin: 69.6% versus 64.0%

EMA recommended analysis: difference = 5.5%, 95% CI (-3.1%, 14.0%)

FDA recommended analysis: ratio = 1.09, 90% CI (0.97, 1.21)

The pre-specified EMA and FDA criteria for equivalence for the primary efficacy endpoint of ORR were met.

*Secondary endpoints: progression free survival, overall survival at Week 48*

**Table 8: Study MYL-Her-3001 (HERITAGE trial) secondary endpoints at Week 48**

| | Ogivri + taxane N=230 | Herceptin + taxane N=228 |
|---|---|---|
| PFS; events<br>Md(PFS) | 102(44.3%)<br>11.1 months | 102(44.7%)<br>11.1 months |
| HR(PFS) | 0.97 (0.74, 1.28) | |
| OS; events<br>Md(OS) | 25(10.9%)<br>Not estimable | 34(14.9%)<br>Not estimable |
| HR(OS) | 0.67 (0.40, 1.13) | |

Results for secondary efficacy endpoints were consistent with the results for ORR.

**Safety results**

***Patient disposition***

**Table 9: Study MYL-Her-3001 (HERITAGE trial) patient disposition (Part 1; up to Week 24: trastuzumab + taxane)**

| | Ogivri + taxane N=249 | Herceptin + taxane N=251 |
|---|---|---|
| Completed 24 weeks of treatment | 185(74%) | 171(68%) |
| Discontinued | | |
| Disease progression | 47(19%) | 58(23%) |
| Death | 6(2.4%) | 3(1.2%) |
| AE | 4(1.6%) | 2(0.8%) |
| Withdrew consent, etc | 5(2.0%) | 12(4.8%) |

**Table 10: Study MYL-Her-3001 (HERITAGE trial) patient disposition (Part-2; Week 25 to Week 48)**

| | | |
|---|---|---|
| Entered Part-2 | 179 (100%) | 163 (100%) |
| Continued taxane in Part-2 | 63(35%) | 65(40%) |
| Discontinued | | |
| Disease progression | 56(31%) | 52(32%) |
| Death | 1(0.6%) | 0 |
| AE | 2(1.1%) | 4(2.5%) |
| Withdrew consent, etc | 4(2.4%) | 9(5.4%) |

**Table 11: Study MYL-Her-3001 (HERITAGE trial) treatment emergent adverse events (to 48 weeks; Parts 1 and 2)**

| Patients with: | Ogivri N=247 | Herceptin N=246 |
|---|---|---|
| TEAEs | 242(98%) | 239(97%) |
| Grade 3+ TEAEs | 165(66%) | 162(66%) |
| Serious TEAEs | 97(38%) | 91(37%) |
| Treatment-related TEAEs | 103(42%) | 88(36%) |
| TEAEs leading to discontinuation of tras | 16(7%) | 16(7%) |

Treatment-emergent adverse event (TEAEs) were similar across both arms of the study, except perhaps for those deemed by the study investigators to be treatment-related TEAEs (42% versus 36%) For Part 2 (mainly monotherapy), the incidence of treatment-related TEAEs was similar for Ogivri and Herceptin (28 patients; 15.6% versus 25 patients; 15.3% ), suggesting that the differences seen between arms through 48 weeks were due to Part 1 of the study (up to 24 weeks) and possibly attributable to concomitant taxane therapy (more women in the Ogivri arm received paclitaxel).

Types of TEAEs were similar across the two arms. The most frequently reported TEAEs were alopecia (56.4%), followed by neutropaenia (56.0%), and diarrhoea (20.9%). These mainly occurred during Part 1 of the study.

*Serious adverse events*

The frequency of serious TEAEs (SAEs) was similar for Ogivri and Herceptin: 38% versus 37%.

The most frequently reported SAEs were:

- Neutropaenia with 68 patients (27.5%) in the Ogivri arm and 62 patients (25.2%) in the Herceptin arm; nearly all were Grade 4.
- Febrile neutropaenia: 11 patients (4.5%) in the Ogivri arm and 10 patients (4.1%) in the Herceptin arm.
- Leukopaenia: 5 patients (2.0%) in the Ogivri arm and 12 patients (4.9%) in the Herceptin arm.
- Pneumonia: 6 patients (2.4%) in the Ogivri arm and 5 patients (2.0%) in the Herceptin arm.

The vast majority of SAEs occurred in Part 1 of the study while patients were receiving combination therapy.

In Part 2, there were no SAEs for neutropaenia.

The majority of SAEs were considered unrelated to study drug.

*Deaths*

- For Parts 1 and 2, through Week 48, 10 patients had fatal TEAEs, 6 in the Ogivri arm (2.4%) and 4 in the Herceptin arm (1.6%).
- For the Part 2 (mainly monotherapy), 2 patients in the Ogivri arm had a fatal TEAE (none in the Herceptin arm); however, neither was considered related to study drug by the investigator.
- Most of the remaining fatal events (Part 1: 4 deaths in each arm) were considered related to taxane, concomitant medication, or underlying or progressive disease.
- Only 1 event of respiratory failure in each arm was considered as possibly related to trastuzumab.

*Adverse events of special interest*

AEs of special interest for trastuzumab include cardiac toxicity, infusion reactions, and pulmonary toxicity.

**Table 12: Study MYL-Her-3001 (HERITAGE trial) adverse events of special interest**

| | Ogivri, n=247 | | | Herceptin, n=246 | | |
|---|---|---|---|---|---|---|
| | Total | Resolved | Grade 3+ | Total | Resolved | Grade 3+ |
| Cardiac failure | 6(2.4%) | 3(1.2%) | 3 | 2(0.8%) | 2(0.8%) | -- |
| Cardiomyopathy | 1(0.4%) | 1(0.4%) | -- | 1(0.4%) | -- | -- |
| Cardiotoxicity | 2(0.8%) | 2(0.8%) | -- | -- | -- | -- |
| Carditis | 1(0.4%) | -- | 1 | -- | -- | -- |
| Congestive cardiomyopathy | -- | -- | -- | 1(0.4%) | 1(0.4%) | -- |
| Left ventricular dysfunction | 2(0.8%) | 2(0.8%) | 2 | 4(1.6%) | 3(1.2%) | 1 |
| Left ventricular failure | -- | -- | -- | 1(0.4%) | -- | -- |
| Metabolic cardiomyopathy | 1(0.4%) | -- | -- | 3(1.2%) | 1(0.4%) | -- |
| Ejection fraction decreased | 16(6.5%) | 12(4.9%) | 1 | 8(3.3%) | 5(2.0%) | 1 |
| Myocardial fibrosis | 1(0.4%) | -- | -- | -- | -- | -- |

**Table 13: Study MYL-Her-3001 (HERITAGE trial) infusion reactions and pulmonary toxicities of special interest**

| | Ogivri, n=247 | Herceptin, n=246 |
|---|---|---|
| Anaphylactic reactions | 2(0.8%) | -- |
| Drug hypersensitivity | 1(0.4%) | 1(0.4%) |
| Hypersensitivity | 5(2.0%) | 7(2.8%) |
| Infusion related reaction | 17(6.9%) | 12(4.9%) |
| Pneumonitis | 4(1.6%) | 2(0.8%) |
| Pulmonary fibrosis | 1(0.4%) | -- |

*Infusion reactions, allergic-type reactions and hypersensitivity*

The nature and severity of these reactions were consistent with known trastuzumab and taxane infusion reactions.

Anaphylactic reaction events were reported in 2 patients in the Ogivri arm (none in the Herceptin arm). Both were reported as SAEs of Grade 3 intensity, and both resolved; 1 was considered related to Ogivri and resolved on the same day, the other event was unrelated to Ogivri but was considered related to concomitant medication (piperacillin/tazobactam).

*Cardiac toxicity*

Patients with abnormal LVEF or other important cardiac problems were exclusions from the HERITAGE trial.

Over 48 weeks, the incidence of significant TEAEs of cardiac toxicity (including cardiac failure, cardiotoxicity, left ventricular dysfunction, and metabolic cardiomyopathy) was low and similar in each arm: Ogivri: 12 patients (4.9%), Herceptin: 10 patients (4.1%).

Cardiac dysfunction in an important identified risk in the risk management plan (RMP) and PI for Herceptin, and medical oncologists are well versed in managing this risk. The same will apply to Ogivri.

*Left ventricular ejection fraction*

Mean, median, minimum and maximum LVEF values did not change appreciably from Baseline to week-48 for either treatment group, and were similar between treatment groups. Few patients, 10 (4.0%) in Ogivri group and 8 (3.3%) patients in the Herceptin group, had LVEF fall below 50% during the study. Most of these patients had previously received anthracyclines, had a previous or concomitant cardiovascular disorder, previous thoracic radiation, diabetes mellitus, or high levels of blood pressure.

### *Immunogenicity*

Immune responses against biological medicines can influence the safety, efficacy, and pharmacokinetics.

The immunogenicity of Ogivri and Herceptin was assessed during 48 weeks by measuring the ADA levels in blood samples. The results showed that there was no clinically meaningful difference between the immunogenicity of Ogivri and Herceptin; and the incidence and levels of ADAs were similar to that previously reported for Herceptin (that is, trastuzumab has low immunogenic potential).

## Approval of the various indications

Herceptin is registered for:

- Neoadjuvant treatment of locally advanced breast cancer
- Adjuvant treatment of early breast cancer
- Treatment of metastatic breast cancer
- Treatment of advanced gastric cancer.

Guidelines from the EMA and FDA allow for the possibility that a biosimilar could be approved for one or more of the indications for the reference biological medicine, given sufficient scientific justification, using a '*totality-of-evidence*' approach. The guidelines discuss:

- mechanism of action;
- PK and distribution;
- dose, route-of-administration;
- immunogenicity; and
- toxicity.

For Ogivri:

- The mechanism of action of trastuzumab is the same in all the indications (that is, to inhibit the proliferation of human tumour cells that overexpress HER2). The target receptor involved in the mechanism of action in (that is, HER2) is the same across all indications. Trastuzumab is indicated only if HER2 positivity is demonstrated.
- Studies on the reference biological medicine (Herceptin) show that the PK is the same for all indications.
- The dosage is the same for all the indications and it is administered by the same route (IV) in all indications.

- Data for the reference biological medicine (Herceptin) show that trastuzumab has low immunogenicity across all indications.
- The available safety information for the reference biological medicine does not indicate that there are any significant differences in expected toxicities for each condition of use and patient population.

Note: Purposefully, the term 'extrapolation' has not been used. The common usage of the term extrapolation is in mathematics, where it refers to forecasting unknown values, beyond the available data. This is in contrast to interpolation, which refers to 'filling-in' values that fall between known values (that is, within the available data).

The following is from Krendyukov A et al.[8]:

> 'When applied to biosimilar medicines, extrapolation is based on the knowledge (from the thorough analytical comparability exercise) that the biosimilar medicine matches the reference medicine in all critical quality attributes. Health Canada recently acknowledged this problem with terminology and consequently deleted the term 'extrapolation' in the last update of their biosimilar guideline in 2016. They instead describe what is meant exactly, namely the authorisation of indications for the biosimilar.'

## Risk management plan

### Summary of RMP evaluation[9]

- The sponsor has applied to register trastuzumab (Ogivri) which is a biosimilar of Herceptin. The sponsor is seeking the same indications as the innovator, which are for the treatment of human epidermal growth factor receptor 2 protein (HER2) positive breast and gastric cancers.
- The sponsor has submitted EU-RMP version 3 (31 March 2017; data lock point 7 March 2017) and Australian specific Annex (ASA) version 1.0 in support of this application.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 14.

[8] Krendyukov A et al. 2018 Extrapolation concept at work with biosimilar: a decade of experience in oncology. *ESMO Open* 2018;3:e000319

[9] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
*Routine pharmacovigilance* practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

**Table 14: Summary of safety concerns**

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|---|---|---|---|---|---|
| | | Routine | Additional | Routine | Additional |
| **Important identified risks** | Cardiac dysfunction | ü | – | ü | - |
| | Administration-Related Reactions | ü | - | ü | – |
| | Haematological Toxicity | ü | - | ü | - |
| | Oligohydramnios | ü | - | ü | - |
| | Pulmonary Disorders | ü | – | ü | - |
| **Important potential risks** | Infections | ü | – | ü | – |
| **Missing information** | Use in male breast cancer patients | ü | – | ü | – |

*Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

*Routine pharmacovigilance* practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

## Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Ogivri EU-Risk Management Plan (RMP) (version 3.0, dated 31 March 2017, data lock point date 07-Mar-2017), with Australian Specific Annex (version 1.1, dated December 2017), included with submission PM-2017-01087-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the PSUR requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).*
>
> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar*

*months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.*

*The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*

## Risk-benefit analysis

### Delegate's considerations

This application is for a biosimilar. The reference biological medicine, Herceptin trastuzumab, was initially registered in the US in 1998 and in Australia in 2000.

The proposed indications are the same as those for the reference biological medicine: early breast cancer, locally advanced breast cancer, metastatic breast cancer, advanced gastric cancer.

The proposed dosage is the same as that for the reference biological medicine.

The sponsor is not proposing to market a subcutaneous formulation.

#### *Evaluation of similarity*

Based on the pivotal *in-vitro* studies and supported by the nonclinical and clinical studies, Ogivri is highly similar to Herceptin.

Marketing approval of all indications is justified.

#### *Differences*

The excipient sorbitol has replaced trehalose. Sorbitol can cause problems if the patient has HFI, which is a rare metabolic disorder (prevalence: 1 in 20,000). Patients receiving Ogivri will be adults, who will know they have HFI. There are other parenteral medicines that also contain sorbitol, although Herceptin (obviously) does not. Hospital pharmacists would clear the use of a parenteral medicine, containing sorbitol, on a case-by-case basis.

The EMA Summary of Product Characteristics (SmPC) has the following:

- Under Section 2. Qualitative and Quantitative Composition

  Excipient with known effect:

  Each vial contains 115.2 mg sorbitol

- Section 4.4 Special Precautions and warnings for use

  Sorbitol: Ogivri contains 115.2 mg sorbitol in each vial. Patients with rare hereditary problems of fructose intolerance must not be given this medicine unless strictly necessary.

- Section 6.1 List of excipients

  L-histidine hydrochloride

  L-histidine

Sorbitol

Macrogol 3350

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

The only reference to sorbitol in the approved FDA PI is in Section 11 'Description', where it is listed as one of the excipients:

- The excipient macrogol replaces polysorbate. Macrogol can cause infusion reactions, but the most likely cause of any infusion reaction would be the active ingredient (trastuzumab). The macrogol excipient is unlikely to lead to any more infusion reactions than polysorbate excipient in the reference biological medicine (Herceptin).
- The sponsor proposes to market Ogivri as 150 mg and 440 mg vials (Herceptin is only marketed in Australia in 60 mg and 150 mg vials). A multidose 440 mg vial of Herceptin has been marketed in the US for many years; and has not caused any problems.

### Proposed action

The Delegate had no reason to say, at this time, that the application for Ogivri should not be approved for registration.

### Advisory Committee considerations[10]

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

## Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Ogivri trastuzumab 150 mg powder for injection vial; and 440 mg powder for injection vial with bacteriostatic water for injection, indicated for:

*Early Breast Cancer*

*Ogivri is indicated for the treatment of HER2-positive early breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.*

*Locally Advanced Breast Cancer*

*Ogivri is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant OGIVRI.*

*Metastatic Breast Cancer*

[10] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (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.
The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

*Ogivri is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:*

*a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;*

*b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or*

*c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.*

*Advanced Gastric Cancer*

*Ogivri is indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.*

**Specific conditions of registration applying to these goods**

- Once approved by the EMA, You [the sponsor] must update the Australian PI in accordance with the approved SmPC as a minor variation application. You [the sponsor] must also supply a copy of the approved EU SmPC as evidence to support this minor variation application.

- The OGIVRI EU-Risk Management Plan (RMP) (version 3.0, dated 31-Mar-2017, data lock point date 07-Mar-2017), with Australian Specific Annex (version 1.1, dated December 2017), included with submission PM-2017-01087-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

- Batch release testing & compliance with Certified Product Details (CPD)

  i. It is a condition of registration that all batches of OGIVRI (trastuzumab) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  ii. It is a condition of registration that each batch of OGIVRI (trastuzumab) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.

- If any reports emerge globally of OGIVRI administered to patients with HFI you [the sponsor] must notify the TGA within 72 hours of receiving the notification and perform a root cause analysis as to why this occurred.

# Attachment 1. Product Information

The PI for Ogivri 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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