NEW ZEALAND DATA SHEET

1. PRODUCT NAME

TRAZIMERA™ 150 mg powder for concentrate for solution for infusion

TRAZIMERA™ 440 mg powder for concentrate for solution for infusion

TRAZIMERA is a biosimilar medicine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRAZIMERA 150 mg vial contains 150 mg trastuzumab.

TRAZIMERA 440 mg vial contains 440 mg trastuzumab and delivers 420 mg of trastuzumab; each vial of solvent contains 20 mL of bacteriostatic water for injection.

The reconstituted TRAZIMERA solution contains 21 mg/mL of trastuzumab.

The humanized antibody against human epidermal growth factor receptor 2 protein (HER2) is produced by recombinant mammalian cells (Chinese hamster ovary (rch)) in suspension culture in a nutrient medium and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

TRAZIMERA is a biosimilar medicine to HERCEPTIN®. The prescribing physician should be involved in any decision regarding interchangeability with other products. Additional information is available at www.medsafe.govt.nz/profs/RIss/Biosimilars.asp

For information on comparative studies, see sections 5.1 and 5.2.

Excipient with known effect

Each vial of solvent (bacteriostatic water for injection) contains benzyl alcohol 1.1% (220 mg) as preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White lyophilised powder or cake.

TRAZIMERA 440mg solvent is a clear to slightly opalescent liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic breast cancer

TRAZIMERA 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; or

- 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.

Early breast cancer

TRAZIMERA is indicated for the treatment of patients with:

- HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy, followed by adjuvant TRAZIMERA; or
- HER2-positive early breast cancer following surgery, sequentially or concurrently with chemotherapy and, if applicable, radiotherapy.

TRAZIMERA should only be used in early breast cancer patients with a normal left ventricular ejection fraction.

Advanced gastric cancer

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

4.2 Dose and method of administration

Dose

HER2 testing is mandatory prior to initiation of TRAZIMERA therapy (see Detection of HER2 overexpression or gene amplification).

Breast cancer

TRAZIMERA may be used in **metastatic breast cancer** with the once weekly dose schedule, or the, alternative three-weekly schedule. The alternative schedule has been tested in clinical trials but has not been compared directly with the standard weekly regimen.

For treatment of **early breast cancer,** either the once weekly schedule or the three-weekly schedule, with loading and subsequent doses, may be used.

Once weekly dose schedule

Loading dose

The recommended initial loading dose of TRAZIMERA is 4 mg/kg body weight administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see section 4.8). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses

The recommended weekly maintenance dose of TRAZIMERA is 2 mg/kg body weight. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see section 4.8).

Three-weekly dose schedule

Loading dose

The recommended initial loading dose of TRAZIMERA is 8 mg/kg body weight administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see section 4.8). Interruption of the infusion and/or medication may help to control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses

The recommended three-weekly maintenance dose of TRAZIMERA is 6 mg/kg body weight administered as a 90-minute intravenous infusion. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion. Patients should be observed for fevers and chills or other infusion- associated symptoms (see section 4.8).

Switching patients from established weekly schedule to three-weekly doses

The first 6 mg/kg dose should be given a week after the last 2 mg/kg dose. As a precaution, all 6 mg/kg doses should be administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see section 4.8). Interruption of the infusion and/or medication may help to control such symptoms. The infusion may be resumed when symptoms abate. Subsequent maintenance doses of 6 mg/kg are given three-weekly.

Advanced gastric cancer

Initial loading dose of TRAZIMERA is 8 mg/kg body weight, followed by 6 mg/kg body weight three weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

In clinical trials, patients with advanced gastric cancer were treated with TRAZIMERA until progression of disease.

Refer to section 5.1 Clinical trials, Advanced gastric cancer for chemotherapy combination dosing.

Duration of treatment

In clinical studies, patients with metastatic breast cancer or advanced gastric cancer were treated with TRAZIMERA until progression of disease. Patients with early breast cancer should be treated for 1 year or until disease recurrence, whichever occurs first. Extending treatment in early breast cancer beyond one year is not recommended. Treatment should be discontinued for any patient experiencing unmanageable toxicity.

Missed doses

If the patient has missed a dose of TRAZIMERA by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent TRAZIMERA maintenance doses should then be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of TRAZIMERA by more than one week, a re-loading dose of TRAZIMERA should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent TRAZIMERA maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

Dose modification

If the patient develops an infusion-related reaction (IRR), the infusion rate of TRAZIMERA IV may be slowed or interrupted (see section 4.4). No reductions in the dose of TRAZIMERA were made during

clinical trials. Patients may continue TRAZIMERA therapy during periods of reversible, chemotherapy-induced myelosuppression, but they should be monitored carefully for complications of neutropenia during this time. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

Special dosage instructions

Elderly

Data suggest that the disposition of TRAZIMERA is not altered based on age (see section 5.2). In clinical trials, patients ≥65 years of age did not receive reduced doses of TRAZIMERA.

Children

The safety and efficacy of TRAZIMERA in paediatric patients <18 years of age have not been established.

Detection of HER2 overexpression or gene amplification

TRAZIMERA should only be used in patients whose tumours have HER2 overexpression or HER2 gene amplification.

To ensure accurate and reproducible results, testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures.

HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks. HER2 gene amplification should be detected using *in situ* hybridisation (ISH) of fixed tumour blocks. Examples of ISH include fluorescence *in situ* hybridisation (FISH), chromogenic *in situ* hybridisation (CISH) and silver *in situ* hybridisation (SISH).

For any other method to be used for the assessment of HER2 protein or gene expression, the test method must be precise and accurate enough to demonstrate overexpression of HER2 (it must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) HER2 overexpression).

For full instructions on assay performance and interpretation please refer to the package inserts of validated FISH, CISH and SISH assays. Official recommendations on HER2 testing may also apply.

Breast cancer

TRAZIMERA treatment is only appropriate if there is strong HER2 overexpression, as described by a 3+ score by IHC or a positive ISH result. For patients with an intensity score of 2+ on IHC, confirmation of HER2 positive status by ISH is mandatory.

Advanced gastric cancer

TRAZIMERA treatment is only appropriate if there is HER2 overexpression, as described by a 3+ IHC score. For cases with a score of less than 3+ by IHC, confirmation of HER2 positive status by ISH is mandatory.

Bright-field ISH technology is recommended for advanced gastric cancer samples to enable evaluation of tumour histology and morphology in parallel. Either FISH or SISH are recommended for detecting HER2 gene amplification in advanced gastric cancer tissue.

Method of administration

In order to prevent medication errors, it is important to check the vial labels to ensure the medicine being prepared and administered is TRAZIMERA (trastuzumab) and not KADCYLA® (trastuzumab emtansine).

TRAZIMERA should be administered by a healthcare professional prepared to manage anaphylaxis and adequate life support facilities should be available. Treatment may be administered in an outpatient setting.

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded in the patient's medical record. Substitution by any other biological medicinal product requires the consent of the prescribing physician.

TRAZIMERA should be administered as an intravenous infusion.

DO NOT ADMINISTER TRAZIMERA AS AN INTRAVENOUS PUSH OR BOLUS.

The reconstituted TRAZIMERA results in a clear to slightly opalescent and colourless to pale yellow-brown solution and should be essentially free of visible particles.

For instructions on reconstitution and dilution of the medicine before administration, see section 6.6.

4.3 Contraindications

TRAZIMERA is contraindicated in patients with known hypersensitivity to trastuzumab or to any of its excipients.

4.4 Special warnings and precautions for use

General

TRAZIMERA therapy should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

Hypersensitivity reactions including anaphylaxis

Severe hypersensitivity reactions have been infrequently reported in patients treated with trastuzumab. Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. The onset of symptoms generally occurred during an infusion, but there have also been reports of symptom onset after the completion of an infusion. Reactions were most commonly reported in association with the initial infusion.

Patients should be observed closely for hypersensitivity reactions. trastuzumab infusion should be interrupted in all patients with severe hypersensitivity reactions. In the event of a hypersensitivity reaction, appropriate medical therapy should be administered, which may include adrenaline, corticosteroids, antihistamines, bronchodilators and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Infusion-related reactions (IRRs)

IRRs are known to occur with the administration of trastuzumab (see section 4.8).

Pre-medication may be used to reduce risk of occurrence of IRRs.

Serious IRRs to trastuzumab infusion including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress and supraventricular tachyarrhythmia have been reported (see section 4.8).

Patients should be observed for IRRs. Interruption of an IV infusion may help control such symptoms and the infusion may be resumed when symptoms abate. These symptoms can be treated with an analgesic/antipyretic such as paracetamol and an antihistamine. Serious reactions have been treated successfully with supportive therapy such as oxygen, intravenous fluids, beta-agonists and

corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome.

In other patients with acute onset of signs and symptoms, initial improvement was followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours or up to one week following an infusion.

Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy or comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab (see Pulmonary reactions below).

Pulmonary reactions

Severe pulmonary events leading to death have been reported with the use of trastuzumab in the post-marketing setting. These events may occur as part of an infusion-related reaction (see Infusion-related reactions (IRRs)), hypersensitivity reactions including anaphylaxis, or with delayed onset. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported.

Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients with dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with trastuzumab.

Cardiac dysfunction

General considerations

Patients treated with trastuzumab are at increased risk of developing congestive heart failure (CHF) (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death (see section 4.8). In addition, caution should be exercised in treating patients with increased cardiac risk (e.g. hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age).

Population pharmacokinetic model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab IV or trastuzumab SC treatment (see section 5.2). Patients who receive anthracycline after stopping trastuzumab may also be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Candidates for treatment with trastuzumab, especially those with prior exposure to anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, ECG and echocardiogram or MUGA scan. Monitoring may help to identify patients who develop cardiac dysfunction, including signs and symptoms of CHF. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatments until 24 months from the last administration of trastuzumab.

If Left Ventricular Ejection Fraction (LVEF) percentage drops 10 points from baseline and to below 50%, trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or clinically significant CHF has developed, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6-8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy unless the benefits for the individual patient are deemed to outweigh the risks.

The safety of continuation or resumption of trastuzumab in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with the standard medications for this purpose. In the pivotal trials most patients who developed heart failure improved with standard heart failure treatment consisting of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a β-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on weekly therapy with trastuzumab without additional clinical cardiac events.

Early breast cancer

For patients with early breast cancer, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab. In patients who receive anthracycline-containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of trastuzumab, or longer if a continuous decrease of LVEF is observed.

Patients with history of myocardial infarction (MI), angina pectoris requiring medication, history of or present CHF (NYHA Class II-IV), other cardiomyopathy, cardiac arrhythmia requiring medication, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medication eligible), and haemodynamic effective pericardial effusion were excluded from adjuvant breast cancer clinical trials with trastuzumab.

Neoadjuvant-adjuvant treatment

In patients with early breast cancer eligible for neoadjuvant-adjuvant treatment, trastuzumab should only be used concurrently with anthracyclines in chemotherapy-naive patients and only with low-dose anthracycline regimens, i.e. with maximum cumulative doses of doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2.

If patients have been treated concurrently with low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery.

Clinical experience in the neoadjuvant-adjuvant setting is limited in patients above 65 years of age.

Adjuvant treatment

Trastuzumab and anthracyclines should not be given concurrently in the adjuvant treatment setting.

In patients with early breast cancer an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when trastuzumab was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin. The incidence was more marked when trastuzumab was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months.

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (>50 years), low level of baseline and declining LVEF (<55%), low LVEF prior to or following the initiation of paclitaxel treatment, trastuzumab treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving trastuzumab after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of trastuzumab and a high body mass index (BMI) (>25 kg/m^2).

Metastatic breast cancer

Trastuzumab and anthracycline should not be given concurrently in the metastatic breast cancer setting.

Advanced gastric cancer

In advanced gastric cancer, patients with a history of documented congestive heart failure, angina pectoris requiring medication, evidence of transmural myocardial infarction on ECG, poorly controlled hypertension (systolic BP >180 mmHg or diastolic BP >100 mmHg), clinically significant valvular heart disease, high risk uncontrollable arrhythmias, baseline LVEF <50% (measured by echocardiography or MUGA) were excluded from Study BO18255 (ToGA) according to the study protocol.

Benzyl alcohol

Benzyl alcohol, used as a preservative in Bacteriostatic Water for Injection in the 440 mg multidose vial, has been associated with toxicity in neonates and children up to 3 years old. When administering trastuzumab to a patient with a known hypersensitivity to benzyl alcohol, trastuzumab should be reconstituted with water for injection, and only one dose per trastuzumab vial should be used. Any unused portion must be discarded. Sterile water for injection, used to reconstitute the 150 mg single dose vials, does not contain benzyl alcohol.

4.5 Interaction with other medicines and other forms of interaction

No formal interaction studies have been performed with trastuzumab in humans. Clinically significant interactions between trastuzumab and the concomitant medication used in clinical trials have not been observed. A comparison of serum levels of trastuzumab given in combination with cisplatin, doxorubicin or epirubicin-plus-cyclophosphamide has not suggested the possibility of any interaction.

Administration of paclitaxel in combination with trastuzumab resulted in a slightly less than two-fold decrease in trastuzumab clearance in a non-human primate study and in a 1.5-fold increase in trastuzumab serum levels in clinical studies. Paclitaxel pharmacokinetics determined during the fourth cycle of the alternative 3-weekly trastuzumab regimen (n=25) were not altered appreciably, relative to parameters determined during the initiation of paclitaxel, prior to introduction of trastuzumab. Similarly, docetaxel pharmacokinetics determined during the first dose of trastuzumab in the standard weekly regimen (n=10) were not altered appreciably relative to those determined 2 weeks earlier for docetaxel alone.

A pharmacokinetic interaction substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer showed that co-administration of trastuzumab and capecitabine and cisplatin had no significant effects on the pharmacokinetics of the two chemotherapy agents compared with co-administration of the two agents without trastuzumab. The pharmacokinetics of trastuzumab were not evaluated in this study.

4.6 Fertility, pregnancy and lactation

Fertility

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab and have revealed no evidence of impaired fertility or harm to the foetus. However, when assessing the risk of reproductive toxicity to humans, it is also important to consider the significance of the rodent form of the HER2 receptor in normal embryonic development and the embryonic death in mutant mice lacking this receptor. Placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (days 120-150 of gestation) foetal development period was observed.

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab and for at least 7 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the foetus.

If a pregnant woman is treated with trastuzumab, becomes pregnant while receiving trastuzumab or within 7 months following the last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable.

Pregnancy - Pregnancy Category D

Trastuzumab should be avoided during pregnancy and as trastuzumab may persist in the circulation for up to 7 months, pregnancy should be avoided for 7 months after the last dose of trastuzumab, unless the anticipated benefit for the mother outweighs the unknown risk to the foetus.

In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab.

Lactation

It is not known whether trastuzumab is secreted in human breast milk. As human IgG is secreted into human breast milk, and the potential for harm to the infant is unknown, breast-feeding should be avoided during trastuzumab therapy and for 7 months after the last dose of trastuzumab (see section 5.3).

4.7 Effects on ability to drive and use machinery

Trastuzumab may have a minor influence on the ability to drive or use machines (see section 4.8). Patients experiencing infusion-related symptoms should be advised not to drive or use machines until symptoms resolve completely.

4.8 Undesirable effects

Table 1 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of trastuzumab alone, or in combination with chemotherapy in the below pivotal clinical trials as well as in the post-marketing setting.

The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Early breast cancer

- **BO16348 (HERA)**: trastuzumab arm (n=1678). Control arm (n=1708)
- **B-31/N9831 Joint Analysis**: trastuzumab arms (n=2345). Control arm (n=1673)
- **BCIRG 006**: trastuzumab arm (n=2133). Control arm (n=1041)
- **BO16216 (TanDEM)**: trastuzumab arm (n=161). Control arm (n=161)
- **MO16432 (NOAH)**: trastuzumab arm (n=115). Control arm (n=116)

Metastatic breast cancer

- **H0648g/H0649g**: trastuzumab arms (n=469 and n=222 respectively)
- **M77001**: trastuzumab arm (n=92). Control arm (n=94).

Advanced gastric cancer

- **BO18255 (ToGA)**: trastuzumab arm (n=294). Control arm (n=290)

All terms included are based on the highest percentage seen in pivotal clinical trials.

Table 1: Summary of adverse drug reactions occurring in patients treated with trastuzumab in clinical trials and in the post-market setting

System organ class	Adverse reaction[1]	Frequency
Infections and infestations	Nasopharyngitis	Very common
	Infection	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Herpes zoster	Common
	Influenza	Common
	Pharyngitis	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Erysipelas	Common
	Cellulitis	Common
	Sepsis	Uncommon
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Febrile neutropenia	Very common
	Anaemia	Very common
	Thrombocytopenia	Very common
	White blood cell count decreased / leukopenia	Very common
	Neutropenia	Very common
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Immune system disorders	Hypersensitivity	Common
	[2]Anaphylactic reaction	Not known
	[2]Anaphylactic shock	Not known
Metabolism and nutrition disorders	Weight decreased/weight loss	Very common
	Weight increased	Very common
	Decreased appetite	Very common
	Anorexia	Very common
	Hyperkalaemia	Not known
	Tumour lysis syndrome	Not known
Psychiatric disorders	Insomnia	Very common
	Depression	Common
	Anxiety	Common
	Thinking abnormal	Common
Nervous system disorders	Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Dysgeusia	Very common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Peripheral neuropathy	Common

System organ class	Adverse reaction[1]	Frequency
	Hypertonia	Common
	Somnolence	Common
	Ataxia	Common
	Paresis	Rare
	Brain oedema	Not known
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and Labyrinth Disorders	Deafness	Uncommon
Cardiac disorders	[3]Blood pressure decreased	Very common
	[3]Blood pressure increased	Very common
	[3]Heart beat irregular	Very common
	[3]Palpitation	Very common
	[3]Cardiac flutter	Very common
	[4]Ejection fraction decreased	Very common
	[2]Cardiac failure (congestive)	Common
	[2,3]Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Pericarditis	Not known
	Bradycardia	Not known
	Gallop rhythm present	Not known
Vascular disorders	Lymphoedema	Very common
	Hot flush	Very common
	[2,3]Hypotension	Common
	Hypertension	Common
	Vasodilation	Common
Respiratory, thoracic and mediastinal disorders	[2,3]Wheezing	Very common
	[2]Dyspnoea	Very common
	Cough	Very common
	Epistaxis	Very common
	Rhinorrhoea	Very common
	Oropharyngeal pain	Very common
	Asthma	Common
	Lung disorder	Common
	[2]Pleural effusion	Common
	[2]Pneumonia	Common
	Pneumonitis	Rare
	[2]Pulmonary fibrosis	Not known
	[2]Respiratory distress	Not known
	[2]Respiratory failure	Not known

System organ class	Adverse reaction[1]	Frequency
	[2]Lung infiltration	Not known
	[2]Acute pulmonary oedema	Not known
	[2]Acute respiratory distress syndrome	Not known
	[2]Bronchospasm	Not known
	[2]Hypoxia	Not known
	[2]Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	[2]Orthopnoea	Not known
	Pulmonary oedema	Not known
	Interstitial lung disease	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	Lip swelling	Very common
	Abdominal pain	Very common
	Stomatitis	Very common
	Constipation	Very common
	Dyspepsia	Very common
	Pancreatitis	Common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular injury	Common
	Hepatitis	Common
	Liver tenderness	Common
	Jaundice	Rare
	Hepatic failure	Not known
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	Swelling face	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Nail disorder	Very common
	Alopecia	Very common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Acne	Common
	Onychoclasis	Common
	Pruritus	Common
	Dermatitis	Common
	Urticaria	Common
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck pain	Common

System organ class	Adverse reaction[1]	Frequency
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like illness	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Peripheral oedema	Very common
	Mucosal inflammation	Very common
	Malaise	Common
	Oedema	Common
Injury, poisoning and procedural complications	Nail toxicity	Very common
	Contusion	Common

[1] Adverse drug reactions (ADRs) were identified as events that occurred with at least a 2% difference compared to the control arm in at least one of the major randomised clinical trials.

[2] Denotes adverse reactions that have been reported in association with a fatal outcome.

[3] Denotes adverse reactions that are reported largely in association with infusion-related reactions. Specific percentages for these are not available.

[4] Observed with combination therapy following anthracyclines and combined with taxanes.

The following information is relevant to all indications:

Infusion-related reactions (IRRs) and hypersensitivity

IRRs such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress were seen in all trastuzumab clinical trials (see section 4.4).

IRRs may be clinically difficult to distinguish from hypersensitivity reactions.

The rate of IRRs of all grades varied between studies depending on the indication, whether trastuzumab was given concurrently with chemotherapy or as monotherapy and data collection methodology.

In early breast cancer, the rate of IRRs ranged from 18% to 54% in the trastuzumab-containing arm compared to 6% to 50% in the comparator arm (which may have contained other chemotherapy). Severe reactions (Grade 3 and above) ranged from 0.5% to 6% in the trastuzumab-containing arm compared to 0.3% to 5 % in the comparator arm.

In metastatic breast cancer, the rate of IRRs ranged from 49% to 54% in the trastuzumab-containing arm compared to 36% to 58% in the comparator arm (which may have contained other chemotherapy). Severe reactions (Grade 3 and above) ranged from 5 % to 7% in the trastuzumab-containing arm compared to 5% to 6% in the comparator arm.

Anaphylactoid reactions were observed in isolated cases.

Cardiac dysfunction

Congestive heart failure (NYHA Class II-IV) is a common adverse reaction to trastuzumab. It has been associated with fatal outcome. Signs and symptoms of cardiac dysfunction, such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with trastuzumab (see section 4.4).

Early breast cancer

Neoadjuvant-adjuvant setting

In the pivotal trial MO16432 (NOAH), trastuzumab was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2), the incidence of symptomatic cardiac dysfunction was 1.7 % in the trastuzumab arm.

Adjuvant setting

In 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy the incidence of NCI-CTC Grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone and in patients who were administered trastuzumab after a taxane (0.3-0.4%). The rate was highest in patients who were administered trastuzumab concurrently with a taxane (2.0%). At 3 years, the cardiac event rate in patients receiving AC→P (doxorubicin plus cyclophosphamide followed by paclitaxel) + H (trastuzumab) was estimated at 3.2%, compared with 0.8% in AC→P treated patients. No increase in the cumulative incidence of cardiac events was seen with further follow-up at 5 years.

At 5.5 years, the rates of symptomatic cardiac or LVEF events were 1.0%, 2.3%, and 1.1% in the AC → D (doxorubicin plus cyclophosphamide, followed by docetaxel), AC → DH (doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab), and DCarbH (docetaxel, carboplatin and trastuzumab) treatment arms, respectively. For symptomatic CHF (NCT-CTC Grade 3-4), the 5-year rates were 0.6%, 1.9%, and 0.4% in the AC→D, AC→DH, and DCarbH treatment arms, respectively. The overall risk of developing symptomatic cardiac events was low and similar for patients in AC→D and DCarbH arms; relative to both the AC→D and DCarbH arms there was an increased risk of developing a symptomatic cardiac event for patients in the AC→DH arm, being discernible by a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events up to 2.3% compared to approximately 1% in the two comparator arms (AC→D and DCarbH).

When trastuzumab was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6% of patients in the 1-year arm after a median follow-up of 12 months. After a median follow-up of 3.6 years the incidence of severe CHF and left ventricular dysfunction after 1-year trastuzumab therapy remained low at 0.8% and 9.8%, respectively.

In Study BO16348, after a median follow-up of 8 years, the incidence of severe CHF (NYHA Class III & IV) in the trastuzumab 1-year treatment arm was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥50% after the event) was evident for 71.4% of trastuzumab-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of trastuzumab-treated patients. Approximately 17% of cardiac dysfunction related events occurred after completion of trastuzumab.

In the joint analysis of Studies NSABP B-31 and NCCTG N9831, with a median follow-up of 8.1 years for the AC→PH group (doxorubicin plus cyclophosphamide, followed by paclitaxel plus trastuzumab), the per patient incidence of new onset cardiac dysfunction, as determined by LVEF, remained unchanged compared to the analysis performed at a median follow-up of 2.0 years in the AC→PH group: 18.5% of AC→PH patients with an LVEF decrease of ≥10% to below 50%. Reversibility of left ventricular dysfunction was reported in 64.5% of patients who experienced a symptomatic CHF in the

AC→PH group being asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.

Metastatic breast cancer

Depending on the criteria used to define cardiac dysfunction, the incidence in the pivotal metastatic trials varied between 9% and 12% in the trastuzumab + paclitaxel subgroup, compared with 1%-4% in the paclitaxel alone subgroup. For trastuzumab monotherapy, the rate was 6%-9%. The highest rate of cardiac dysfunction was seen in patients receiving trastuzumab + anthracycline/cyclophosphamide (27%), and was significantly higher than in the anthracycline/cyclophosphamide alone subgroup (7%-10%). In Study M77001 with prospective monitoring of cardiac function, the incidence of symptomatic heart failure was 2.2% in patients receiving trastuzumab and docetaxel, compared with 0% in patients receiving docetaxel alone. Most of the patients (79%) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for heart failure.

Advanced gastric cancer

In Study BO18255 (ToGA), at screening, the median LVEF value was 64% (range 48%-90%) in the FP arm and 65% (range 50%-86%) in the trastuzumab + FP arm.

The majority of the LVEF decreases noted in BO18255 Study (ToGA) were asymptomatic, with the exception of 1 patient in the trastuzumab arm whose LVEF decrease coincided with cardiac failure.

Table 2: Summary of LVEF change from baseline (BO18255 study)

LVEF decrease[#]: Lowest post-screening value	**FP (n=290) (% of patients in each treatment arm)**	**FP+H (n=294) (% of patients in each treatment arm)**
LVEF decrease ≥10% to <50%	1.1%	4.6%
Absolute value <50%	1.1%	5.9%
LVEF decrease ≥10% to ≥50%	11.8%	16.5%

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + trastuzumab;

[#]Only includes patients whose method of assessment at that visit is the same as at their initial assessments (FP: n=187 and FP+H: n=237).

Table 3: Cardiac adverse events (BO18255 study)

	FP (n=290) (% of patients in each treatment arm)	**FP+H (n=294) (% of patients in each treatment arm)**
Total Cardiac Events	6%	6%
≥Grade 3 NCI-CTC(v3.0) criteria	3%[a]	1%[b]

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + trastuzumab;

[a] 9 patients experienced 9 Events;

[b] 4 patients experienced 5 Events.

Overall, there were no significant differences in cardiac dysfunction between the treatment arm and the comparator arm.

Haematological toxicity

Breast cancer

Monotherapy – Study H0649g

Haematological toxicity is infrequent following the administration of trastuzumab monotherapy in the metastatic setting, WHO Grade 3 leucopenia, thrombocytopenia and anaemia occurring in <1% of patients. No WHO Grade 4 toxicities were observed.

Combination therapy – Studies H0648g and M77001

WHO Grade 3 or 4 haematological toxicity was observed in 63% of patients treated with trastuzumab and an anthracycline/cyclophosphamide compared to an incidence of 62% in patients treated with the anthracycline/cyclophosphamide combination without trastuzumab.

There was an increase in WHO Grade 3 or 4 haematological toxicity in patients treated with the combination of trastuzumab and paclitaxel compared with patients receiving paclitaxel alone (34% vs. 21%). Haematological toxicity was also increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32% Grade 3/4 neutropenia versus 22%, using HCl-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with trastuzumab + docetaxel (23% versus 17% for patients treated with docetaxel alone).

Early breast cancer setting – BO16348 (HERA) study

Using NCI-CTC criteria, in the HERA trial, 0.4% of trastuzumab-treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

Advanced gastric cancer

The most frequently reported adverse events categorised under the Blood and Lymphatic System Disorders SOC (Grade ≥3) are shown below (Table 4) by trial treatment.

Table 4: Blood and Lymphatic System Disorders (SOC) adverse events >1%

	FP (n=290) (% of patients in each treatment arm)	**FP+H (n=294) (% of patients in each treatment arm)**
Neutropenia	30%	27%
Anaemia	10%	12%
Febrile neutropenia	3%	5%
Thrombocytopenia	3%	5%

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + trastuzumab.

The total percentage of patients who experienced an adverse event of ≥Grade 3 NCI CTCAE v3.0 categorised under this SOC were 38% in the FP arm and 40% in the FP+H arm.

Overall, there were no significant differences in haematotoxicity between the treatment arm and the comparator arm.

Hepatic and renal toxicity

Breast cancer

WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of trastuzumab as single agent, in the metastatic setting. This toxicity was associated with progression of disease in the liver in 60% of these patients.

WHO Grade 3 or 4 hepatic toxicity was less frequently observed among patients receiving trastuzumab and paclitaxel than among patients receiving paclitaxel (7% compared with 15%). No WHO Grade 3 or 4 renal toxicity was observed.

Advanced gastric cancer

In Study BO18255 (ToGA) no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

NCI-CTCAE (v3.0) Grade ≥3 renal toxicity was not significantly higher in patients receiving trastuzumab than those in the fluoropyrimidine/cisplatin arm (3% and 2% respectively).

NCI-CTCAE (v3.0) Grade ≥3 adverse events in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported adverse event and was not significantly higher in patients receiving trastuzumab than those in the fluoropyrimidine/cisplatin arm (1% and <1% respectively).

Diarrhoea

Breast cancer

Monotherapy – Study H0649G

Of patients treated with trastuzumab monotherapy in the metastatic setting, 27% experienced diarrhoea.

In the HERA trial (median follow-up 1 year), 7% of trastuzumab-treated patients had diarrhoea.

Combination therapy – Studies H0648g and M77001

An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has been observed in patients receiving trastuzumab in combination with chemotherapy compared with patients receiving chemotherapy-alone or trastuzumab alone.

Early breast cancer setting – HERA study

In the HERA trial, 8% of trastuzumab treated patients experienced diarrhoea during the first year of treatment.

Advanced gastric cancer

In Study BO18255 (ToGA), 109 patients (37%) in the trastuzumab treatment arm versus 80 patients (28%) in the comparator arm experienced any grade diarrhoea. Four percent (4%) of patients in the fluoropyrimidine/cisplatin arm experienced Grade ≥3 diarrhoea vs. 9% in the trastuzumab arm.

Infection

An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, has been observed primarily in patients treated with trastuzumab + paclitaxel compared with patients receiving paclitaxel alone or trastuzumab-alone.

Immunogenicity

In the neoadjuvant-adjuvant EBC study (BO22227), at a median follow-up exceeding 70 months, 10.1% (30/296) of patients treated with intravenous trastuzumab developed antibodies against trastuzumab. Neutralising anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the trastuzumab intravenous arm.

The clinical relevance of these antibodies is not known. The presence of anti-trastuzumab antibodies had no impact on pharmacokinetics, efficacy (determined by pathological complete response [pCR] and event-free survival [EFS]) and safety determined by occurrence of administration related reactions (ARRs) of intravenous trastuzumab.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

There is no experience with overdosage in human clinical trials. Single doses higher than 10 mg/kg have not been tested.

Treatment of overdose should consist of general supportive measures.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC03

Mechanism of action

Trastuzumab is a recombinant humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG_1 isotype that contains human framework regions with the complementarity-determining regions of a murine anti-p185 HER2 antibody that binds to HER2.

The HER2 proto-oncogene or c-erbB2 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 15%-20% of primary breast cancer. The overall rate of HER2 positivity in advanced gastric cancer as observed during screening for Study BO18255 is 15% for IHC3+ and IHC2+/FISH+ or 22.1% when applying the broader definition of IHC3+ or FISH+. 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 protein.

Studies indicate that patients whose tumours have amplification or overexpression of HER2 have a shortened disease-free survival compared to patients whose tumours do not have amplification or overexpression of 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.

Clinical trials

Early Breast Cancer

Trastuzumab in combination with neoadjuvant-adjuvant chemotherapy

The use of trastuzumab for the neoadjuvant-adjuvant treatment of locally advanced breast cancer has been studied in Study MO16432 (NOAH), a multicentre randomised trial, designed to investigate the concurrent administration of trastuzumab with neoadjuvant chemotherapy, including both an anthracycline and a taxane, followed by adjuvant trastuzumab, up to a total treatment duration of 1 year. The trial recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory breast cancer. Patients with HER2+ tumours were randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant trastuzumab (n=116), or neoadjuvant chemotherapy alone (n=118).

Trastuzumab was administered concurrently with 10 cycles of neoadjuvant chemotherapy as follows;

- Doxorubicin (60 mg/m^2) and paclitaxel (150 mg/m^2) in combination with trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg maintenance, administered 3-weekly) for 3 cycles, followed by
- Paclitaxel (175 mg/m^2) and trastuzumab (6mg/kg, administered 3-weekly) for 4 cycles, followed by
- CMF on day 1 and 8 every 4 weeks for 3 cycles, in combination with 4 cycles of trastuzumab (6mg/kg administered 3-weekly), followed by

- up to 7 additional cycles of trastuzumab (6mg/kg, administered 3-weekly) alone to complete 1 year after starting trastuzumab

The primary endpoint for the study, event-free survival (EFS), was defined as the time from randomisation to disease recurrence or progression (local, regional, distant or contralateral), or death of any cause. The efficacy results from NOAH (full analysis population, defined as all patients who were randomised in the study following the intent-to-treat principle, with the exception of 3 patients whose data could not be evaluated) are summarised in the table below. The median duration of follow-up in the trastuzumab arm was 3.8 years.

Table 5: Overview of efficacy analyses MO16432 (NOAH)

Parameter	Chemo + trastuzumab n=115	Chemo only n=116	p-value	HR (95% CI)
Event-free survival (EFS) No. patients with event	46	59	p=0.0275	0.65 (0.44, 0.96)
Total pathological complete response^ (95% CI)	40% (31.0, 49.6)	20.7% (13.7, 29.2)	p=0.0014	

^ defined as absence of any invasive cancer both in the breast and axillary nodes;
HR: hazard ratio.

The addition of trastuzumab to neoadjuvant chemotherapy, followed by adjuvant trastuzumab for a total duration of 52 weeks, resulted in a 35% reduction in the risk of disease recurrence/progression. The hazard ratio translates into an absolute benefit, in terms of 3-year event-free survival rate estimates of 13 percentage points (65 % vs. 52 %) in favour of the trastuzumab arm.

To date, results are not available comparing the efficacy of trastuzumab administered with chemotherapy in the adjuvant setting with that obtained in the neoadjuvant/adjuvant setting.

Trastuzumab in combination with adjuvant chemotherapy

The use of trastuzumab in the setting of early breast cancer (after surgery and in association with chemotherapy and, if applicable radiotherapy) has been studied in four multicentre, randomised, phase III trials of patients with HER2 positive breast cancer who have completed surgery. In these clinical trials, localised breast cancer was limited to operable, primary adenocarcinoma of the breast with positive axillary nodes or node negative disease with additional indicators of a higher degree of risk.

The design of these studies is summarised in Table 6 and efficacy results are presented in Tables 7-10.

Table 6: Clinical trials in early breast cancer

	HERA trial n=3386	NSABB B-31 and NCCTG N9831 trials (joint analysis) n=3763	BCIRG 006 n=3222
Eligible patients	Node positive or node negative [n=1098] and tumour size >1 cm; *Protocol initially unrestricted but amended and node negative patients with tumours ≤1 cm [n=93, 8.5%] and node negative patients with tumours >1 and ≤2 cm [n=509,46.4%] were included*	Node positive or node negative [n=190] and tumour size • >2 cm regardless of hormonal status; or • >1 cm and ER–ve (n=63 node-negative and tumour size ≤2 cm)	Node positive or node negative and at least 1 of the following: • tumour size >2 cm and ER and PR -ve, or • histologic and/or nuclear grade 2-3, or • age <35 years.

	HERA trial n=3386	NSABB B-31 and NCCTG N9831 trials (joint analysis) n=3763	BCIRG 006 n=3222
Trastuzumab dosage regimen	Loading dose 8 mg/kg, followed by 6 mg/kg (q3w)	Loading dose 4 mg/kg, followed by 2 mg/kg (q1w)	Loading dose 4 mg/kg, followed by 2 mg/kg (q1w). After chemo, 6 mg/kg (q3w)
Duration of trastuzumab treatment	1yr or 2yrs	52 weeks	52 weeks
Chemotherapy regimen(s)	Various	AC (q3w) followed by IV paclitaxel as a continuous IV infusion (**AC→P)**. Paclitaxel: 80 mg/m^2 q1w for 12 weeks or 175 mg/m^2 q3w for 4 cycles (day 1 of each cycle)	AC followed by docetaxel **(AC→D)** or docetaxel and carboplatin (**DCarb)** Docetaxel (IV infusion over 60 min): **(AC→D):** 100 mg/m^2 q3w for 4 cycles or **(DCarb):** 75 mg/m^2 q3w for 6 cycles Carboplatin (at target AUC): 6 mg/mL/min (IV infusion over 30-60 min) q3w for a total of 6 cycles.
Timing of trastuzumab in relation to chemotherapy	After completion of (neo)adjuvant a	Concurrent **(AC→PH)** or sequential **(AC→P→H)**	Concurrent **(AC→DH** and **DCarbH)**
Median follow-up	1 year (initial evaluation) 8 years (follow-up evaluation)	2 years	3 years

AC=doxorubicin + cyclophosphamide; q3w=every 3 weeks; q1w=weekly; chemo=chemotherapy;

[a] 89% of subjects received adjuvant chemotherapy; 5% received neoadjuvant chemotherapy and 6% received a combination of neoadjuvant and adjuvant chemotherapy.

The HERA trial was designed to compare 1 and 2 years of 3-weekly trastuzumab treatment vs. observation in patients with HER2 positive breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a comparison of 2 years trastuzumab treatment vs. 1 year trastuzumab treatment was performed. Patients assigned to receive trastuzumab were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks for either 1 or 2 years. The efficacy results from the HERA trial are summarised in the following table:

Table 7: Efficacy results from the HERA trial at 12 months[1] and 8 years[2] of median follow-up

Parameter	Observation	Trastuzumab 1yr treatment	p-value	HR (95% CI)
Disease-free survival				
No. of patients with event (1 year[1])	12.9%	7.5%	<0.0001	0.54 (0.44,0.67)
No. of patients with event (8 year[2])	33.6%	27.7%	<0.0001	0.76 (0.67, 0.86)
Overall survival				
No. of patients with event (1 year[1])	2.4%	1.8%	0.24	0.75 (0.47,1.21)
No. of patients with event (8 year[2])	20.6%	16.3%	0.0005	0.76 (0.65, 0.88)

HR: Hazard ratio;

[1] co-primary endpoint of DFS of 1 year vs. observation met the pre-defined statistical boundary;

[2] final analysis (includes crossover of 52% of patients from the observation arm to trastuzumab).

The HERA study included a subgroup of patients (n=602) with small tumours (<2 cm) and node-negative disease. In this subgroup, the relative risk reduction was similar to the overall trial population (HR=0.50; 95% CI 0.21-1.15). However, the benefit in terms of absolute difference in rate of recurrence after 1 year of follow-up was smaller (2.7% recurrence rate with trastuzumab vs. 5.5% with observation).

In the final analysis (8-year median follow-up) extending trastuzumab treatment for a duration of 2 years did not show additional benefit over treatment for 1 year [DFS HR in the intent to treat (ITT) population of 2 years vs. 1 year = 0.99 (95% CI: 0.87, 1.13); p-value=0.90 and OS HR=0.98 (0.83, 1.15); p-value=0.78]. The rate of asymptomatic cardiac dysfunction was increased in the 2-year treatment arm (8.1% vs. 4.6% in the 1-year treatment arm). More patients experienced at least one Grade 3 or 4 adverse event in the 2-year treatment arm (20.4%) compared with the 1-year treatment arm (16.3%).

The efficacy results from the joint analysis of the NCCTG 9831 and NSABP B-31 trials at the time of the definitive analysis of DFS* are summarised in the following table:

Table 8: Summary of efficacy results from the joint analysis Studies NSABP B-31 and NCCTG N9831 at the time of the definitive DFS analysis*

Parameter	**AC→P**	**AC→PH**	**p-value**	**HR (95% CI)**
Disease recurrence Rate (trastuzumab vs. observation)	15.5%	8.0%	<0.0001	0.48 (0.39, 0.59)
Survival Deaths (trastuzumab vs. observation)	5.5%	3.7%	0.014**	0.67 (0.48, 0.92)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab; HR: Hazard ratio.

* At median duration of follow-up was 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm.

** p-value for OS did not cross the pre-specified statistical boundary for comparison of AC→PH vs. AC→P.

For the primary endpoint, DFS, the addition of trastuzumab to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence. The hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 11.8 percentage points (87.2 % versus 75.4 %) in favour of the AC→PH (trastuzumab) arm.

At the time of a safety update, after a median of 3.5-3.8 years follow-up, an analysis of DFS reconfirms the magnitude of the benefit shown in the definitive analysis of DFS. Despite the cross-over to trastuzumab in the control arm, the addition of trastuzumab to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The addition of trastuzumab to paclitaxel chemotherapy also resulted in a 37 % decrease in the risk of death.

The pre-planned final analysis of OS from the joint analysis of Studies NSABP B-31 and NCCTG N9831 was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC→P H group). Treatment with AC→PH resulted in a statistically significant improvement in OS compared with AC→P (stratified HR=0.64; 95% CI [0.55, 0.74]; log-rank p-value <0.0001). At 8 years, the survival rate was estimated to be 86.9% in the AC→PH arm and 79.4% in the AC→P arm, an absolute benefit of 7.4% (95% CI: 4.9%, 10.0%).

The final OS results from the joint analysis of Studies NSABP B-31 and NCCTG N9831 are summarised in the table below:

Table 9: Final overall survival analysis from the joint analysis of trials NSABP B-31 and NCCTG N9831

Parameter	**AC→P (n=2032)**	**AC→PH (n=2031)**	**p-value**	**HR (95% CI)**
Death (OS event) No. patients with event (%)	418 (20.6%)	289 (14.2%)	<0.0001	0.64 (0.55, 0.74)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab.

DFS analysis was also performed at the final analysis of OS from the joint analysis of Studies NSABP B-31 and NCCTG N9831. The updated DFS analysis results (stratified HR=0.61; 95% CI [0.54, 0.69]) showed a similar DFS benefit compared to the definitive primary DFS analysis, despite 24.8% patients in the AC→P arm who crossed over to receive trastuzumab. At 8 years, the disease-free survival rate was estimated to be 77.2% (95% CI: 75.4, 79.1) in the AC→PH arm, an absolute benefit of 11.8% compared with the AC→P arm.

The efficacy results from the BCIRG 006 are summarised in the following tables:

Table 10: Overview of efficacy analyses BCIRG 006 AC→D versus AC→DH

Parameter	**AC→D n=1073**	**AC→DH n=1074**	**p-value**	**HR (95% CI)**
Disease-free survival (DFS) No. patients with event	195	134	<0.0001	0.61 (0.49, 0.77)
Death (OS event) No. patients with event	80	49	0.0024	0.58 (0.40,0.83)

AC → D=doxorubicin plus cyclophosphamide, followed by docetaxel; AC → DH=doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab; CI=confidence interval.

Table 11: Overview of efficacy analyses BCIRG 006 AC→D versus DCarbH

Parameter	**AC→D *n*=1073**	**DCarbH *n*=1075**	**p-value**	**HR (95% CI)**
Disease-free survival (DFS) No. patients with event	195	145	0.0003	0.67 (0.54, 0.83)
Death (OS event) No. patients with event	80	56	0.00182	0.66 (0.47,0.93)

AC → D=doxorubicin plus cyclophosphamide, followed by docetaxel; DCarbH=docetaxel, carboplatin and trastuzumab; CI=confidence interval.

Metastatic breast cancer

Trastuzumab monotherapy or in combination with chemotherapy

Trastuzumab monotherapy has been used in clinical trials for patients with metastatic breast cancer who have tumours that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease.

Trastuzumab has also been used in clinical trials in combination with paclitaxel or an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (AC) as first line therapy for patients with metastatic breast cancer who have tumours that overexpress HER2.

Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m2 infused over 3 hours) with or without trastuzumab. Patients could be treated with trastuzumab until progression of disease.

Trastuzumab monotherapy, when used as second- or third-line treatment of women with metastatic breast cancer which overexpresses HER2, results in an overall tumour response rate of 15% and a median survival of 13 months.

The use of trastuzumab in combination with paclitaxel as first-line treatment of women with metastatic breast cancer that overexpresses HER2 significantly prolongs the median time to disease progression, compared with patients treated with paclitaxel alone. The increase in median time to disease progression for patients treated with paclitaxel is 3.9 months (6.9 months vs. 3.0 months). Tumour response and one-year survival rate are also increased for trastuzumab in combination with paclitaxel versus paclitaxel alone.

Trastuzumab has also been studied in a randomised, controlled trial, in combination with docetaxel, as first-line treatment of women with metastatic breast cancer. The combination of trastuzumab and docetaxel significantly increased response rate (61% vs. 34%) and prolonged the median time to disease progression (by 5.6 months) compared with patients treated with docetaxel alone. Median survival was also significantly increased in patients receiving the combination, compared with those receiving docetaxel alone (31.2 months vs. 22.7 months).

Trastuzumab in combination with anastrozole

The TAnDEM trial was a multi-centre, randomised, open-label, phase III study comparing trastuzumab + anastrozole with anastrozole alone for the first-line treatment of metastatic breast cancer in HER2 overexpressing, hormone-receptor (i.e. oestrogen-receptor (ER) and/or progesterone-receptor (PR)) positive post-menopausal patients. Two hundred and seven patients were randomised to receive oral anastrozole (1 mg/day) with or without trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg weekly). Patients who had previously received trastuzumab were excluded from this trial.

Median progression-free survival was doubled in the trastuzumab + anastrozole arm compared to the anastrozole alone arm (4.8 months vs. 2.4 months; p=0.0016). For the other parameters, the improvements seen for trastuzumab + anastrozole were: overall response (16.5% vs. 6.7%); clinical benefit rate (42.7% vs. 27.9%); time to progression (4.8 months vs. 2.4 months). For time to response and duration of response no difference could be recorded between the arms. There was no significant difference in overall survival, however, more than half of the patients in the anastrozole alone arm crossed over to a trastuzumab-containing regimen after progression of disease.

Advanced gastric cancer

Study BO18255 (ToGA) was a randomised, open-label, multicentre phase III study investigating trastuzumab in combination with a fluoropyrimidine and cisplatin (FP) versus chemotherapy alone as first-line therapy in patients with HER2 positive, inoperable, locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.

Patients were eligible if they had 3+ levels of HER2 overexpression based on a 0-3+ scale by IHC assessment of tumour tissue and/or those whose tumours had HER2 gene amplification as determined by a FISH test (see section 4.2).

After satisfying the screening eligibility criteria, including assessment of HER2 status, patients were randomly assigned (1:1) to receive either trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) + fluoropyrimidine/cisplatin (FP+H) or FP alone. The chemotherapy regimen was chosen between 5-FU/cisplatin and capecitabine/cisplatin at the investigator's discretion and could be determined on an individual patient basis.

The efficacy results from ToGA are summarised in Table 12. The primary endpoint was overall survival, defined as the time from the date of randomisation to the date of death from any cause. At the time of analysis a total of 349 randomised patients had died: 182 patients (62.8%) in the control arm and 167 patients (56.8%) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer.

Overall survival was significantly improved in the FP+H arm compared to the FP arm (p=0.0046, log-rank test). The median survival time was 11.1 months with FP and 13.8 months with FP+H. The risk of death was decreased by 26% (HR=0.74; 95% CI 0.60-0.91) for patients in the FP+H arm compared to the FP arm.

Post-hoc subgroup analyses indicate that targeting tumours with higher levels of HER2 protein (IHC 2+/FISH+ and IHC 3+/regardless of FISH status) results in a greater treatment effect. The median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR=0.65 (95% CI 0.51-0.83) and the median progression-free survival was 5.5 months vs. 7.6 months, HR=0.64 (95% CI 0.51-0.79).

Table 12: Summary of efficacy from Study BO18255

Trastuzumab dosage regimen	**Every 3 weeks**			
Chemotherapy regimens (FP)	• Capecitabine: 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles (Days 1 to 15 of each cycle). • 5-FU: 800 mg/m^2/day as a continuous IV infusion over 5 days, given every 3 weeks for 6 cycles (Days 1 to 5 of each cycle). The 5-FU infusion could be started at the same time as the cisplatin infusion on Day 1. • Cisplatin: 80 mg/m^2 every 3 weeks for 6 cycles (on Day 1 of each cycle) as a 2h IV infusion with hydration and premedication (steroids and anti-emetics).			
Efficacy parameters	**FP n=290**	**FP+H n=294**	**HR (95% CI)**	**p-value**
Overall Survival, Median months	11.1	13.8	0.74 (0.60-0.91)	0.0046
Progression-Free Survival, Median months	5.5	6.7	0.71 (0.59-0.85)	0.0002
Time to Disease Progression, Median months	5.6	7.1	0.70 (0.58-0.85)	0.0003
Overall Response Rate, %	34.5	47.3	1.70[a] (1.22, 2.38)	0.0017
Duration of Response, Median months	4.8	6.9	0.54 (0.40-0.73)	<0.0001

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + trastuzumab;

[a] Odds ratio;

Progression-free survival: time between day of randomisation and first documentation of progressive disease (PD) or date of death, whichever occurred first;

Time to disease progression: time between randomisation and first occurrence of PD;

Overall response: occurrence of either a confirmed complete (CR) or a partial (PR) best overall response as determined by RECIST criteria from confirmed radiographic evaluations of target and non-target lesions;

Duration of response: time from when response (CR or PR) was first documented to the first documented disease progression. This was only calculated for patients who had a best overall response of CR or PR.

TRAZIMERA clinical studies

The biosimilar clinical development program for TRAZIMERA included a total of two randomised, multicenter, double-blinded, active-controlled trials were conducted in adult patients (n=933) with the use of intravenous trastuzumab in combination with chemotherapy.

Study B3271002 was a trial comparing TRAZIMERA to Herceptin-EU when administered in combination with paclitaxel in patients with HER-2 positive metastatic breast cancer. The primary endpoint for this study was objective response rate (ORR) achieved by Week 25 in accordance with RECIST 1.1 based on the assessments of a central radiology review. The analysis of the primary endpoint met the pre-specified equivalence criterion.

Study B3271004 was a trial comparing TRAZIMERA to Herceptin-EU when administered in combination with Taxotere and carboplatin in patients with operable HER-2 positive breast cancer in the neoadjuvant setting. Secondary endpoints of the study included pathologic complete response (pCR) rate defined as the absence of invasive neoplastic cells in the breast and lymph nodes, safety and immunogenicity. The percentage of patients achieving pCR, based on a qualified local pathologist, was comparable in the 2 treatment groups.

In both studies, the safety and immunogenicity results support comparable safety profiles for TRAZIMERA and Herceptin-EU. There is no clinically meaningful difference in efficacy or safety between TRAZIMERA and Herceptin-EU reference product when administered intravenously in subjects with HER-2 positive breast cancer.

Pivotal clinical studies conducted to support similarity between TRAZIMERA and the reference biologic drug included the following:

- Study B3271001 (primary comparative PK study) was a 3-arm, double-blind randomised (1:1:1), parallel-group, single-dose study comparing the PK of TRAZIMERA, Herceptin-EU (European sourced Herceptin), and Herceptin-US (US sourced Herceptin) administered via IV infusion to healthy male subjects.
- Study B3271002 (primary comparative efficacy and safety study) in HER2-positive metastatic breast cancer patients. This study evaluated the similarity of efficacy (as a primary endpoint), safety, PK, and immunogenicity of TRAZIMERA versus Herceptin-EU in combination with paclitaxel.

The other supportive clinical study conducted to support similarity between TRAZIMERA and the reference biologic drug:

- Study B3271004 was conducted in HER2-positive early breast cancer patients, where similarity of the efficacy of TRAZIMERA was evaluated as a secondary endpoint along with similarity of PK (primary endpoint), safety, and immunogenicity versus Herceptin-EU in combination with docetaxel and carboplatin.

Comparative bioavailability studies – Pharmacokinetics

Refer to section 5.2.

Comparative safety and efficacy

Efficacy

Study B3271002

The primary endpoint for this study was the Objective Response Rate (ORR) defined as the percentage of patients within each treatment group that achieved response, either complete response (CR) or partial response (PR), by Week 25 of the study (window ±14 days) and subsequently confirmed by Week 33. The intent to treat (ITT) population was the primary analysis population.

The analysis of the primary endpoint met the pre-specified equivalence criterion. In the ITT population, the ORR was similar in both treatment groups based on central radiology assessments (62.5% in the TRAZIMERA group and 66.5% in the Herceptin-EU group). The risk ratio for the ORR between the 2 treatment groups was 0.940 (95% CI: 0.842, 1.049) (TRAZIMERA over Herceptin-EU), which are within the pre-specified equivalence margins of 0.80 to 1.25.

Table 13: Analysis of objective response rate derived from central radiology assessments - ITT population (Study B3271002)

	TRAZIMERA (N=352)	**Herceptin-EU(N=355)**	**Risk Ratio[a] Estimate (95% CI)**
Objective Response Rate			
n (%)	220 (62.5)	236 (66.5)	0.940
(95% CI)	(57.2, 67.6)	(61.3, 71.4)	(0.842, 1.049)

Notes: Objective Response Rate was defined as the percentage of patients within each treatment group who achieved Complete Response or Partial Response by Week 25 of the study which was subsequently confirmed by Week 33 ±14 days (or early discontinuation), in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Abbreviations: CI=confidence interval; EU=European Union; ITT=intent-to-treat; n/N=number of patients with observation/total number of patients.

[a]. Risk Ratio and associated 95% CI were based on the Miettinen and Nurminen method.

In the TRAZIMERA group, 220 patients (62.5%) had PR or CR, 76 patients (21.6%) had stable disease, and 18 patients (5.1%) had progressive disease. In the Herceptin-EU group, the corresponding numbers (%) of patients were 236 (66.5%), 74 (20.8%), and 11 (3.1%).

All the analysed secondary endpoints, 1-year progression-free survival rate, duration of response and 1-year survival rate, concluded no statistically significant difference between the 2 treatment groups.

- In the ITT population, the percentage of patients who had disease progression (based on central radiology assessments) or died was comparable in the 2 treatment groups (40.9% [n=144] in the TRAZIMERA group and 41.7% [n=148] in the Herceptin-EU group).
- In the ITT population, the percentage of patients who had confirmed response (CR or PR) based on central radiology assessments with or without subsequent progression or death was comparable in the 2 treatment groups (63.6% [n=224] in the TRAZIMERA group and 67.0% [n=238] in the Herceptin-EU group). Of these, 151 (67.4%) in the TRAZIMERA group and 157 (66.0%) in the Herceptin-EU group were without subsequent progression or death up to Week 53.
- In the ITT population, the percentage of patients who died was comparable in both treatment groups (11.9% [n=42] in the TRAZIMERA group and 12.1% [n=43] in the Herceptin-EU group). The estimated survival probability at Month 12 was 89.31% (95% CI: 85.48%, 92.17%) in the TRAZIMERA group and 87.36% (95% CI: 83.27%, 90.51%) in the Herceptin-EU group.

Study B3271004

Secondary efficacy endpoints analyzed were the Pathological Complete Response (pCR) and Objective Response Rate (ORR).

Analysis of patients with pCR in the per-protocol (PP) population for TRAZIMERA and Herceptin-EU was 47.0% (95% CI: 36.9% to 57.2%) and 50.0% (95% CI: 39.0% to 61.0%), respectively. The estimated stratified difference between TRAZIMERA and Herceptin-EU was -2.81% (95% CI: -16.58% to 10.96%).

Analysis of ORR based on central radiology assessments in the PP population for TRAZIMERA and Herceptin-EU was 88.1% (95% CI: 80.2% to 93.7%) and 82.0% (95% CI: 72.5% to 89.4%), respectively. The estimated stratified difference was 5.96% (95% CI: -4.01% to 15.94%).

Safety

Overall, the safety profile of TRAZIMERA was comparable with that of Herceptin-EU or Herceptin-US.

5.2 Pharmacokinetic properties

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects from 18 phase I, II and III trials receiving intravenous trastuzumab IV. A two-compartment model with parallel linear and non-linear elimination from the central compartment was used to describe trastuzumab concentration-time profile. Due to the non-linear elimination, total clearance increased with decreasing concentrations. Linear elimination clearance was 0.127 L/day for breast cancer (MBC/EBC) and 0.176 L/day for AGC. The nonlinear elimination parameter values were 8.81 mg/day for the maximum elimination rate (Vmax) and 8.92 mg/L for the Michaelis-Menten constant (Km). The central compartment volume was 2.62 L for patients with breast cancer and 3.63 L for patients with AGC.

The population predicted PK exposures (with 5th-95th Percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for breast cancer and AGC patients treated with the approved q1w and q3w regimens are shown in Table 14 (Cycle 1) and Table 15 (steady-state) below.

Table 14: Population predicted Cycle 1 PK exposures values (with 5^{th}-95^{th} percentiles) for IV regimens in breast cancer and AGC patients

Regimen	Primary tumour type	N	C_{min} (µg/mL)	C_{max} (µg/mL)	AUC (µg.day/mL)
	MBC/EBC	1195	29.4	178	1373

Regimen	Primary tumour type	N	C_{min} (µg/mL)	C_{max} (µg/mL)	AUC (µg.day/mL)
8mg/kg + 6mg/kg q3w			(5.8-59.5)	(117-291)	(736-2245)
	AGC	274	23.1 (6.1-50.3)	132 (84.2-225)	1109 (588-1938)
4mg/kg + 2mg/kg qw	MBC/EBC	1195	37.7 (12.3-70.9)	88.3 (58-144)	1066 (586-1754)

Table 15: Population predicted steady state PK exposures values (with 5th-95th Percentiles) for trastuzumab IV dosing regimens in breast cancer and AGC patients

Regimen	Primary tumour type	N	$C_{min,ss}$ (µg/mL)	$C_{max,ss}$ (µg/mL)	AUCss (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	47.4 (5-115)	179 (107-309)	1794 (673-3618)	12	0.173-0.283
	AGC	274	32.9 (6.1-88.9)	131 (72.5-251)	1338 (557-2875)	9	0.189-0.337
4mg/kg + 2mg/kg qw	MBC/EBC	1195	66.1 (14.9-142)	109 (51.0-209)	1765 (647-3578)	12	0.201-0.244

Trastuzumab washout

Trastuzumab washout time period was assessed following intravenous administration using the respective population PK models. The results of these simulations indicate that at least 95% of patients will reach serum trastuzumab concentrations that are <1 µg/mL (approximately 3% of the population predicted $C_{min,ss}$, or about 97% washout) by 7 months after the last dose.

Special populations

Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. The data from Study H0649g suggest that the disposition of trastuzumab is not altered by patient characteristics such as age or serum creatinine. The population pharmacokinetic analysis also shows that the estimated creatinine clearance (Cockcroft and Gault) does not correlate with the pharmacokinetics of trastuzumab.

Elderly

Age has been shown to have no effect on the disposition of trastuzumab (see section 4.2).

TRAZIMERA comparative pharmacokinetic studies

Pharmacokinetic comparability of TRAZIMERA and Herceptin was evaluated in Study B3271001 in 105 healthy adult subjects in a three arm, double-blind, randomised, (1:1:1) parallel group, single dose study comparing TRAZIMERA, Herceptin-EU and Herceptin-US administered intravenously.

The 90% CIs for test-to-reference ratios of C_{max}, AUC_t, and AUC_{inf} were contained within the pre-specified acceptance boundaries of 80% to 125% for the comparisons of TRAZIMERA to Herceptin-US and TRAZIMERA to Herceptin-EU. The test-to-reference ratios (90% CIs of the ratios) of adjusted geometric means of C_{max}, AUC_t, and AUC_{inf} were 97.41% (90.71%, 104.62%), 99.94% (93.08%, 107.31%), and 99.83% (93.06%, 107.09%), respectively, for the TRAZIMERA to Herceptin-US comparison; and 91.49% (85.32%, 98.09%), 92.66% (86.44%, 99.34%), and 92.15% (86.03%, 98.69%), respectively, for the TRAZIMERA to Herceptin-EU comparison.

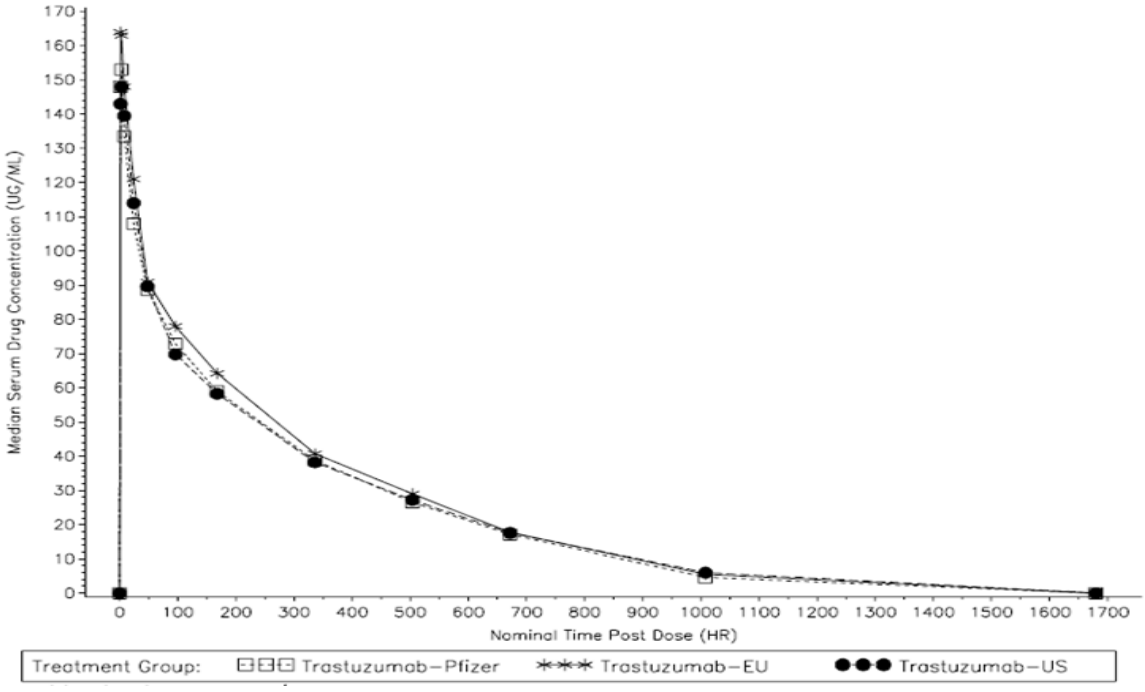
Table 16: Study summary of statistical comparisons of pharmacokinetic exposure parameters (C_{max}, AUC_t, and AUC_{inf}) between test and reference products (Study B3271001)

Trastuzumab From measured data Adjusted Geometric Means Arithmetic Mean (CV %)				
Parameter	**Test**	**Reference**	**% Ratio (Test/Reference) of Adjusted Geometric Means**	**90% Confidence Interval for Ratio[a]**
	TRAZIMERA	**Herceptin-EU**		
AUC_t (µg•hr/mL)	35210	38000	92.66	(86.44, 99.34)
AUC_{inf} (µg•hr/mL)	36650	39770	92.15	(86.03, 98.69)
C_{max} (µg/mL)	157	171	91.49	(85.32, 98.09)
Parameter	**TRAZIMERA**	**Herceptin-US**	**% Ratio (Test/Reference) of Adjusted Geometric Means**	**90% Confidence Interval for Ratio[a]**
AUC_t (µg•hr/mL)	35210	35230	99.94	(93.08, 107.31)
AUC_{inf} (µg•hr/mL)	36650	36710	99.83	(93.06, 107.09)
C_{max} (µg/mL)	157	161	97.41	(90.71, 104.62)
Parameter	**Herceptin-EU**	**Herceptin-US**	**% Ratio (Test/Reference) of Adjusted Geometric Means**	**90% Confidence Interval for Ratio[a]**
AUC_t (µg•hr/mL)	38000	35230	107.85	(100.50, 115.75)
AUC_{inf} (µg•hr/mL)	39770	36710	108.34	(101.05, 116.16)
C_{max} (µg/mL)	171	161	106.48	(99.20, 114.30)

Abbreviations: AUC_{inf}=area under the concentration-time curve from time zero to infinity; AUC_t=area under the concentration-time curve from time zero to time t; C_{max}=maximum observed concentration; CI=confidence interval; EU=European Union; US=United States.

[a] The ratios (and 90% CIs) are expressed as percentages.

Figure 1: **Median serum concentration-time profiles of TRAZIMERA, Herceptin-EU, and Herceptin-US following a single IV dose to healthy subjects at 6 mg/kg (Study B3271001)**



In Study B3271004 in patients with early breast cancer treated with TRAZIMERA or Herceptin-EU in combination with Taxotere and carboplatin, the primary endpoint of the study was the percent of patients with Cycle 5 C_{trough} (Cycle 6 predose trastuzumab concentration) >20µg/mL. The analysis of the primary endpoint met the non-inferiority criterion. The study demonstrated a comparable percentage of patients with steady state (Cycle 5) C_{trough} >20µg/mL of TRAZIMERA and Herceptin-EU.

The primary endpoint was the number (%) of patients reporting trough plasma concentration (C_{trough}) >20 µg/mL at Cycle 5 (pre-dose Cycle 6). There were 93 (92.1%) patients with C_{trough} >20 µg/mL at Cycle 5 in the TRAZIMERA group and 83 (93.3%) patients in the Herceptin-EU group. The stratified estimated difference (standard error [SE]) between TRAZIMERA and Herceptin-EU was -0.76 (3.70) (95% CI: -8.02 to 6.49). The lower limit of the 95% CI of the stratified difference between TRAZIMERA and Herceptin-EU (8.02%) was above the non-inferiority margin of -12.5%.

In general, the mean trough concentration at each study cycle in the TRAZIMERA group was comparable to the respective mean trough concentration in the Herceptin-EU group.

5.3 Preclinical safety data

There was no evidence of acute or multiple dose-related toxicity in studies of up to 6 months, or reproductive toxicity in teratology, female fertility or late gestational toxicity/placental transfer studies. Trastuzumab is not genotoxic. No long-term animal studies have been performed to establish the carcinogenic potential of trastuzumab, or to determine its effects on fertility in males.

Lactation

A study conducted in lactating cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

histidine hydrochloride monohydrate
histidine
sucrose
polysorbate 20

Solvent vial (for use with 440 mg vial only)

Water for Injection containing 1.1% benzyl alcohol (Bacteriostatic Water for Injection).

6.2 Incompatibilities

No incompatibilities between TRAZIMERA and polyvinylchloride, polyethylene, polypropylene, or ethylene vinyl acetate bags or glass IV bottles have been observed.

Dextrose (5%) solution should not be used since it causes aggregation of the protein. TRAZIMERA should not be mixed or diluted with other medicines.

6.3 Shelf life

Vial

48 months

Shelf-life of the reconstituted solution

TRAZIMERA 440 mg vial

Reconstituted solutions made with Bacteriostatic Water for Injection for the 440 mg vial of TRAZIMERA, as supplied, are stable for 28 days when stored refrigerated at 2ºC-8ºC. The reconstituted solution contains preservative and is therefore suitable for multiple use. Any remaining reconstituted solution should be discarded after 28 days.

When administering TRAZIMERA to a patient with a known hypersensitivity to benzyl alcohol (see section 4.4), TRAZIMERA should be reconstituted with sterile Water for Injection. In case TRAZIMERA is reconstituted with sterile Water for Injection, only one dose per TRAZIMERA vial should be used. The reconstituted solution should be used immediately. Any unused portion must be discarded.

TRAZIMERA 150 mg vial

The 150 mg vials are reconstituted with sterile Water for Injection and are for single use only.

The reconstituted product is physically and chemically stable for 48 hours at 2ºC-8ºC (refrigerate, do not freeze) after dissolving with water for injection.

From a microbiological point of view, the reconstituted solution should be further diluted immediately. If not further diluted immediately, in-use storage times and conditions prior to dilution are the responsibility of the user. The shelf-life of the reconstituted solution is 24 hours at 2ºC-8ºC, unless reconstitution has taken place in controlled and validated aseptic conditions in which case the shelf-life is 48 hours at 2ºC-8ºC.

Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product

The infusion solution (0.9% sodium chloride infusion solution) containing the reconstituted product is physically and chemically stable for 24 hours (do not store above 30ºC).

From a microbiological point of view, the TRAZIMERA infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2ºC to 8ºC, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Vials

Store vials at 2ºC-8ºC.

This medicine should not be used after the expiry date shown on the pack.

TRAZIMERA should be stored in the original package in order to protect from light.

Unopened vials of TRAZIMERA may be removed from refrigeration and stored up to 30°C for a single period of up to 3 months. Once removed from refrigeration and stored under these conditions, discard after 3 months. A date field is provided on the carton to record the discard date.

For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

TRAZIMERA 440 mg multi-dose vials

Each pack contains one vial of TRAZIMERA (440 mg trastuzumab) and one 20 mL vial of Bacteriostatic Water for Injection.

TRAZIMERA 150 mg single-dose vials

Each pack contains one vial of TRAZIMERA (150 mg trastuzumab).

6.6 Special precautions for disposal and other handling

Appropriate aseptic technique should be used.

The 440 mg vial of TRAZIMERA is reconstituted with 20 mL of Bacteriostatic Water for Injections, containing 1.1% benzyl alcohol as a preservative (supplied). This yields a solution for multiple use, containing 21 mg/mL trastuzumab, at a pH of approximately 6.0. Use of other reconstitution solvents should be avoided except for sterile Water for Injections without preservative (not supplied) in case of a patient with known hypersensitivity to benzyl alcohol.

The 150 mg vial of TRAZIMERA is reconstituted with 7.2 mL of sterile Water for Injection.

TRAZIMERA should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted TRAZIMERA may result in problems with the amount of TRAZIMERA that can be withdrawn from the vial.

Instructions for reconstitution – 440 mg vial

1. Using a sterile syringe, slowly inject 20 mL of sterile Bacteriostatic Water for Injection into the vial containing the lyophilised TRAZIMERA, directing the stream into the lyophilised cake.
2. Swirl vial gently to aid reconstitution. DO NOT SHAKE

Instructions for reconstitution – 150 mg vial

1. Using a sterile syringe, slowly inject 7.2 mL of sterile Water for Injection into the vial containing the lyophilised TRAZIMERA, directing the stream into the lyophilised cake.
2. Swirl vial gently to aid reconstitution. DO NOT SHAKE

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted TRAZIMERA results in a clear to slightly opalescent and colourless to pale yellow-brown solution and should be essentially free of visible particles.

Instructions for dilution

Weekly schedule

Determine the volume of the reconstituted solution required based on a loading dose of 4 mg trastuzumab/kg body weight, or a maintenance dose of 2 mg trastuzumab/kg body weight:

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (4 mg/kg for loading or 2 mg/kg for maintenance)}}{\text{21 (mg/mL, concentration of reconstituted solution)}}$$

Three-weekly schedule

Determine the volume of the reconstituted solution required based on a loading dose of 8 mg trastuzumab/kg body weight, or a maintenance dose of 6 mg trastuzumab/kg body weight:

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (8 mg/kg for loading or 6 mg/kg for maintenance)}}{\text{21 (mg/mL, concentration of reconstituted solution)}}$$

Preparation and stability of the admixture

The appropriate amount of reconstituted solution should be withdrawn from the vial using a sterile needle and syringe and added to an infusion bag containing 250 mL of 0.9% sodium chloride. Dextrose (5%) solution should not be used (see section 6.2). The bag should be gently inverted to mix the solution in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-bacterial preservative or bacteriostatic agent, aseptic technique must be observed. Parenteral medicines should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately (see section 6.4).

Disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

18 June 2020.

10. DATE OF REVISION OF THE TEXT

24 September 2021

Summary table of changes

Section Changed	Summary of new information
6.6	Preparation and stability of the admixture: Addition of instruction to use sterile needle and syringe for dilution.