



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Trastuzumab

Proprietary Product Name: Herceptin

Sponsor: Roche Products Pty Ltd

August 2015

TGA Health Safety
Regulation

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- 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, in that it will provide 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 the most common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Transaminase
ARR	Administration-related reaction
AST	Aspartate Transaminase
AUC	Area under the curve
CL	Clearance
C _{max}	Maximum concentration
CR	Complete Response
C _{trough}	Trough concentration [the concentration at the end of the dosage interval]
DFS	Disease-free survival
ECG	Electrocardiograph
EFS	Event-free survival
EPP	Efficacy Per-Protocol population
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HER2	human epidermal growth factor receptor 2
ICH	International Conference on Harmonisation
ITT	Intention to Treat
IV	Intravenous
LDH	Lactate Dehydrogenase
ORR	Overall Response rate
OS	Overall Survival
pCR	Pathological Complete Response
PI	Product Information
PK	Pharmacokinetics
RECIST	Response evaluation criteria in solid tumours
rHuPH20	recombinant human hyaluronidase
SAE	Serious Adverse Event
SC	Subcutaneous
T _{max}	Time of maximum concentration
tpCR	Total Pathological Complete Response
TTR	Time to Response

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New route of administration, new strength, change in dosage, new dose form
<i>Decision:</i>	Approved
<i>Date of decision:</i>	13 March 2015
<i>Active ingredient:</i>	Trastuzumab
<i>Product name:</i>	Herceptin
<i>Sponsor's name and address:</i>	Roche Products Pty Ltd PO Box 255, Dee Why NSW 2099
<i>Dose form:</i>	Solution for Injection
<i>Strength:</i>	120mg/ml
<i>Container:</i>	Colourless 6 mL glass vial
<i>Pack size:</i>	1 vial
<i>Approved therapeutic use:</i>	<p><i>Early Breast Cancer: Herceptin SC is indicated for the treatment of HER2-positive localised breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.</i></p> <p><i>Locally Advanced Breast Cancer: Herceptin SC is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin.</i></p> <p><i>Metastatic Breast Cancer: Herceptin SC is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:</i></p> <ul style="list-style-type: none"> - <i>as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;</i> - <i>in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease;</i> <i>or</i> - <i>in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.</i>
<i>Route of administration:</i>	Subcutaneous (SC) injection
<i>Dosage:</i>	HER2 testing is mandatory prior to initiation of Herceptin SC therapy. The recommended fixed dose of Herceptin SC is 600 mg, irrespective of the patient's body weight, administered every three weeks.
<i>ARTG number:</i>	220402

Product background

Herceptin (trastuzumab) is a recombinant deoxyribonucleic acid (DNA) derived humanised monoclonal antibody (immunoglobulin G1kappa (IgG1 kappa)) that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 (HER2). It is able to inhibit the in vitro proliferation of a human breast tumour-derived cell line that overexpresses the HER2 gene.

The HER2 (or c-erbB2) proto-oncogene encodes for a single transmembrane spanning, receptor-like protein of 185 kDa which is structurally related to the epidermal growth factor receptor. Overexpression of HER2 is observed in 25% to 30% of primary breast and 6.8% to 42.6% of advanced gastric cancers. A consequence of HER2 gene amplification is an increase in HER2 protein expression on the surface of these tumour cells, which results in a constitutively activated HER2 receptor. Studies indicate that patients whose tumours have amplification or overexpress HER2 have a particularly aggressive form of tumour and a shortened disease-free survival compared to patients whose tumours do not have amplification or overexpress HER2.

Trastuzumab has been shown, both in in vitro assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. In vitro, trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2. In animal models in vivo, murine anti-HER2 antibody inhibited the growth of human tumours overexpressing HER2, indicating that trastuzumab is likely also to have anti-proliferative activity in vivo against human breast tumours expressing high levels of HER2.

This AusPAR describes the application Roche Products Pty Ltd to register a new route, new dosage regimen and new formulation of the monoclonal antibody Herceptin® (trastuzumab [rch]). No new indications are proposed; the sponsor is proposing that this new formulation only be used for the treatment of human epidermal growth factor receptor 2 protein (HER 2) positive breast cancer as follows:

Early Breast Cancer: *Treatment of HER2-positive localised breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.*

Locally Advanced Breast Cancer: *Treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin.*

Metastatic Breast Cancer: *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.*

This application does not seek registration for use in gastric cancer.

The new route of administration is via subcutaneous (SC) injection delivered over 2 to 5 minutes at a dose of 600 mg, regardless of body weight. The currently approved route for Herceptin is by intravenous (IV) injection.¹

¹ The following dosage forms and strengths are currently registered for IV use (1) A vial containing 150 mg trastuzumab powder for injection (Aust R 73229); and (2) A 60 mg trastuzumab powder for injection (Aust R 171014).

The rationale for this application is convenience in terms of speed of administration (2 to 5 minutes for SC versus 90 mins for first infusion and 30 minutes for subsequent IV infusions) and SC rather than IV cannulation. The PrefHER study² reported that the majority of women preferred the SC over the IV formulation. The proposed new formulation is a fixed dose (600 mg, 3 weekly) with no loading dose proposed versus 8 mg/kg IV trastuzumab loading thereafter 3 weekly 6 mg/kg until 12 months of treatment completed. The latter is not the TGA registered dose but is widely used in clinical practice.

In their application, the sponsor has also proposed to update the Product Information (PI) with new data from the HERA study, a pivotal study that formed the basis of the TGA's previous approval of trastuzumab for the adjuvant treatment of early HER2 positive breast cancer.

The new SC formulation of Herceptin® contains recombinant human hyaluronidase. The name 'hyaluronidase' is only a temporary measure until the approval of a proper Non-proprietary Name (INN) for this excipient.³

Regulatory status

The product received initial approval from the TGA in November of 2000.

At the time of lodgement of this new application in Australia (February 2014), similar applications had been lodged in the European Union (March 2012), Switzerland (April 2012), Canada and New Zealand (both September 2012). No application was planned for the USA.

- The application in Europe was approved in August 2013.
- The application in Canada was withdrawn in July 2013. The stated reason was that the indication for enrolment in the pivotal study (neoadjuvant/adjuvant treatment) was not an approved indication in Canada.
- The application in Switzerland was withdrawn (August 2013) *'because the company could not address queries from Swissmedic within the deadline'*. In response to the TGA evaluator's question the sponsor stated the following: *'For the submission in Switzerland, the sponsor decided that the requests from Swissmedic, which included introduction of an applicator and provision of additional data relating to adjuvant breast cancer administration, could not be provided within the required regulatory timelines; the sponsor's withdrawal from Canada and Switzerland were not related to safety concerns.'* NB: Application was re-submitted on June 30th 2015.
- The application in New Zealand was still under evaluation.
- No application has been lodged with the FDA.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

² Pivot X, Gligorov J et al. , Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHER): an open-label randomised study. *Lancet Oncol.* 2013 Sep;14(10):962-70

³ An INN and subsequently an ABN has subsequently been approved as *vorhyaluronidase alfa*.

II. Quality findings

Drug substance (active ingredient)

Trastuzumab is composed of 1,328 amino acids and has a molecular weight of approximately 148 kDa and its structure and biochemistry have been described previously.

The drug substance is identical to that used for the currently registered products:

- Herceptin (trastuzumab rch) 60mg powder for intravenous injection vial (AUST R 171014).
- Herceptin (trastuzumab rch) 150mg powder for intravenous injection vial (AUST R 73229).

The drug substance is manufactured by Chinese Hamster Ovary (CHO) cells into which the DNA coding for the humanised immunoglobulin light and heavy chains has been inserted. The drug substance manufacture consists of cell culture fermentation and purification. The master cell bank and the working cell bank remain the same when comparing the production process of trastuzumab SC used to manufacture Herceptin SC and the approved process of trastuzumab used to manufacture for Herceptin IV.

The production process of is identical to the approved process of trastuzumab used to manufacture for Herceptin IV administration except that an extra harvest criterion has been introduced in the fermentation process.

Cell banking processes are satisfactory. All viral/prion safety issues have been addressed previously, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

The physical, chemical and biological properties of the drug substance are identical to that of the currently registered Herceptin IV products. The relevant impurity removal steps have not been changed either. Data show consistent removal of impurities by the trastuzumab SC process and is comparable to the trastuzumab IV processes.

The specification of trastuzumab SC is comparable to trastuzumab IV with respect to identity, activity and purity; and an additional identity test is added to distinguish between trastuzumab for SC and IV application. Appropriate validation data have been submitted in support of the test procedures.

Drug product

Herceptin solution for SC injection (Herceptin SC) formulation contains hyaluronidase (human recombinant), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. Other excipients include histidine hydrochloride, histidine, trehalose dihydrate, polysorbate 20, methionine and Water for Injections.

The final Herceptin SC drug product is a sterile, colourless to yellowish, clear to opalescent liquid solution (120 mg/mL,) for SC injection in a 6 mL single-use vial.

The container is a colourless 6 mL glass vial (type I glass) closed by means of a rubber stopper (rubber laminated with fluoro-resin) and an aluminium overseal with flip-off disk.

The product is manufactured by thawing frozen drug substance and mixing with the required excipients including hyaluronidase. After compounding, the drug product bulk solution is filtered following by sterile filtration and filled into vials.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Long term storage testing of Herceptin SC drug product validation batches is carried out on vials stored at 2 to 8°C for up to 24 months, under accelerated conditions (15°C for 12 months) and stress conditions (25°C, 60% relative humidity for 6 months). The product is not photo stable.

The data available from primary stability studies and on supportive stability data collected during the development of the drug product support the proposed 18 months drug product shelf life when stored at 2 to 8°C protected from light.

Biopharmaceutics

Biopharmaceutic studies were not been assessed during the quality evaluation.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

Outstanding important issues

The excipient, recombinant human hyaluronidase, does not have an INN. The agreed interim name, 'hyaluronidase (human recombinant)', does not comply with TGO 69⁴.

The sponsor indicated on 8 September 2014 that: the company applied for an INN and the INN 'vorhyaluronidase alfa' for recombinant hyaluronidase was published in Proposed List of INNs on July 7 2014. If no formal objections to the proposed name are received after the permissible period of four months, the proposed name will be included in the forthcoming list of Recommended INNs. Pending on the result of the INN application, the company is planning to apply for an Australian Approved Name (AAN).

The agreed name is only a temporary measure while waiting for approval of a proper INN. The sponsor has committed to applying for an INN prior to completion of the Category 1 evaluation and before registration can occur. The evaluator recommends that an approved AAN is required irrespective of the INN application.³

Conclusions and Recommendations

The quality evaluator recommends that Herceptin SC trastuzumab (rch) 120 mg/ml solution for SC injection should be approved once the issue around the nomenclature for the hyaluronidase excipient has been resolved.

III. Nonclinical findings

Introduction

The recommended SC dose is 600 mg every three weeks irrespective of the patient's body weight. The SC formulation (solution for injection) contains the excipient hyaluronidase (human recombinant; rHuPH20) as a permeation enhancer to enable SC administration of large volumes. This excipient increases tissue permeability. It is, therefore, used in

⁴ Therapeutic Goods Order No. 69 - General requirements for labels for medicines (27/08/2001).

medicine in conjunction with other drugs to speed their dispersion and delivery, enabling large volumes to be delivered without pain or discomfort.

The nonclinical submission comprised data previously submitted and evaluated in the sponsor's original application to register Herceptin and the sponsor's application to register rituximab SC plus new studies on pharmacology, pharmacokinetics, repeat-dose toxicity and local tolerance. Only the new studies are evaluated in this report. The safety of hyaluronidase is discussed in the AusPAR for MabThera SC (<http://www.tga.gov.au/auspar/auspar-rituximab-3>).

Pharmacology

Primary pharmacology

An in vivo primary pharmacology study in Balb/c nude mice compared the anti-tumour activity of the IV and SC trastuzumab formulations on Calu-3 NSCLC (HER2 -positive) xenografts. Similar dose levels (1, 3 and 10 mg/kg trastuzumab) were administered by both IV and SC routes. Tumour growth was not inhibited at the lowest dose (1 mg/kg) regardless of route, while the mid dose (3 mg/kg) generated similar trough concentrations (9.4 to 10.4 µg/mL) and tumour inhibition (38 to 39%) for both routes of administration. At the highest dose (10 mg/kg) higher trough concentrations for the IV route (95.7 compared to 61.3 µg/mL) corresponded to greater tumour inhibition (66% compared to 48%) when compared to the SC route. It would appear that similar trough concentrations for the IV and SC routes could result in similar anti-tumour efficacy.

Pharmacokinetics

Data from mini-pig and mouse studies showed bioavailability for the SC route in both these species was in the range of 81.8 to 90.2%, suggesting relatively high systemic exposure could be achieved using the SC route. The bioavailability of trastuzumab in mini-pigs was independent of the presence of hyaluronidase (90.2% without hyaluronidase compared to 87.2% with 6000 IU/mL hyaluronidase), with no apparent effect of hyaluronidase on plasma area under the serum concentration versus time curve (AUC), although the peak plasma concentration (C_{max}) was higher with hyaluronidase (129 compared to 101 µg/mL at the SC dose of 108 mg). The time to reach peak serum levels (T_{max}) of trastuzumab for the SC route was shortened by addition of hyaluronidase. All three groups dosed with hyaluronidase had T_{max} values of 24 h, while one group without hyaluronidase had a T_{max} of 72 h showing the ability of hyaluronidase to increase the rate of absorption following SC dosing.

Data on exposure to trastuzumab in monkeys from the repeat-dose toxicity study by weekly dosing showed accumulation from dose one (Day 1) through Day 29 to Day 78. However, the initial increase from Day 1 to Day 28 (2.6 times the Day 1 value) was followed by a much lower increase from Day 29 to Day 78 (1.3 times the Day 29 value).

Toxicology

A 13 week repeat-dose SC toxicity study (with 17 weeks recovery period) in Cynomolgus monkeys was provided in support of the proposed new route of administration. This study complied with current standards of experimental conduct and was used to assess the effect of hyaluronidase on the toxicity profile of trastuzumab. It was noted that a dose of 30 mg/kg SC was used in an attempt to achieve a systemic exposure to trastuzumab comparable to that observed in a 3 month IV Cynomolgus monkey study, which used a dose of 25 mg/kg trastuzumab (plus two lower doses) and submitted in the original

trastuzumab application; exposures were shown to be comparable ($AUC_{0-7 \text{ days}}$: 166 [SC] compared with 177 [IV] mg.h/mL). A single dose level in the new study is acceptable given the similar finding in the SC study compared with the IV study. The hyaluronidase dose in the monkey study was 3000 U/kg/week (compared to the clinical dose of 200 U/kg/week).

Overall, the study animals remained in good health with no apparent adverse effects resulting from treatment with the SC trastuzumab formulation. Transient variations in electrocardiogram (ECG) recordings were limited to one sex and lacked biological significance, suggesting they were not treatment-related. The presence of anti-trastuzumab antibodies was only found in 3 samples from one animal during the recovery period; no anti-trastuzumab antibodies were found during dosing period. In contrast, a total of seven out of twenty (7/20) animals were shown to have anti-hyaluronidase antibodies at Day 78 analysis. Exposure to trastuzumab was above that likely in humans with relative exposure ratios up to 8.

Macroscopic and microscopic examination of the injection site did not reveal any clear pattern of treatment-related change from once weekly SC injection.

Relative exposure

Exposure ratios have been calculated based on animal/human plasma AUC. Human reference values are from Clinical Study B022227, where an assessment was conducted in patients treated over varying treatment cycles of SC trastuzumab at the proposed therapeutic dose (600 mg/3 weeks). The exposure in monkeys was up to 8 times the human exposure.

Table 1: Relative Monkey: Human exposure

Species	Study duration Route	Dose	AUC*	Exposure ratio
Monkey (Cynomolgus)	13 weeks SC	30 mg/kg/week	47.4 (Day 1) [142.2]	2.3
			125 (Day 29) [375]	6
			166 (Day 78) [498]	8
Human (patients, n=>220)	12 cycles (12 x 3 weeks) SC	600 mg/3 weeks	2.61 [62.64]	-

* AUC values for monkeys are converted from AUC_{0-168h} in mg.h/mL to $AUC_{0-3 \text{ weeks}}$ in mg.h/mL [in square brackets]. The AUC value for humans is cycle 12 AUC_{τ} (that is, $AUC_{0-3 \text{ weeks}}$) of 2.61 mg·day/mL (Study B022227) and converted to 62.64 mg·h/mL [in square brackets].

Hyaluronidase safety has also been assessed by the TGA in an evaluation of a proposed formulation (rituximab + hyaluronidase) to be used via the SC route. Studies in Cynomolgus monkeys given hyaluronidase at doses up to 220 kU/kg/week hyaluronidase (compared to the clinical dose of 200 U/kg for a 50 kg patient) were conducted using the proposed clinical route over an acceptable duration. No target organ toxicity was evident in repeat-dose toxicity studies. Signs of local injection site reactions were seen in animals receiving ≥ 0.2 mg/kg/week SC (test concentration: 1 mg/mL), with no other clinically relevant signs of toxicity observed.

Local tolerance

Assessment of local tolerance in rabbits following a single trastuzumab (60 mg/injection of the proposed clinical formulation) SC injection looked at early (24 h, n=3) and delayed

(96 h, n=3) onset effects. Animals remained in good health with no signs of toxicity and no evidence of tissue damage at the injection site. Microscopic examination of the injection site was unremarkable. This study used a single SC injection, which would not replicate the likely repeated SC dosing that will take place in humans. Repeated SC injection in the repeat-dose toxicity study in Cynomolgus monkeys did not result in significant macroscopic changes, while microscopic findings of infiltration of lymphocytes/macrophages occurred at a similar frequency in both treated and control animals.

Nonclinical summary and conclusions

- The nonclinical submission consisted of studies to support the use of the SC formulation of trastuzumab. The data are appropriate to support the proposed new route of administration.
- The proposed SC (+ hyaluronidase) and current IV formulations were tested and compared for anti-tumour activity in Balb/c nude mice with HER2 positive xenografts. Anti-tumour activity correlated with trough concentrations of trastuzumab, with similar activity and trough concentration for both SC and IV formulations at 3 mg/kg but greater activity (66% versus 48%) and trough concentration (95.7 versus 61.3 µg/mL) for IV when compared to the SC route at 10 mg/kg.
- Pharmacokinetic studies showed that the bioavailability of trastuzumab for the SC route was unaffected by the presence of hyaluronidase in mini-pigs (SC bioavailability was > 80%) but the absorption was faster with hyaluronidase than without this excipient (T_{max} 24 versus 72 hr).
- A repeat-dose toxicity study (13 weeks) in the Cynomolgus monkey showed no apparent adverse effects (local or systemic) resulting from SC treatment similar to the IV study (reviewed in a previous submission⁵) in the same species. No anti-trastuzumab antibodies were detected during dosing but three out of thirty-six (3/36) samples from the recovery period contained antibodies. Anti-hyaluronidase antibodies were seen at the end of dosing (Day 78) in seven out of twenty (7/20) monkeys. The exposures to trastuzumab (8 times the clinical dose) in the monkey study were greater than exposure in humans resulting from clinical use.
- Local tolerance was tested in rabbits with the SC formulation. There were no treatment-related reactions.
- Overall, the SC formulation of trastuzumab lacked toxicity (repeat-dose and local tolerance) and had its desired inhibitory activity against HER2-positive tumours in mice. Hyaluronidase was shown (in the rituximab evaluation⁵) to lack relevant toxicity at SC doses up to 1100 times the proposed clinical dose.
- There are no objections on nonclinical grounds to the registration of Herceptin® solution for SC injection for the proposed indications.

Revisions to the draft PI documents were recommended to the Delegate by the nonclinical evaluator but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

⁵ <http://www.tga.gov.au/auspar/auspar-rituximab-3>

Introduction

The submission contained two clinical trials.

The trastuzumab component of the formulation used in the clinical studies was referred to as 'trastuzumab v 1.0 SC'. An altered manufacturing process is being proposed for the trastuzumab to be included in the marketed formulation ('trastuzumab v 1.1 SC'). The sponsor stated the comparability of trastuzumab produced by the two manufacturing processes was demonstrated using quality data contained in the submission.

There have been no previous applications for SC trastuzumab. IV trastuzumab was initially approved by the TGA for the treatment of metastatic HER2 positive (HER2+ve) breast cancer in 2000. In subsequent applications it was approved for use as adjuvant treatment of localised HER2+ve breast cancer (2006), in combination with aromatase inhibitors for metastatic HER2+ve breast cancer (2008), for HER2+ve gastric cancer (2010) and adjuvant treatment of locally advanced HER2+ve breast cancer (2012).

A related product, trastuzumab emtansine (Kadcyla), was approved by the TGA in 2013 for the treatment of metastatic HER2+ve breast cancer in subjects who have previously received trastuzumab. Other registered agents that act through inhibition of the HER2 receptor include pertuzumab and lapatinib.

The sponsor of the current submission has also lodged an application with the TGA for a subcutaneous formulation of another monoclonal antibody (rituximab/Mabthera) formulation which also contains hyaluronidase. At the time of this submission, that application had not been decided.

Apart from minor editorial changes, all proposed changes to the clinical aspects of the PI are based on data submitted in support of SC administration or updated data from the HERA study.

Clinical Rationale

HER2 (or ErbB2) is a receptor that is expressed in a variety of normal epithelial cell types. It is one of a family of four receptors (the ErbB family) that activate a network of intracellular signalling pathways that affect cell proliferation and survival.⁶ HER2-positivity (that is, overexpression of the HER2 protein or amplification of the HER2 gene) is found in approximately 25 to 30% of breast cancers.⁷ HER2-positive breast cancer is associated with reduced disease-free survival and overall survival compared to HER2-negative disease.⁸

Previously evaluated studies have demonstrated efficacy for trastuzumab in the treatment of HER2-positive breast cancer in both the early and advanced disease settings. All these studies utilised IV administration of the drug.

The rationale for the SC route of administration proposed in this submission was summarised in the sponsor's Clinical Overview as follows:

'The currently approved formulation of trastuzumab IV requires a loading dose, which is given over 90 minutes; if well tolerated, subsequent infusions may be given over 30 minutes. Instead, trastuzumab SC can be administered over 2-5 min; this shorter administration time could possibly lead to improved convenience for patients, which is particularly important when patients are treated for prolonged periods of time. Other potential benefits of SC administration include providing an

⁶ Yarden Y and Sliwkowski M. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol.* 2001; 2: 127-37.

⁷ Tsang RY and Finn RS. Beyond trastuzumab: novel therapeutic strategies in HER2-positive metastatic breast cancer. *British Journal of Cancer.* 2012; 106: 6-13

⁸ Slamon DJ, Clark GM, Wong SG et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987; 235: 177-82.

alternative route of administration for patients with poor venous access as well as lower resource utilization (eg, nursing time needed for IV administration and patient monitoring, other treatment center costs, patient travel etc).'

Guidance

The following EU guidelines which have been adopted by the TGA are considered relevant to the current submission:

- Guideline on the evaluation of anticancer medicinal products⁹
- Guideline on the investigation of pharmacokinetics of therapeutic proteins¹⁰.

Compliance with these guidelines is considered in the relevant sections of this report.

Contents of the clinical dossier

Scope of the clinical dossier

For the SC administration component the following clinical data was submitted:

- One Phase I pharmacokinetic study (BP22023) conducted in healthy volunteers and breast cancer patients
- One pivotal Phase III study (BO22227) which compared IV and SC administration with respect to efficacy, safety and pharmacokinetics
- Two population pharmacokinetic analyses (Report Nos: 1045694 and 12-0215v2)
- One pooled analysis (dated 2011) of administration reactions occurring in clinical trials (Report No: 1048158)
- Literature references.

For the PI update component the following clinical data was submitted:

- A full clinical study report for the HERA trial
- Literature references.

Paediatric data

The submission did not include paediatric data. As HER2+ve breast cancer is a disease of adults, this is acceptable.

Good clinical practice

The study reports for the clinical trials submitted with this application included assurances that they were conducted in accordance with the principles of the Declaration of Helsinki and the principles of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice.

⁹ Guideline On The Evaluation Of Anticancer Medicinal Products In Man (CPMP/EWP/205/95/Rev.3.Corr); 2005.

¹⁰ Guideline On The Clinical Investigation of The Pharmacokinetics Of Therapeutic Proteins (CHMP/EWP/89249/2004); 2007.

Pharmacokinetics

Studies providing pharmacokinetic data

The PK data included in the submission related to the new SC route of administration and consisted of the following:

- An initial Phase I study (BP22023), which examined the PK of single IV and SC weight-adjusted doses of trastuzumab in healthy male volunteers and in female patients with a history of early HER2+ve breast cancer
- A population PK analysis (Report No: 1045694) that used the data from BP22023 and aimed to identify a suitable fixed-dose regimen for SC use in the pivotal Phase III study
- The pivotal Phase III efficacy and safety study comparing IV and SC administration (BO22227) in which PK data were collected from all subjects
- Another population PK analysis (Report No: 12-0215v2) of the PK data collected in the Phase III study.

None of the studies were excluded from consideration due to study deficiencies.

Evaluator's conclusions on pharmacokinetics

The proposed SC regimen results in increased systemic exposure to trastuzumab compared to the approved 3 weekly IV regimen. The efficacy of the SC regimen would therefore be expected to be at least comparable to that of the IV regimen. The increased systemic exposure may have implications for safety.

Pharmacodynamics

No new pharmacodynamic data were included in the submission.

Dosage selection for the pivotal studies

The proposed fixed dose SC regimen (600 mg every 3 weeks, with no loading dose) was chosen based on the findings of the population PK analysis (Report No. 1045694) of data from the Phase I study (see Attachment 2).

The study design, conduct and analysis of this study were considered satisfactory.

Efficacy

Studies providing efficacy data

One pivotal Phase III study (BO22227) which compared IV and SC administration with respect to efficacy, safety and pharmacokinetics was submitted.

Evaluator's conclusions on efficacy with subcutaneous administration

The data on pCR from the pivotal study suggest that the proposed SC regimen will produce a degree of efficacy that is non-inferior to that obtained with the currently approved IV 6 mg/kg every 3 weeks (q3w) regimen. The pivotal study also compared the PK profiles of IV and SC administration and found that the SC route produced higher levels of systemic exposure to trastuzumab

If the PK findings are accepted then it is improbable that SC administration would be associated with inferior efficacy. However, the following issues are considered relevant:

1. Use of pCR as a primary endpoint

According to the EU guideline on anticancer agents adopted by the TGA¹¹, acceptable primary endpoints for Phase III oncology trials are survival-type endpoints such as overall survival, progression-free survival and disease-free survival. Response rate measures such as objective response rate (ORR) and pathological Complete Response (pCR) are generally not acceptable.

pCR has been proposed as a possible surrogate endpoint (in place of survival-type endpoints) to enable the early approval of new drugs for the treatment of breast cancer. The FDA has released a draft guideline on the subject.¹² A pooled analysis of neoadjuvant clinical trials¹³ demonstrated that patients who achieved a pCR had longer event-free survival and overall survival than those who were left with residual tumour. This association was stronger in patients with more aggressive forms of disease (for example, hormone receptor negative disease) than in patients with less aggressive forms (for example, hormone receptor positive disease). However, the analysis could not demonstrate a relationship between the magnitude of a treatment's effect on pCR rate and the magnitude of its effect on Event-Free Survival (EFS) and Overall Survival (OS). Therefore, it cannot be assumed that non-inferiority in terms of pCR will translate into non-inferiority in terms of EFS and OS.

The current debate regarding the use of pCR concerns its use as a surrogate endpoint for *new* drugs in the situation where data on hard clinical endpoints such as EFS and OS are not yet available. For trastuzumab, a beneficial effect of the drug on these endpoints has already been demonstrated (for the IV form). The use of pCR as a surrogate endpoint to demonstrate comparable efficacy between the IV and SC forms therefore seems a reasonable approach. The alternative would be to require demonstration of non-inferiority between the two routes of administration using a hard clinical endpoint such as EFS. This would require a very large trial, which would take several years to complete.

Despite the wording of the EU guideline it is noted that the EMA itself has approved the current application. Overall, it is considered that the use of pCR as the primary efficacy endpoint is acceptable.

2. *Lack of blinding*

The clinical evaluator noted that local pathologists assessed the primary endpoint of pCR. It appears that these pathologists were not blinded to treatment allocation and that there was no independent review of their findings. This may have introduced some bias into the trial findings.¹⁴

3. *Efficacy in metastatic disease*

The sponsor is seeking approval for the new SC regimen in the treatment of metastatic disease. The population included in the pivotal study consisted of subjects

¹¹ Guideline On The Evaluation Of Anticancer Medicinal Products In Man (CPMP/EWP/205/95/Rev.3.Corr); 2005.

¹² Food and Drug Administration. Guidance for Industry - Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval. 2012.

¹³ Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014 Feb 13. pii: S0140-6736(13)62422-8. doi: 10.1016/S0140-6736(13)62422-8. [Epub ahead of print]

¹⁴ The sponsor submitted a response to the TGA regarding the Pathology Assessment Protocol and the issue of blinding. The Delegate's discussion of this issue is detailed on pages 35-36 of this AusPAR under *Comments on the pathology assessment protocol Points 1-3*.

with localised or locally advanced disease. Patients with metastatic disease were excluded. The study also compared the proposed SC regimen with the 6 mg/kg q3w IV regimen. In Australia the only regimen approved for use in metastatic disease is the 2 mg/kg once a week (q1w) regimen (see Table 2). This was the dosage regimen used in the pivotal efficacy studies in this setting. An application for approval of the 6 mg/kg q3 weeks IV regimen in metastatic disease was not approved by the TGA.

Table 2: Approved indications and approved and proposed dosage regimens.

Shaded areas indicate changes that are the subject of the current application.

Approved Indication	RoA	Loading dose	Subsequent doses	Duration
Localised Breast Cancer Treatment of HER2-positive localised breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.	IV	8 mg/kg	6 mg/kg every 3 weeks	1 year
	IV	4 mg/kg	2 mg/kg every 1 week	1 year
	SC	-	600 mg every 3 weeks	1 year
Locally Advanced Breast Cancer Treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant HERCEPTIN.	IV	8 mg/kg	6 mg/kg every 3 weeks	1 year
	SC	-	600 mg every 3 weeks	1 year
Metastatic Breast Cancer Treatment of patients with metastatic breast cancer who have tumours that overexpress HER2: As monotherapy for the treatment of those patients who have received one or more	IV	4 mg/kg	2 mg/kg every 1 week	Until disease progression

Approved Indication	RoA	Loading dose	Subsequent doses	Duration
chemotherapy regimens for their metastatic disease; In combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or In combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.	SC	-	600 mg every 3 weeks	Until disease progression
Advanced Gastric Cancer ¹ 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.	IV	8 mg/kg	6 mg/kg every 3 weeks	Until disease progression

¹The current application for Herceptin SC did not include the gastric cancer indication. RoA-Route of administration.

Simulations using a population PK model suggested that trastuzumab systemic exposure with the 600 mg q3w SC regimen would be at least comparable to that obtained with the 2 mg/kg q1w regimen (see *Dosage selection for the pivotal studies; Report No. 1045694 Results*). Trastuzumab for metastatic disease is funded in Australia through Medicare, using an arrangement separate to the Pharmaceutical Benefits Scheme. Under this

arrangement both the 2 mg/kg q1w regimen and the 6 mg/kg q3w regimen are funded¹⁵, even though the latter is not approved by the TGA. It is therefore likely that the 6 mg/kg q3w regimen is being used. For these reasons this reviewer considers it reasonable to extrapolate the efficacy findings of the pivotal study to the metastatic disease setting.

Overall, when the efficacy results are considered together with the pharmacokinetic results, it is concluded that efficacy of the proposed SC regimen has been adequately established.

Evaluator's conclusions on clinical efficacy - PI update

The 8 year follow-up of the study confirms that one year of adjuvant treatment with trastuzumab in patients with early breast cancer (after completion of surgery and chemotherapy, with or without radiotherapy) results in significant benefit in terms of disease-free survival and overall survival. These benefits have been maintained despite 52% of subjects in the observation arm having also received trastuzumab. The latest results have also shown that prolonging treatment with trastuzumab to a total of 2 years does not result in improved efficacy.

The sponsor proposes to update the efficacy data in the 'Clinical Trials' section of the PI by replacing the results obtained after 2 years of follow-up with those obtained at 8 years, and by including the results of the comparison of the two trastuzumab arms at 8 years. These changes are generally acceptable.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data.

- Pivotal efficacy Study B022227
- Phase I Study BP22023

Patient exposure

A total of 661 subjects received at least one dose of trastuzumab in the two submitted studies. A total of 355 subjects received at least one SC dose. Table 3 summarises the patient exposure.

Table 3: Exposure to trastuzumab SC and IV in clinical studies.

Study	Subjects	SC	IV	Total
B022023 Part 1	Healthy volunteers	18	6	24
	Patients	-	6	6*
Part 2	Patients	40	-	40*
B022227	Patients	297	298	595
Totals		355	310	661*

¹⁵ Medicare Australia. Late stage metastatic breast cancer – Trastuzumab (Herceptin).

*Four subjects in BP22023 received a single IV dose and a single SC dose. There were therefore 66 unique subjects in this study.

The main safety data come from the Phase III study and the following review of adverse events will focus on the findings of that trial.

The extent of trastuzumab exposure in the Phase III study is summarised in Table 4. The percentage of planned dose received and the number of cycles received were equivalent in the two arms. The extent of exposure to each of the planned chemotherapy agents (docetaxel, 5-fluorouracil, epirubicin and cyclophosphamide) was also comparable in the two study arms.

Table 4: Study BO22227. Extent of trastuzumab exposure

Class	Trastuzumab IV (N=298)	Trastuzumab SC (N=297)
Overall		
Dose intensity (mg/week)		
n	298	297
Mean	137.89	194.10
Std Dev	28.334	7.379
Median	135.63	196.36
Range	86.9–234.6	163.2–208.0
Percentage of Planned Dose Intensity		
n	294	297
Mean	97.05	97.05
Std Dev	3.860	3.690
Median	98.18	98.18
Range	70.7–102.0	81.6–104.0
Number of Cycles		
n	298	297
Mean	16.7	16.7
Std Dev	3.63	3.61
Median	18.0	18.0
Range	1–20	1–18
Number of Patients with Dose Delay/Interruption/Modification		
None	105 (35.2%)	108 (36.4%)
1 cycle	93 (31.2%)	73 (24.6%)
2 cycles	39 (13.1%)	61 (20.5%)
3 cycles	26 (8.7%)	27 (9.1%)
4 cycles	14 (4.7%)	18 (6.1%)
>4 cycles	21 (7.0%)	10 (3.4%)

Dose Intensity = Actual Total Cumulative Dose / Actual Duration for every patient

Safety issues with the potential for major regulatory impact

Liver toxicity

Trastuzumab has not previously been associated with significant hepatic toxicity. The new data in this submission did not suggest any such toxicity.

Haematological toxicity

Trastuzumab has not previously been associated with major haematological toxicity. The studies included in this submission did not raise any new concerns in this area.

Serious skin reactions

In the HERA study dermatological serious adverse events (SAEs) occurred more frequently in the trastuzumab arms (4 and 12 events) than in the observation arm (1 event only). Skin toxicity would be expected with trastuzumab as a manifestation of hypersensitivity events. In the pivotal study for SC administration there was only one

serious dermatological AE: a case of erythema multiforme in the SC arm which was considered unrelated to trastuzumab.

There were no reports of Stevens-Johnson syndrome or toxic epidermal necrolysis.

Cardiovascular safety

Trastuzumab is known to be associated with an increased incidence of cardiac failure. This was confirmed in the updated HERA report. Cardiac toxicity appeared comparable in the two arms of the pivotal study for SC administration.

Unwanted immunological events

Hypersensitivity reactions and infusion related reactions are known to occur with trastuzumab. The incidence of such events was higher with SC administration. Similarly, the incidence of anti-trastuzumab antibody development was higher in the SC arm.

Postmarketing data

No postmarketing data were included in the submission.

Evaluator's conclusions on safety

SC administration

The PK data included in this submission demonstrate that the proposed SC dosage regimen will be associated with some increase in systemic exposure to trastuzumab compared with IV administration. A potential concern would therefore be that the new regimen might be associated with increased toxicity.

The main safety concern arising out of the submitted data is that SC administration appeared to be associated with a 50% increase in the incidence of serious adverse events (22% SC versus 14% IV). If this were a real difference, it would be clinically important. There are a number of inconsistencies in the safety results that may cast doubt upon any conclusion that the increased SAE rate was due to increased systemic exposure:

- There was no apparent increase in the rate of Grade 3 or higher AEs in the SC arm (54% SC versus 52% IV)
- Exploratory analyses did not demonstrate a relationship between the incidence of SAEs and patients with higher AUC values
- The increase in SAEs was greatest in the 'Infections and Infestations' category. There was no obvious pattern to the types of serious infections observed in the SC arm and it appears that an increased risk of *serious* infections has not previously been identified for trastuzumab.

There was also an imbalance in the proportion of subjects who discontinued treatment due to an AE (5.7% SC versus 2.7% IV). This was predominantly due to an excess of patients discontinuing due to cardiac AEs. However, when all the available data from the study on cardiac toxicity are considered, SC administration does not appear to be associated with an increased risk.

SC administration is associated with local injection site reactions in approximately 11% of subjects. Such reactions were infrequent (45 events after 4,957 injections) and mild or moderate in intensity.

SC administration is also associated with an increased risk of developing anti-trastuzumab antibodies (14.6% SC versus 7.1% IV). However, preliminary data suggest that these

antibodies are not associated with changes in PK, loss of efficacy or increased risk of administration related reactions (such as hypersensitivity).

PI update (HERA study)

The toxicity of trastuzumab in the 8 year follow-up analysis of the HERA study is generally consistent with that previously described for the drug. The risk of cardiac failure and infusion reactions is increased with trastuzumab treatment. The 2 year trastuzumab regimen is associated with greater toxicity than the 1 year regimen. The new data suggest that trastuzumab treatment may be associated with an increased risk of malignancy. The sponsor should be asked to comment on this issue.

The sponsor proposes to update the PI by including information on the negative safety aspects of the 2 year regimen and by updating data on cardiac toxicity. The proposed changes are generally acceptable.

First Round Benefit-Risk Assessment

Subcutaneous administration

First round assessment of benefits

The benefits of SC administration of trastuzumab are:

- At least non-inferior efficacy to that obtained with IV administration
- Patient convenience in terms of shorter administration times
- Avoidance of IV cannulation, at least in subjects receiving trastuzumab monotherapy.

First round assessment of risks

The risks of SC administration of trastuzumab are:

- A possible 50% increase in the incidence of serious AEs compared to IV administration
- Infrequent injection site reactions which are mild or moderate in severity
- An increased risk of the development anti-trastuzumab antibodies. The available evidence suggests that antibody development is not associated with clinically significant consequences.

First round assessment of benefit-risk balance

It can be reasonably concluded that SC administration will be as efficacious as IV administration. However, the apparent increase in the incidence of SAEs compared to IV administration raises concerns regarding safety.

The efficacy benefits of trastuzumab treatment in patients with HER2+ve breast cancer are substantial. For example, in the adjuvant setting, trastuzumab treatment is associated with significant improvements in disease-free and overall survival. Even if the increased SAE rate with SC use were a real phenomenon, the benefits of its use would still outweigh its risks. However the benefit-risk balance of SC administration would be less favourable than that of IV administration.

The benefits of convenience and avoidance of IV cannulation may be important in some patients. On balance, it is considered that the application for SC administration could be approved. However, it is recommended that the PI for the SC formulation should include

an adequate statement in the 'Precautions' section alerting prescribers to the possible increased risk of serious AEs.

PI update (HERA Study)

First round assessment of benefits

The 8 year analysis of the HERA study confirmed that use of the drug in the adjuvant setting is associated with significant improvements in disease-free survival and overall survival.

First round assessment of risks

The 8 year analysis indicates that the toxicity profile of trastuzumab is generally consistent with that previously documented.

First round assessment of benefit-risk balance

The benefit-risk balance of trastuzumab in the adjuvant setting remains favourable.

First Round Recommendation Regarding Authorisation

SC administration

It is recommended that the application for the SC route of administration be approved, subject to changes in the PI outlined below.

PI update (HERA Study)

It is recommended that the proposed changes to the PI be approved, subject to the changes outlined below.

Clinical Questions

Pharmacokinetics

1. In Study BP22023, four female subjects who participated in Cohort 2 of Part 1 (6 mg/kg IV) also participated in Cohort A of Part 2 (8 mg/kg SC). Please provide an analysis of PK parameters observed in these four subjects, including an estimate of absolute bioavailability.

Efficacy

2. In Study B022227, it appears that the pathologist undertaking the assessment of pCR was not blinded to study treatment. Blinded assessment would have been preferable. According to the study protocol, pCR was to be assessed by the local pathologist following surgery and would not be independently reviewed. However, the published version of the study states that: '*Review of pathological tumour assessment results was done by a masked medical reviewer*'. Please clarify whether any central blinded assessment of pCR was undertaken in the study. If no central blinded assessment was undertaken, please provide a justification for such a study design.

3. A further analysis of Study B022227 was planned when all subjects had completed 2 years of treatment-free follow-up. Please advise when this analysis will be available.
4. In Study B022227, a high proportion of subjects had clinical lymph node involvement at baseline. What proportion of subjects in each arm had histological confirmation of lymph node involvement prior to neoadjuvant treatment (for example by sentinel lymph node biopsy or fine needle aspiration)? In this subgroup of patients, what was the total pathological complete response (tpCR) rate in each arm?

Safety

5. In the HERA study there was an excess of neoplastic serious AEs in the trastuzumab arms, with notable increases in the incidence of contralateral breast cancer, melanoma and thyroid cancer as shown in the Table 5.

Table 5: Incidence of neoplastic serious AEs

	Observation	1 year trastuzumab	2 year trastuzumab
All neoplasms	35	69	94
- contralateral breast cancer	9	23	23
- malignant melanoma	0	8	6
- thyroid cancer	1	1	7

Trastuzumab is not known to be associated with an increased risk of neoplasms/malignancies. Is the sponsor able to provide an explanation for these observations?

Second Round Evaluation of clinical data submitted in response to questions

For details of the sponsor's responses to the *Clinical questions 1-4* above and the clinical evaluator's comments on these responses, please see Attachment 2.

Second Round Benefit-Risk Assessment

The benefit-risk balance for SC administration is unchanged following evaluation of the sponsor's additional information. The benefit-risk balance of trastuzumab in the adjuvant setting remains favourable based on the updated report of the HERA study.

Second Round Recommendation Regarding Authorisation

It is recommended that the application for SC administration be approved. It is also recommended that the proposed changes to the PI based on the updated HERA study report be approved.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP version 12.0 dated 19 November 2013 (data lock point 19 November 2013) and an Australian-specific Annex version 1.0 dated February 2014 and a Periodic Safety Update Report (PSUR) from 25 September 2013 to 24 March 2014 (inclusive) which were reviewed by the TGA's Post-Market Surveillance Branch (PMSB).

As the TGA has previously evaluated an Australian RMP (AUS-RMP) (version 2.0 dated July 2011) for trastuzumab (Herceptin), the focus of this evaluation is on the changes to the RMP that could have an impact on the safety profile and any new safety related information since the last evaluation.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 6.

Table 6: Summary of Ongoing safety concerns

Important Identified Risks of HERCEPTIN

• Cardiac dysfunction
• Administration related reactions
• Haematotoxicity
• Oligohydramnios
• Pulmonary disorders

Important Potential Risks of HERCEPTIN

• Infections
• Medication errors *
• Immunogenicity/hypersensitivity and anaphylaxis of subcutaneous formulation*
• Relative short-term safety of the higher absolute dose intensity of SC versus IV formulation*

Important Missing Information about HERCEPTIN

• Safety of 75mg/m ² vs. 100mg/m ² docetaxol dose*
• Relative long-term safety of the higher absolute dose intensity of SC versus IV formulation*
• Treatment in male patients*

* newly identified

Pharmacovigilance plan

The sponsor has proposed routine and additional pharmacovigilance activities to monitor the safety concerns. The additional pharmacovigilance activities include the following studies performed overseas:

- A cardiac adverse event specific Study BO20652 (OHERA)
- A QT¹⁶ and drug interaction study in the US: H4613g (HER-Q-Les) (completed in 2013)

¹⁶ In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarisation and repolarisation of

- Study ML20529 in Netherlands to evaluate the effect of candesartan in preventing trastuzumab associated cardiotoxicity
- A pregnancy registry in the US: H4621g (MoTHER)
- Study BO2227 (HannaH) to compare the pharmacokinetics, efficacy and safety of SC with IV trastuzumab
- Two year and five year follow-up for Study BO2227
- Study MO22982 (PrefHER) to evaluate patient preference and health care professional satisfaction with SC trastuzumab
- Five year follow-up for Study MO28048 (SafeHER) to assess the safety of assisted and self-administered SC trastuzumab treatment as adjuvant therapy in patients with operable HER2 positive early breast cancer.

Risk minimisation activities

The sponsor has proposed routine risk minimisation activities to mitigate the safety concerns.

Reconciliation of issues outlined in the RMP report

Table 7 summarises the PMSB's first round evaluation of the RMP, the sponsor's responses to issues raised by the PMSB and the PMSB's evaluation of the sponsor's responses.

Table 7: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
<p>1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for further information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should</p>	<p><i>The sponsor has reviewed the Clinical and Non-Clinical Evaluation Reports and the questions raised by evaluators. The sponsor does not perceive there to be any additional safety considerations.</i></p>	<p>The sponsor's response is satisfactory.</p>

the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
provide information that is relevant and necessary to address the issue in the RMP.		
2. The sponsor should clarify the circumstances surrounding the decision to withdraw its application to register the SC injection solution in Canada and Switzerland, and specify whether it was related to any safety concerns.	<p><i>The sponsor decided to withdraw the regulatory file (without prejudice to re-filing) supporting Herceptin 600 mg solution for injection (SC vial) in Canada. The main reason for the withdrawal related to the fact that the neoadjuvant indication is not approved in Canada and the pivotal trial supporting the non-inferiority of the Herceptin SC formulation to the Herceptin IV formulation (BO22227) was conducted in the neoadjuvant setting. For the submission in Switzerland, the sponsor decided that the requests from Swissmedic, which included introduction of an applicator and provision of additional data relating to adjuvant breast cancer administration, could not be provided within the required regulatory timelines; the sponsor's withdrawal from Canada and Switzerland were not related to safety concerns.</i></p>	The sponsor's response is satisfactory.
3. As the TGA has previously evaluated an AUS-RMP (version 2.0 dated July 2011) for trastuzumab (Herceptin), the focus of this evaluation is on the changes to the RMP that	<p><i>The sponsor acknowledges this comment from TGA.</i></p>	n/a

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
<p>could have an impact on the safety profile and any new safety related information since the last evaluation.</p>		
<p>4. The evaluator noted that in its assessment report dated June 2013, the Committee for Medicinal Products for Human Use (CHMP) in the EU required a Phase IV clinical trial concerning the safety of 100 mg/m² docetaxel and SC Herceptin in patients with metastatic breast cancer with specific focus on active cardiac monitoring. The sponsor should provide an update on its planning of this study. Pending the TGA's decision on the current submission, the sponsor should clarify whether Australian patients will be included in this post-authorisation clinical trial.</p>	<p><i>To address the CHMP's request for a Phase IV clinical trial concerning the safety of 100 mg/m² docetaxel and SC Herceptin in patients with metastatic breast cancer, the sponsor submitted a draft study protocol to the CHMP and Pharmacovigilance Risk Assessment Committee (PRAC) on the 13 November 2013.</i></p> <p><i>The proposed clinical study is a multicentre, open-label, single-arm study of Herceptin SC given in combination with Perjeta® (pertuzumab) IV and docetaxel chemotherapy in the first-line treatment of patients with HER2-positive advanced breast cancer (metastatic or locally recurrent). The sponsor plans to submit clinical trial applications for this study in fourth quarter of 2014 and the first study patient to be enrolled is estimated for first quarter of 2015. There are currently no plans to include Australian patients in this clinical trial.</i></p>	<p>The sponsor's response is acceptable. As cardiac dysfunction is listed as an identified risk, the sponsor is expected to give specific consideration of all reported occurrences in the PSURs. The sponsor should include the planned Phase IV safety trial in their next update to the RMP. The protocol for the safety trial should be submitted to the TGA for review once it becomes available. The sponsor must also include any safety related findings from the Phase IV clinical trial in the future PSURs.</p>
<p>5. The justification provided by the sponsor for removing 'Quality Assurance of HERs Testing in Australia' would appear to be</p>	<p><i>The sponsor acknowledges the TGA's assessment.</i></p>	<p>n/a</p>

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
reasonable and therefore acceptable.		
<p>6. Recommendations regarding revisions of the draft PI and Consumer Medicine Information (CMI) are made to the TGA Delegate. These draft documents should not be revised until the Delegate's Overview has been received. However, the sponsor should provide comments on the recommendations.</p>	<p><i>The sponsor has not revised the PI or CMI in response to any recommendations from the RMP evaluator but has made a comment on PI comments made by the evaluator in Recommendation 7 below.</i></p>	<p>The sponsor's response is satisfactory.</p>
<p>7. Since the commencement of the evaluation, the TGA has received a PSUR covering the period from 25 September 2013 to 24 March 2014 (inclusive). This report provides updates and new information related to the safety profile of trastuzumab. It is recommended to the Delegate that relevant sections of the draft PI be revised as follows:</p> <p>The duration for an effective contraception to be used after trastuzumab treatment should be increased from six months to seven months;</p> <p>The frequency for the following adverse reactions should be increased from common to very common based on Joint Analysis and/or 'SC alignment': white blood cell count decrease/leukopaenia –</p>	<p><i>In relation to all recommendations a. b. and c., a recent Safety Related Request (SRR) was submitted by the sponsor which included these changes. This SRR was approved by TGA on 12 May 2014.</i></p>	<p>The sponsor's response is satisfactory. As the recommended changes to the PI have been approved, no further action is required.</p>

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
<p>15.4%, infection – 24.0%, ejection fraction decreased – 22.0%, nail disorder – 13.4%;</p> <p>A frequency should be assigned to following adverse reactions based on a new clinical trial data review: dermatitis – 5% common, and urticarial – 0.7% uncommon.</p>		

It was also recommended to the Delegate that the relevant content of the CMI be updated accordingly to provide adequate information to patients.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

Details on the following outstanding issues are detailed in the Table 7 *Reconciliation of issues outlined in the RMP report* above.

Recommendation 4: As cardiac dysfunction is listed as an identified risk, the sponsor is expected to give specific consideration of all reported occurrences in the PSURs. The sponsor should include the planned Phase IV safety trial in their next update to the RMP. The protocol for the safety trial should be submitted to the TGA for review once it becomes available. The sponsor must also include any safety related findings from the Phase IV clinical trial in future PSURs.

Additional recommendations: 'Discontinuation of treatment due to adverse events' is a related safety issue. The sponsor should include this risk as an 'identified risk' in the Australian Specific Annex. The sponsor should also report the following in future PSURs:

1. The number of discontinuation events for the SC and IV formulation respectively
2. The number of discontinuation events due to left ventricular dysfunction by quartile of treatment duration.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

EU-RMP version 12.0 dated 19 November 2013 (data lock point 19 November 2013) with Australian-specific Annex version 1.0 dated February 2014, to be revised to the satisfaction of the TGA, should be implemented.

VI. Overall conclusion and risk/benefit assessment

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

Introduction

The proposed means of testing efficacy is the demonstration of non-inferiority between the IV and SC formulation as determined by pathological complete response rates in the primary tumour and axillary nodes following neoadjuvant treatment. The study was not powered to demonstrate disease-free survival or overall survival, thus response rates to the neoadjuvant treatment are being used as the primary endpoint. It is important to demonstrate equivalent safety profiles between the two formulations, particularly the cardiac safety, and to ensure the rates of completion of the twelve months of treatment do not differ as efficacy is linked to completion of the course.

Quality

The quality evaluator recommended that Herceptin SC trastuzumab (rch) 120 mg/mL solution for SC injection should be approved once the issue around the nomenclature for the hyaluronidase excipient has been resolved.

Conditions of Registration: Batch Release Testing

It is a condition of registration that, as a minimum, the first five independent batches of Herceptin SC trastuzumab (rch) 120 mg/mL solution for subcutaneous injection (provisional AUST R 220402) imported into Australia are 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.

The sponsor should supply:

1. Certificates of Analysis of all active ingredient (drug substance) and final product.
2. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
3. Evidence of the maintenance of registered storage conditions during transport to Australia.
4. Three containers (usually 3 to 5 vials) of each batch for testing by the Therapeutic Goods Administration Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Nonclinical

- There are no objections on nonclinical grounds to the registration of Herceptin® solution for SC injection for the proposed indications. The new SC formulation of Herceptin contains recombinant human hyaluronidase.
- The data are appropriate to support the proposed new route of administration.
- The proposed SC (with hyaluronidase) and current IV formulations were tested and compared for anti-tumour activity in Balb/c nude mice with HER2 positive xenografts. Anti-tumour activity correlated with trough concentrations of trastuzumab, with similar activity and trough concentration for both SC and IV formulations at 3 mg/kg,

but greater activity (66% versus 48%) and trough concentration (95.7 versus 61.3 µg/mL) for IV when compared to the SC route at 10 mg/kg.

- PK studies showed that the addition of hyaluronidase did not affect bioavailability of trastuzumab for the SC route (> 80% in mini-pigs) and increased the absorption rate compared to that without hyaluronidase (T_{max} 24 versus 72 h). Hyaluronidase was shown (previously evaluated in the rituximab SC formulation) to lack relevant toxicity at SC doses up to 1100 times the proposed clinical dose.
- A repeat-dose toxicity study (at 8 times the clinical dose) showed no apparent adverse effects (local or systemic) resulting from SC treatment similar to the IV study (reviewed in a previous submission) in the same species. No anti-trastuzumab antibodies were detected during dosing but three out of thirty-six samples from the recovery period contained antibodies. Anti-hyaluronidase antibodies were seen at the end of dosing (Day 78) in seven out of twenty monkeys.
- There were no local treatment-related reactions.
- Overall, the SC formulation of trastuzumab lacked toxicity (repeat-dose and local tolerance) and had its desired inhibitory activity against HER2-positive tumours in mice.

Clinical

The clinical data reviewed:

- One Phase I pharmacokinetic study (BP22023) conducted in healthy volunteers and breast cancer patients
- One pivotal Phase III study (BO22227) which compared IV and SC administration with respect to efficacy, safety and pharmacokinetics
- Two population pharmacokinetic analyses (Report Nos: 1045694 and 12-0215v2);
- One pooled analysis (dated 2011) of infusion reactions occurring in clinical trials (Report No: 1048158)
- Literature references.

The submitted data was evaluated using TGA adopted EU Guidelines as follows:

- Guideline on the evaluation of anticancer medicinal products in man
- Guideline on the investigation of pharmacokinetics of therapeutic proteins.

Pharmacokinetics/Pharmacodynamics

The key PK parameters are summarised in the clinical evaluation report (Attachment 2).

The key findings with the proposed SC regimen were:

1. Increasing systemic exposure (C_{trough} > AUC) to trastuzumab over time compared to 3 weekly IV regimen, especially in those with low body weight
2. Systemic absorption of hyaluronidase was below limits of quantification at all times
3. In the 4 paired samples from subjects who received IV and SC formulation, there was significant variation in the absolute bioavailability (44.7 to 90.3%). Population PK model estimated the bioavailability to be 77.1%
4. Body weight affects SC trastuzumab PK, with linear increases in clearance (CL) with increasing weight.

Comment: The absolute bioavailability varied widely in the 4 subjects who had paired samples. The Ctough levels at the 600 mg dose were well above the target trough so were not expected to have implications for efficacy. The efficacy of the SC regimen would therefore be expected to be at least comparable to that of the IV regimen. The increased systemic exposure may have implications for safety.

Clinical Efficacy

Study BO22227 HannaH study enHANced treatment with NeoAdjuvant Herceptin).

Phase III, randomised, open-label trial with two parallel groups (IV and SC) conducted in the neoadjuvant setting (with treatment continued post-operatively) in patients with HER2+ve localised or locally advanced breast cancer. All patients received eight 21 day cycles of neoadjuvant chemotherapy (4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil + epirubicin + cyclophosphamide [FEC]). In addition, patients were randomised (1:1) to receive eight 21 day neoadjuvant cycles of either IV or SC trastuzumab, concurrent with the chemotherapy. Patients then underwent surgery and postoperative endocrine therapy and radiation therapy as determined by local practice, and continued to receive trastuzumab (originally randomised) for a further ten 21 day cycles. Total intended duration of trastuzumab treatment was therefore 18 cycles (approximately 12 months).

The trial was conducted in 81 centres in 24 countries (Russia 10; Germany 8; Brazil 6; France, Peru and Spain 5 each; Thailand, Taiwan and South Africa 4 each; Poland, Colombia, Korea, Italy, Turkey and Hungary 3 each; Sweden, Slovakia and, Czech Republic 2 each; Canada, China, Estonia, Guatemala, Mexico, Panama 1 each).

Primary objectives:

- a. To compare for trastuzumab IV and SC:
 - Predicted Ctough concentrations pre-surgery and post-surgery
 - Pathological complete response rates (pCR).
- b. To evaluate for trastuzumab IV and trastuzumab SC arm:
 - Total pathological complete response (tpCR)
 - Overall response rate (ORR)
 - Time-to-response (TTR)
 - Event-free-survival (EFS)
 - Overall survival (OS)
 - Safety and tolerability
 - Immunogenicity.

The trial is ongoing and the date of data cut-off for the submitted study report was 9 July 2012. The report itself was dated September 2013. The median duration of follow-up at the time of data cut-off was 19.7 months in the IV arm and 20.4 months in the SC arm.

Inclusion criteria and exclusion criteria are shown in Attachment 2. Dose delays were permitted but not reductions of trastuzumab. The study included subjects with clinical Stage I (with tumour size ≥ 1 cm) to Stage IIIC disease which represents a broad range of risk

Comment: Neoadjuvant therapy in Australian practice is usually given to downstage large, locally advanced tumours or node-positive breast cancer, or to render breast-conserving surgery possible in those with smaller tumours. There was a very

broad range of stages of disease in this trial and this study population includes more with earlier stage disease than perhaps would receive neoadjuvant treatment in Australia.

Randomisation was stratified by breast cancer type (inflammatory versus locally advanced versus operable) and oestrogen receptor status (positive versus negative versus unknown). There was no blinding to treatment allocation.

Comments on the pathology assessment protocol:

1. There was central confirmation of HER2 status.
2. Somewhat confusingly, the published report in the Lancet Oncology (2012;13:869-78) states '*Review of pathological tumour assessment results was done by a masked medical reviewer*', and later in the same article, '*In our study, pathological response was assessed by the local pathologist after review of pathological tumour assessment results by a masked medical reviewer*'. From this, it could be inferred there was an expert pathologist's review following the initial reporting as a review is a reconsideration of a decision already made. The sponsor's response on this matter indicates that the sponsor was able to determine by a retrospectively conducted survey of the clinical sites that in 73.7% of cases, it was deemed due to local practice, the reporting pathologist was unaware of the treatment allocation. The review by Roche medical reviewers was of the report to ensure clarity and completeness not to re-examine the specimens and to confirm the diagnosis, therefore does not constitute 'a masked review' of the pCR. While the Delegate accepts that in the majority of cases where it could be established, pathologists were not aware of the treatment allocation, meaning the risk of bias being introduced is relatively low, the PI statement needed modification to reflect clearly how the assessment was undertaken. The Delegate proposed the following statement be included in the PI '*In the majority of cases, it was retrospectively determined the pathologist assessing the primary specimens and nodes was masked to treatment allocation and no supplemental independent review was performed*'. This was accepted by the sponsor.
3. The presence of nodal metastases was confirmed only by sentinel node biopsy (as Fine Needle Aspiration (FNA) results were not recorded) in small numbers: 20 (IV) and 11 (SC) with most being assessed as positive by clinical examination and/or ultrasound. This raises uncertainty about the initial rate of nodal involvement in the absence of pre-treatment histological confirmation; consequently the rates of tPCR are uncertain. The Delegate acknowledges the PI does not include any such claims of efficacy for this secondary endpoint.

Analysis populations

The intent-to-treat (ITT) population included all patients who had at least one efficacy assessment after first study drug administration.

The efficacy per-protocol (EPP) population was a subset of the Intent-to-treat (ITT) population, limited to those who had completed the neoadjuvant regimen without significant protocol violations. The EPP was the main analysis set for the analysis of the primary efficacy outcome of pCR.

The safety analysis population (SP) included all patients who received at least one dose of study medication (chemotherapy or trastuzumab).

Some 596 patients were randomised; 299 to the IV arm and 297 to the SC arm.

Withdrawals due to AEs were more common in the SC arm (13 versus 5) but other patient disposition factors were similar.

Results for the primary efficacy outcome

The results for the primary endpoint of pCR in the EPP are shown in the table below. The pCR rate was 40.7% in the IV arm and 45.4% in the SC arm, with the difference being +4.7% in favour of the SC arm. The lower 97.5% confidence interval for the difference was -4.0% which was above the predetermined limit of -12.5%. Non-inferiority was therefore concluded. The results in the ITT population were similar (IV = 37.4% versus SC = 42.2%; difference = 4.8%; lower 97.5% CI = -3.3%).

Table 8: Study BO22227 – Results for pCR (primary endpoint) - EPP

	Trastuzumab IV (N=263)	Trastuzumab SC (N=260)
pCR (absence of invasive neoplastic cells in breast)	107 (40.7 %)	118 (45.4 %)
Non-Responders	156 (59.3 %)	142 (54.6 %)
Exact 95% CI for pCR Rate (1)	[34.7; 46.9]	[39.2; 51.7]
Difference in pCR (SC minus IV arm)		4.70
Lower bound one-sided 97.5% CI for the difference in pCR (2)		-4.0

(1) Confidence Interval for one sample binomial using Pearson-Clopper method.

(2) Continuity correction of Anderson and Hauck (1986) has been used in this calculation.

Secondary endpoints

tpCR. While the reported *tpCR* rate was numerically higher in the SC arm (39.2% versus 34.2%; difference = 5.01%; 2-sided 95%CI = -3.5 to 13.5), there are uncertainties about the accuracy of this assessment (see *Comments on pathology assessment protocol* above).

ORR and *TTR* were similar in both arms and the data were too immature to make a meaningful assessment of *EFS* and *OS*. Further analyses of *EFS* and *OS* are planned when all subjects have completed two years and five years of follow-up (after completion of trastuzumab treatment). Submission of these analyses as a Category 1 submission is a condition of registration.

The following additional exploratory analyses were also presented in the study report:

- The previously observed increased pCR rates with ER-negative tumours
- No association between pCR rates and higher Ctrough values (at pre-dose Cycle 8) compared to non-responders
- Analyses of the effects of baseline bodyweight and Ctrough (at pre-dose Cycle 8) on pCR rate. An analysis of pCR rate by quartiles of baseline bodyweight did not suggest reduced efficacy with SC administration in heavier patients. An analysis by Ctrough quartiles suggested that in subjects with low Ctrough levels, pCR rate might be reduced in the SC arm (30% versus 44%). However, in a multiple logistic regression analysis for pCR, which included Ctrough, body weight and treatment arm as covariates, no significant effects were observed.

Efficacy summary

There appears to be equivalence for the shorter term efficacy marker (pCR) between the two formulations following 8 cycles of neoadjuvant treatment. Given trastuzumab has been demonstrated to have a long term effect on survival, the early equivalence is supportive of the two formulations, both having similar efficacy and pCR is an adequate surrogate in this setting. However, this study was not powered to demonstrate longer term efficacy measures such as event-free and overall survival. Factors which might influence efficacy include discontinuations (see below), as these would result in a shorter duration of therapy than the currently recommended 12 months. However, the study was not powered to detect such potential differences in these longer term endpoints.

Clinical Safety

A total of 661 subjects received at least one dose of trastuzumab in the two submitted studies. A total of 355 subjects received at least one SC dose.

The rates of AEs (irrespective of relationship to treatment) were similar with the only notable difference being injection site pain (6.1% versus 0%) and erythema 7.1% versus 2.7%) being more common with SC versus IV administration, respectively. Treatment-related AEs were similar and most easily assessed in the monotherapy adjuvant phase (23% for IV versus 25% for SC).

Deaths were increased in the SC arm compared to the IV arm (3 versus 1) but this did not appear to be attributable to the different formulation.

Serious adverse events were notably increased in the SC arm (22% versus 14%), and this was in both in the neoadjuvant (14.1% versus 10.1%) and adjuvant phase (8.1% versus 3.4%). The incidence of SAEs that were considered related to treatment was comparable; 10% for SC versus 8% for IV.

Comment: this lower rate of attribution argues somewhat against the sponsor's assertion in the Lancet Oncology publication that investigators might have adopted a more conservative attitude to the study arm, attributing SAEs more readily to the SC mode of administration.

There was no pattern suggestive of increasing SAE rates with increasing AUC or decreasing body weight. The results for Grade ≥ 3 AEs were similar. Further analyses of patients with low bodyweights showed that the SAE rate in these subjects was actually lower than the SAE rate in the population as a whole. These data suggest that the higher SAE rate in the SC arm is unlikely to be due to the fixed dose SC regimen producing higher AUC values in low body weight subjects. Multiple logistic regression analyses were conducted comparing the occurrence of SAEs (and Grade ≥ 3 AEs) between treatment arms. AUC (median AUC value of Cycle 7 and 12) and body weight were included as covariates. None of the covariates showed a statistically significant effect on the frequency of SAEs or Grade ≥ 3 AEs.

Discontinuations due to adverse events

Discontinuations due to AEs are a potential risk for diminished efficacy in both the neoadjuvant and adjuvant setting, and certainly in the metastatic setting. The PHARE study¹⁷ demonstrated that 6 months of adjuvant treatment with trastuzumab for early breast cancer was not non-inferior to 12 months of treatment. Women at high risk due to having locally advanced or inflammatory breast cancer, such as in this population (and the populations for which trastuzumab is registered in Australia) are even more likely to need the full 12 months of treatment.

The proportion of patients who developed at least one AE leading to study withdrawal was higher in the SC arm: 2.7% (IV) versus 5.7% (SC). The overall incidence of discontinuation due to left ventricular dysfunction (LVD) was 0.8% (4/297) in the IV arm versus 3.4% (10/298) in the SC arm. There was no clear pattern among the other conditions leading to discontinuations.

Of those 10 withdrawals due to LVD in the SC arm, 2 occurred before the completion of 6 months of treatment (Days 77 and 140), 4 after 6 to 9 months of treatment and the remaining 4 cases discontinued after 9 to 12 months of treatment. Of the 4 subjects in the IV arm who discontinued due to LVD, 1 occurred at the 6 month mark (Day 182), 1 after 6 to 9 months of treatment and the remaining 2 cases stopped after 9 to 12 months of

¹⁷ Lancet Oncol. 2013 Jul;14(8):741-8

treatment. In patients who were withdrawn due to cardiac toxicity, abnormal left ventricular ejection fraction (LVEF) values generally improved to normal after discontinuation of trastuzumab and in some, treatment with anti-failure therapy).

Comment: the treatment duration for 2 subjects (and possibly a third case who discontinued on Day 191 = 6.4 months) in the SC arm would be considered suboptimal compared with one subject in the IV arm. The impact on efficacy of trastuzumab of discontinuation after >6 months but <12 months of treatment is not known. Given the low numbers of LVD discontinuations within each quartile, it is not possible to determine whether there is an increased risk of LVD with the SC formulation or not. The study was not powered to identify differences in the adverse event rates and EFS or OS arising from such discontinuations. Thus this is an area of uncertainty and an important area for pharmacovigilance. The Delegate considers that as a condition of registration, the premature treatment discontinuation due to AEs be included as an identified risk in the RMP for the SC formulation and the sponsor is required to collect postmarketing data about the overall rates of discontinuation and those due to LVD (by quartile of treatment duration) to determine whether a safety signal emerges when used in larger numbers of patients. The sponsor agreed to include the higher rates of discontinuations due to AEs in the Precautions section of the PI, including those due to the higher rate of LVD with the SC formulation although the small numbers of patients involved mean that the relation to SC treatment is uncertain. The sponsor agreed to the Delegate's request that the PI contain a clear statement that the concomitant usage of Herceptin SC with other agents that can affect left ventricular function has not been studied. Given that there is a choice between the IV and SC preparations, it is important that this information is included to ensure prescribers are aware and inform patients of this uncertainty and patients make an informed choice. Inclusion of this uncertainty may also encourage reporting of discontinuations among prescribers. This issue may be further clarified by the Sapphire study, where concomitant pertuzumab and Herceptin SC were given in the metastatic setting; this study is to be submitted for evaluation as soon as the clinical study report is available as a condition of registration.

There are more discontinuations due to respiratory events in the SC arm (3 versus 1) but the numbers are low.

Adverse events of special interest

Cardiac AEs

The proportion of patients who developed at least one cardiac AE was comparable in the two arms: 13.1% (IV) versus 13.5% (SC). Events indicative of cardiac failure (such as LVD and cardiac failure) occurred with comparable frequencies.

Grade ≥ 3 cardiac AEs were slightly higher (1.0% for IV versus 1.7% for SC) as were cardiac SAEs (0.7% for IV versus 1.7% for SC).

LVEF measurements showing the worst overall value for each subject in the Safety Population were similar in the two arms.

Administration-related reactions (ARRs)

ARRs were more common in the SC arm: 47.8% versus 37.2%. In terms of body systems, the excess of events was most prominent in the skin (22.5% versus 30.3%) and respiratory tract (13.8% versus 17.5%). Grade 3 ARR occurred in 6 subjects in the IV arm (2.0%) and 5 subjects in the SC arm (1.7%). Two events of hypersensitivity in the IV arm were classified as serious. There were no serious ARR in the SC arm.

Injection-site reactions

Some 11.1% of subjects experienced a total of 45 events after a total of 4,957 injections. All were Grade 1 or 2.

Laboratory tests, ECG, vital signs

Abnormalities occurred at similar rates between the two arms and there were no new safety signals.

Anti-drug antibodies

Anti-trastuzumab antibodies: At least one positive post-baseline test occurred in 7.1% of subjects in the IV arm (21/296) and 14.6% of subjects in the SC arm (43/295). Of these subjects, 5 in the IV arm and 6 in the SC arm had also had positive results at baseline. Neutralising antibodies were detected post-baseline in 1 subject in the IV arm and 2 subjects in the SC arm. An exploratory analysis showed that antibody-positive subjects did not have notably lower trastuzumab C_{trough} values at pre-dose Cycle 8 or pre-dose Cycle 13 compared to antibody-negative subjects in either the SC or the IV arm. Similarly, there were no apparent differences in rates of pCR or ARRs.

Anti-rHuPH20 antibodies (anti-hyaluronidase antibodies) were detected in 16.3% of SC subjects (48/295). Of these, 21 had also had a positive test at baseline. No neutralising antibodies were detected.

Safety discussion

The main safety issues identified were an apparent increase in serious adverse events in the Herceptin SC arm, although those considered attributable to the treatment occurred at a similar rate between the two therapies. There was an increase in discontinuations which has the potential to adversely affect efficacy. There was a slightly higher rate of discontinuations due to LVD (3% higher in the SC arm) but the study numbers too small for a clear risk to be identified. This is an area of active pharmacovigilance and the sponsor has studies underway which should help clarify this further. Submission of these to the TGA for evaluation is a condition of registration.

Predictably, there were higher rates of local minor injection site irritation but otherwise there were no serious administration-related reactions with the new formulation.

Clinical evaluator's recommendation

The clinical evaluator recommended that the application for the registration of be approved.

Risk management plan

The Post Marketing Surveillance Branch reviewed the EU-RMP version 12.0 dated 19 November 2013 (data lock point 19 November 2013) and the Australian-specific Annex version 1.0 dated February 2014, PSUR from 25 September 2013 to 24 March 2014 (inclusive).

The RMP evaluator and the Delegate requested that the sponsor collect information on early discontinuation due to LVD. LVD is listed as a separate identified risk in the RMP but the sponsor clarified that they are not always informed of early discontinuations and why they occurred.

A number of recommendations for the RMP have been provided by the RMP evaluator and the sponsor should address these matters and follow up where appropriate with the Post Marketing Surveillance Branch.

Risk-benefit analysis

Delegate's considerations

Data Deficiencies/Limitations

The non-inferiority pivotal trial was designed to demonstrate pCR rates and PK of the respective products. It was not powered to demonstrate longer term, more established efficacy endpoints (such as disease-free survival) efficacy nor to detect a difference in less common safety endpoints such as LVD. Postmarketing studies are underway and pharmacovigilance activities are important for these to be determined.

Summary of Issue/s

Demonstration of efficacy equivalence of the SC formulation is reliant upon non-inferiority in the short term outcome, pathological complete response, in the neoadjuvant setting. Demonstration of PK equivalence was a co-primary endpoint. The open-label trial was designed to use pathological complete response rates following completion of the neoadjuvant component as a surrogate for overall benefit; while continued postoperatively, the study was not powered to demonstrate longer term efficacy and safety outcomes. The mature data are still to follow and are required to be submitted to the TGA. Additional postmarketing studies are underway to address this.

1. The co-primary endpoint of non-inferiority of the rates of pCR with Herceptin SC compared to Herceptin IV was achieved.
2. The pharmacokinetic results for the co-primary endpoint, C_{trough} pre-dose Cycle 8, showed non-inferiority of steady-state C_{trough} values for the Herceptin SC arm (fixed dosing) compared to the Herceptin IV arm (body weight adjusted dosing).
3. While there were higher rates of serious adverse events in the Herceptin SC arm, those attributable to the treatment were similar in both arms.
4. Discontinuation rates with the subcutaneous formulation were higher, including for LVD (although the numbers were small, the absolute Herceptin IV arm rates were low and the study was not powered to detect such differences). The PI contains relevant information to inform the prescriber.

There were no PK, efficacy or safety data information regarding outcomes in patients switching from one formulation to another as likely to occur once chemotherapy has been completed. The PrefHER study is designed to address this issue and its submission for evaluation is a condition of registration.

Delegate's proposed action

Following several rounds of PI negotiations (including a mutual stop clock), the application was approved on 13 March 2015 with the conditions of registration listed below in addition to those proposed by the quality evaluator. The sponsor had already agreed to implementation of the EU-RMP version 12.0 dated 19 November 2013 (data lock point 19 November 2013) with Australian-specific Annex version 1.0 dated February 2014, to be revised to the satisfaction of the TGA.

Conditions of registration

The following are proposed as conditions of registration:

1. Submission for evaluation as Category 1 applications of the:
 - a. Two and five year updates of the event-free survival and overall survival for the Hannah (B022227) study as soon as available
 - b. Clinical study report for the PrefHER (M022982) study for evaluation as soon as available
 - c. Clinical study report for the SafeHER study as soon as available
 - d. Clinical study report for the Sapphire study (Herceptin SC with pertuzumab) as soon as available.

Previously agreed Conditions of Registration

1. Implementation of the EU-RMP version 12.0 dated 19 November 2013 (data lock point 19 November 2013) with Australian-specific Annex version 1.0 dated February 2014, to be revised to the satisfaction of the TGA
2. Batch Release Testing by Laboratories Branch

It is a condition of registration that, as a minimum, the first five independent batches of Herceptin SC trastuzumab (rch) 120mg/ml solution for subcutaneous injection (provisional AUST R 220402) imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA's OLSS.

The sponsor should supply:

- i. Certificates of Analysis of all active ingredient (drug substance) and final product
- ii. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included)
- iii. Evidence of the maintenance of registered storage conditions during transport to Australia
- iv. Three containers (usually 3 to 5 vials) of each batch for testing by the Therapeutic Goods Administration together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

This report has been prepared with the generation of an Australian Public Accessible Record in mind, and is intended to include the salient points and incorporate the outcomes of the PI negotiations.

Response from Sponsor

As this application was not referred to the TGA's Advisory Committee on Prescription Medicines (ACPM) for advice, the sponsor did not submit a formal Pre ACPM response. The sponsor has however reviewed the Delegate's Overview (see above) and has agreed it is an appropriate and accurate summary of the decision process.

Advisory Committee Considerations

This application was not referred to the ACPM for advice.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of the new product Herceptin SC trastuzumab (rch) 600 mg/5 mL solution for injection, indicated for:

Early Breast Cancer: Herceptin SC is indicated for the treatment of HER2-positive localised breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.

Locally Advanced Breast Cancer: Herceptin SC is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin.

Metastatic Breast Cancer: Herceptin SC is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:

- *as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;*
- *in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or*
- *in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer*

Specific conditions of registration applying to these goods

1. The trastuzumab EU Risk Management Plan (RMP), version 12.0 dated 19 November 2013 (data lock point 19 November 2013) with Australian-specific Annex version 1.0 dated February 2014, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. Batch Release Testing by OLSS As a minimum, the first five independent batches of Herceptin SC trastuzumab (rch) 120 mg/mL solution for subcutaneous injection (provisional AUST R 220402) imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by OLSS, TGA.
3. Submission for evaluation, each as Category I applications
 - a. 2 and 5 year updates of the event-free survival and overall survival for the HannaH (B022227) study as soon as available.
 - b. Clinical study report for the PrefHER (M022982) study for evaluation as soon as available.
 - c. Clinical study report for the SafeHER study as soon as available.
 - d. Clinical study report for the Sapphire study (Herceptin SC with pertuzumab) as soon as available.

Attachment 1. Product Information

The Product Information approved for Herceptin at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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