TRAZIMERA™

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name

TRAZIMERA

1.2 Strength

150 mg and 440 mg

1.3 Pharmaceutical Dosage Form

Powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Active Ingredient: trastuzumab.

2.2 Quantitative Declaration

Each 150 mg vial delivers 150 mg of trastuzumab.

Each 440 mg vial delivers 420 mg of trastuzumab (delivers 20 mL of reconstituted solution containing 21 mg/mL trastuzumab).

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White lyophilized powder or cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

Metastatic breast cancer

TRAZIMERA is indicated for the treatment of patients with metastatic breast cancer (MBC) who have tumors that overexpress human epidermal growth factor receptor 2 (HER2):

- as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease.
- in combination with paclitaxel or docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- in combination with an aromatase inhibitor for the treatment of patients with hormone-receptor positive MBC.

Early breast cancer

TRAZIMERA is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC):

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant TRAZIMERA, for locally advanced (including inflammatory) breast cancer or tumours >2 cm in diameter (see sections 4.4 and 5.1).

Advanced gastric cancer

TRAZIMERA in combination with capecitabine or intravenous 5-fluorouracil and a platinum agent is indicated for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

4.2 Posology and method of administration

HER2 testing is mandatory prior to initiation of therapy (see sections 4.4 and 5.1). TRAZIMERA treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see section 4.4), and should be administered by a healthcare professional only.

TRAZIMERA intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only.

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is TRAZIMERA (trastuzumab) and not Kadcyla (trastuzumab emtansine).

Posology

Metastatic breast cancer

Three-weekly schedule

The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Weekly schedule

The recommended initial loading dose of TRAZIMERA is 4 mg/kg body weight. The recommended weekly maintenance dose of TRAZIMERA is 2 mg/kg body weight, beginning one week after the loading dose.

Administration in combination with paclitaxel or docetaxel

In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of trastuzumab and immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated.

Administration in combination with an aromatase inhibitor

In the pivotal trial (BO16216) trastuzumab and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab and anastrozole at administration.

Early breast cancer

Three-weekly and weekly schedule

As a three-weekly regimen the recommended initial loading dose of TRAZIMERA is 8 mg/kg body weight. The recommended maintenance dose of TRAZIMERA at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

See section 5.1 for chemotherapy combination dosing.

Advanced gastric cancer

Three-weekly schedule

The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Breast cancer and gastric cancer

Duration of treatment

Patients with MBC or advanced gastric cancer (AGC) should be treated with TRAZIMERA until progression of disease. Patients with EBC should be treated with TRAZIMERA for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended (see section 5.1).

Dose reduction

No reductions in the dose of trastuzumab were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the product label for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

If left ventricular ejection fraction (LVEF) percentage drops ≥10 points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of TRAZIMERA should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

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 maintenance doses should 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.

Special populations

Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition.

Paediatric population

There is no relevant use of TRAZIMERA in the paediatric population.

Method of administration

TRAZIMERA loading dose should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus. TRAZIMERA intravenous infusion should be administered by a health-care provider prepared to manage anaphylaxis and an emergency kit should be available. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms (see sections 4.4 and 4.8). Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

For instructions on reconstitution of TRAZIMERA intravenous formulation before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients.
- Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

4.4 Special warnings and precautions for use

HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures (see section 5.1).

Currently no data from clinical trials are available on re-treatment of patients with previous exposure to TRAZIMERA in the adjuvant setting.

Cardiac dysfunction

General considerations

Patients treated with trastuzumab products are at increased risk for developing CHF (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab product therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have 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, LVEF of <55%, older age.

All candidates for treatment with TRAZIMERA, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who develop cardiac dysfunction. 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. A careful risk-benefit assessment should be made before deciding to treat with TRAZIMERA.

Trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment based on population pharmacokinetic analysis of all available data (see section 5.2). Patients who receive anthracyclines after stopping trastuzumab may possibly 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.

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. In all patients cardiac function should be

monitored during treatment (e.g., every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction. 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 if no clinical benefit of TRAZIMERA therapy has been seen.

The safety of continuation or resumption of trastuzumab in patients who experience cardiac dysfunction has not been prospectively studied. If LVEF percentage drops ≥10 points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic CHF has developed, discontinuation of TRAZIMERA should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

If symptomatic cardiac failure develops during TRAZIMERA therapy, it should be treated with standard medicinal products for CHF. Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on therapy without additional clinical cardiac events.

Metastatic breast cancer

Trastuzumab and anthracyclines should not be given concurrently in combination in the MBC setting.

Patients with MBC who have previously received anthracyclines are also at risk of cardiac dysfunction with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

Early breast cancer

For patients with EBC, 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 medical treatment, history of or existing CHF (NYHA Class II-IV), LVEF of <55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant EBC pivotal trials with trastuzumab and therefore treatment cannot be recommended in such patients.

Adjuvant treatment

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

In patients with EBC 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 and 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. In one of the 3 pivotal studies conducted in which a median follow-up of 5.5 years was available (BCIRG006) a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed in patients who were administered trastuzumab concurrently with a taxane following anthracycline therapy up to 2.37% compared to approximately 1% in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and trastuzumab).

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (>50 years), low LVEF (<55%) at baseline, prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and prior or concurrent use of anti-hypertensive medicinal products. 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 body mass index (BMI) >25 kg/m^2.

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment, TRAZIMERA should be used concurrently with anthracyclines only in chemotherapy-naive patients and only with low-dose

anthracycline regimens i.e., maximum cumulative doses of doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2.

If patients have been treated concurrently with a full course of low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to two trials (MO16432 and BO22227).

In the pivotal trial MO16432, trastuzumab was administered intravenously concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2).

The incidence of symptomatic cardiac dysfunction was low in the trastuzumab arms (up to 1.7%).

In the pivotal trial BO22227, trastuzumab was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m^2); at a median follow-up exceeding 70 months, the incidence of cardiac failure/congestive cardiac failure was 0.3% in the trastuzumab intravenous arm.

Clinical experience is limited in patients above 65 years of age.

Infusion-related reactions and hypersensitivity

Serious infusion-related reactions (IRRs) to trastuzumab infusion including dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported (see section 4.8). Pre-medication may be used to reduce risk of occurrence of these events. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms (see section 4.2). These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. The majority of patients experienced resolution of symptoms and subsequently received further infusions of trastuzumab. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and

corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with TRAZIMERA (see section 4.3).

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Pulmonary events

Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting (see section 4.8). These events have occasionally been fatal. 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. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with TRAZIMERA (see section 4.3). Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed. Clinically significant interactions between trastuzumab and the concomitant medicinal products used in clinical trials have not been observed.

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents

Pharmacokinetic data from studies BO15935 and M77004 in women with HER2-positive MBC suggested that exposure to paclitaxel and doxorubicin (and their major metabolites 6-α-hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) was not altered in the presence of trastuzumab

(8 mg/kg or 4 mg/kg IV loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w IV, respectively).

However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13-dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite was unclear.

Data from study JP16003, a single-arm study of trastuzumab (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m^2 IV) in Japanese women with HER2-positive MBC, suggested that concomitant administration of trastuzumab had no effect on the single dose pharmacokinetics of docetaxel. Study JP19959 was a substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer to study the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab. The results of this substudy suggested that the exposure to the bioactive metabolites (e.g., 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab.

Pharmacokinetic data from Study H4613g/GO01305 in patients with metastatic or locally advanced inoperable HER2-positive cancer suggested that trastuzumab had no impact on the PK of carboplatin.

Effect of antineoplastic agents on trastuzumab pharmacokinetics

By comparison of simulated serum trastuzumab concentrations after trastuzumab monotherapy (4 mg/kg loading/2 mg/kg q1w IV) and observed serum concentrations in Japanese women with HER2-positive MBC (study JP16003) no evidence of a PK effect of concurrent administration of docetaxel on the pharmacokinetics of trastuzumab was found.

Comparison of PK results from two Phase II studies (BO15935 and M77004) and one Phase III study (H0648g) in which patients were treated concomitantly with trastuzumab and paclitaxel and two Phase II studies in which trastuzumab was administered as monotherapy (W016229 and MO16982), in women with HER2-positive MBC indicates that individual and mean trastuzumab trough serum concentrations varied within and across studies but there was no clear effect of the concomitant administration of paclitaxel on the pharmacokinetics of trastuzumab. Comparison of trastuzumab PK data from Study M77004 in which women with HER2-positive MBC were treated

concomitantly with trastuzumab, paclitaxel and doxorubicin to trastuzumab PK data in studies where trastuzumab was administered as monotherapy (H0649g) or in combination with anthracycline plus cyclophosphamide or paclitaxel (Study H0648g), suggested no effect of doxorubicin and paclitaxel on the pharmacokinetics of trastuzumab.

Pharmacokinetic data from Study H4613g/GO01305 suggested that carboplatin had no impact on the PK of trastuzumab.

The administration of concomitant anastrozole did not appear to influence the pharmacokinetics of trastuzumab.

4.6 Pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception during treatment with TRAZIMERA and for 7 months after treatment has concluded (see section 5.2).

Pregnancy

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 intravenous formulation and have revealed no evidence of impaired fertility or harm to the foetus. Placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (days 120-150 of gestation) foetal development period was observed. It is not known whether trastuzumab can affect reproductive capacity. As animal reproduction studies are not always predictive of human response, trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential 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. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with TRAZIMERA, or if a patient becomes pregnant while receiving TRAZIMERA or within 7 months following the last dose of TRAZIMERA, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

A study conducted in lactating Cynomolgus monkeys at doses 25 times that of the weekly human

maintenance dose of 2 mg/kg trastuzumab intravenous formulation 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. It is not known whether trastuzumab is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during TRAZIMERA therapy and for 7 months after the last dose.

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

Trastuzumab may have a minor influence on the ability to drive or use machines (see section 4.8). Patients experiencing infusion-related symptoms (see section 4.4) should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

Amongst the most serious and/or common adverse reactions reported in trastuzumab usage to date are cardiac dysfunction, infusion-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

Tabulated list of adverse reactions

Presented in Table 1 are adverse reactions that have been reported in association with the use of intravenous trastuzumab alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting.

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

Table 1: Undesirable Effects Reported with Intravenous Trastuzumab Monotherapy or in Combination with Chemotherapy in Pivotal Clinical Trials (N=8386) and in Post-Marketing

System organ class	Adverse reaction
Infections and infestations	Infection
	Nasopharyngitis
	Neutropenic sepsis

System organ class	Adverse reaction
	Cystitis
	Herpes zoster
	Influenza
	Sinusitis
	Skin infection
	Rhinitis
	Upper respiratory tract infection
	Urinary tract infection
	Erysipelas
	Cellulitis
	Pharyngitis
	Sepsis
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression
	Neoplasm progression
Blood and lymphatic system disorders	Febrile neutropenia
	Anaemia
	Neutropenia
	White blood cell count decreased/leukopenia
	Thrombocytopenia
	Hypoprothrombinaemia
	Immune thrombocytopenia
Immune system disorders	Hypersensitivity
	Anaphylactic reaction[+]
	Anaphylactic shock[+]
Metabolism and nutrition disorders	Weight decreased/Weight loss
	Anorexia
	Tumour lysis syndrome
	Hyperkalaemia
Psychiatric disorders	Insomnia
	Anxiety
	Depression
	Thinking abnormal
Nervous system disorders	Tremor[1]

System organ class	Adverse reaction
	Dizziness
	Headache
	Paraesthesia
	Dysgeusia
	Peripheral neuropathy
	Hypertonia
	Somnolence
	Ataxia
	Paresis
	Brain oedema
Eye disorders	Conjunctivitis
	Lacrimation increased
	Dry eye
	Papilloedema
	Retinal haemorrhage
Ear and labyrinth disorders	Deafness
Cardiac disorders	Blood pressure decreased[1]
	Blood pressure increased[1]
	Heart beat irregular[1]
	Palpitation[1]
	Cardiac flutter[1]
	Ejection fraction decreased[*]
	Cardiac failure (congestive)[+]
	Supraventricular tachyarrhythmia[+,1]
	Cardiomyopathy
	Pericardial effusion
	Cardiogenic shock
	Pericarditis
	Bradycardia
	Gallop rhythm present
Vascular disorders	Hot flush
	Hypotension[+,1]
	Vasodilatation

System organ class	Adverse reaction
Respiratory, thoracic and mediastinal disorders	Wheezing[+,1]
	Dyspnoea[+]
	Cough
	Epistaxis
	Rhinorrhoea
	Pneumonia[+]
	Asthma
	Lung disorder
	Pleural effusion[+]
	Pneumonitis
	Pulmonary fibrosis[+]
	Respiratory distress[+]
	Respiratory failure[+]
	Lung infiltration[+]
	Acute pulmonary oedema[+]
	Acute respiratory distress syndrome[+]
	Bronchospasm[+]
	Hypoxia[+]
	Oxygen saturation decreased[+]
	Laryngeal oedema
	Orthopnoea
	Pulmonary oedema
	Interstitial lung disease
Gastrointestinal disorders	Diarrhoea
	Vomiting
	Nausea
	Lip swelling[1]
	Abdominal pain
	Dyspepsia
	Constipation
	Stomatitis
	Haemorrhoids
	Dry mouth

System organ class	Adverse reaction
Hepatobiliary disorders	Hepatocellular injury
	Hepatitis
	Liver tenderness
	Jaundice
	Hepatic failure
Skin and subcutaneous tissue disorders	Erythema
	Rash
	Swelling face[1]
	Alopecia
	Nail disorder
	Palmar-plantar erythrodysaesthesia syndrome
	Acne
	Dry skin
	Ecchymosis
	Hyperhydrosis
	Maculopapular rash
	Pruritus
	Onychoclasis
	Dermatitis
	Urticaria
	Angioedema
Musculoskeletal and connective tissue disorders	Arthralgia
	Muscle tightness[1]
	Myalgia
	Arthritis
	Back pain
	Bone pain
	Muscle spasms
	Neck pain
	Pain in extremity
Renal and urinary disorders	Renal disorder
	Glomerulonephritis membranous
	Glomerulonephropathy

System organ class	Adverse reaction
	Renal failure
Pregnancy, puerperium and perinatal conditions	Oligohydramnios
	Renal hypoplasia
	Pulmonary hypoplasia
Reproductive system and breast disorders	Breast inflammation/mastitis
General disorders and administration site conditions	Asthenia
	Chest pain
	Chills
	Fatigue
	Influenza-like symptoms
	Infusion related reaction
	Pain
	Pyrexia
	Mucosal inflammation
	Peripheral oedema
	Malaise
	Oedema
Injury, poisoning and procedural complications	Contusion

+ Denotes adverse reactions that have been reported in association with a fatal outcome.

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

* Observed with combination therapy following anthracyclines and combined with taxanes

Description of selected adverse reactions

Cardiac dysfunction

Congestive heart failure (NYHA Class II-IV) is a common adverse reaction associated with the use of trastuzumab and has been associated with a fatal outcome (see section 4.4). 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).

In 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy, the

incidence of grade 3/4 cardiac dysfunction (specifically symptomatic Congestive Heart Failure) was similar in patients who were administered chemotherapy alone (i.e., did not receive trastuzumab) and in patients who were administered trastuzumab sequentially after a taxane (0.3-0.4%). The rate was highest in patients who were administered trastuzumab concurrently with a taxane (2.0%). In the neoadjuvant setting, the experience of concurrent administration of trastuzumab and low dose anthracycline regimen is limited (see section 4.4).

When trastuzumab was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6% of patients in the one-year arm after a median follow-up of 12 months. 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 patients. Approximately 17% of cardiac dysfunction related events occurred after completion of trastuzumab.

In the pivotal metastatic trials of intravenous trastuzumab, the incidence of cardiac dysfunction varied between 9% and 12% when it was combined with paclitaxel compared with 1%-4% for paclitaxel alone. For monotherapy, the rate was 6%–9%. The highest rate of cardiac dysfunction was seen in patients receiving trastuzumab concurrently with anthracycline/cyclophosphamide (27%), and was significantly higher than for anthracycline/cyclophosphamide alone (7%-10%). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF 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 CHF.

Infusion reactions, allergic-like reactions and hypersensitivity

It is estimated that approximately 40% of patients who are treated with trastuzumab will experience some form of infusion-related reaction. However, the majority of infusion-related reactions are mild to moderate in intensity (NCI-CTC grading system) and tend to occur earlier in treatment, i.e., during infusions one, two and three and lessen in frequency in subsequent infusions. Reactions include chills, fever, dyspnoea, hypotension, wheezing, bronchospasm,

tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting and headache (see section 4.4). The rate of infusion-related reactions of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy.

Severe anaphylactic reactions requiring immediate additional intervention can occur usually during either the first or second infusion of trastuzumab (see section 4.4) and have been associated with a fatal outcome.

Anaphylactoid reactions have been observed in isolated cases.

Haematotoxicity

Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly. The frequency of occurrence of hypoprothrombinemia is not known. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Pulmonary events

Severe pulmonary adverse reactions occur in association with the use of trastuzumab and have been associated with a fatal outcome. These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency (see section 4.4).

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. Neutralizing 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 the 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.

There are no immunogenicity data available for trastuzumab in gastric cancer.

TRAZIMERA Comparative Clinical Studies

The results of the TRAZIMERA clinical trial program support comparable safety profiles for TRAZIMERA and Herceptin (see section 5.1).

4.9 Overdose

There is no experience with overdose in human clinical trials. Single doses of trastuzumab alone greater than 10 mg/kg have not been administered in the clinical trials; a maintenance dose of 10 mg/kg q3w following a loading dose of 8 mg/kg has been studied in a clinical trial with advanced gastric cancer patients. Doses up to this level were well tolerated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the HER2. Overexpression of HER2 is observed in 20%-30% of primary breast cancers. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8%-34.0% for IHC and 7.1%-42.6% for FISH. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. The extracellular domain of the receptor (ECD, p105) can be shed into the blood stream and measured in serum samples.

Mechanism of action

Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Detection of HER2 overexpression or HER2 gene amplification

Detection of HER2 overexpression or HER2 gene amplification in breast cancer

Trastuzumab should only be used in patients whose tumours have HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. HER2 overexpression should be detected using an IHC-based assessment of fixed tumour blocks (see section 4.4). HER2 gene amplification should be detected using FISH or CISH of fixed tumour blocks. Patients are eligible for trastuzumab treatment if they show strong HER2 overexpression as described by a 3+ score by IHC or a positive FISH or CISH result.

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

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 2.

Table 2: Recommended Scoring System to Evaluate the IHC Staining Patterns in Breast Cancer

Score	**Staining pattern**	**HER2 overexpression assessment**
0	No staining is observed or membrane staining is observed in <10% of the tumour cells	Negative
1+	A faint/barely perceptible membrane staining is detected in >10% of the tumour cells. The cells are only stained in part of their membrane.	Negative
2+	A weak to moderate complete membrane staining is detected in >10% of the tumour cells.	Equivocal
3+	Strong complete membrane staining is detected in >10% of the tumour cells.	Positive

In general, FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2, or if there are more than 4 copies of the HER2 gene per tumour cell if no chromosome 17 control is used.

In general, CISH is considered positive if there are more than 5 copies of the HER2 gene per nucleus in greater than 50% of tumour cells.

For full instructions on assay performance and interpretation please refer to the package inserts of

validated FISH and CISH assays. Official recommendations on HER2 testing may also apply.

For any other method that may be used for the assessment of HER2 protein or gene expression, the analyses should only be performed by laboratories that provide adequate state-of-the-art performance of validated methods. Such methods must clearly be precise and accurate enough to demonstrate overexpression of HER2 and must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) overexpression of HER2.

Detection of HER2 over expression or HER2 gene amplification in gastric cancer

Only an accurate and validated assay should be used to detect HER2 over expression or HER2 gene amplification. IHC is recommended as the first testing modality and in cases where HER2 gene amplification status is also required, either a silver-enhanced *in situ* hybridization (SISH) or a FISH technique must be applied. SISH technology is however, recommended to allow for the parallel evaluation of tumor histology and morphology. To ensure validation of testing procedures and the generation of accurate and reproducible results, HER2 testing must be performed in a laboratory staffed by trained personnel. Full instructions on assay performance and results interpretation should be taken from the product information leaflet provided with the HER2 testing assays used.

In the ToGA (BO18255) trial, patients whose tumours were either IHC3+ or FISH positive were defined as HER2 positive and thus included in the trial. Based on the clinical trial results, the beneficial effects were limited to patients with the highest level of HER2 protein overexpression, defined by a 3+ score by IHC, or a 2+ score by IHC and a positive FISH result.

In a method comparison study (study D008548) a high degree of concordance (>95%) was observed for SISH and FISH techniques for the detection of HER2 gene amplification in gastric cancer patients.

HER2 over expression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks; HER2 gene amplification should be detected using *in situ* hybridisation using either SISH or FISH on fixed tumour blocks.

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 3.

Table 3: Recommended Scoring System to Evaluate the IHC Staining Patterns in Gastric Cancer

Score	Surgical specimen - staining pattern	Biopsy specimen - staining pattern	HER2 overexpression assessment
0	No reactivity or membranous reactivity in <10% of tumour cells	No reactivity or membranous reactivity in any tumour cell	Negative
1+	Faint/barely perceptible membranous reactivity in ≥10% of tumour cells; cells are reactive only in part of their membrane	Tumour cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumour cells stained	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of tumour cells	Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of tumour cells	Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Positive

In general, SISH or FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2.

Clinical efficacy and safety

Metastatic breast cancer

Trastuzumab has been used in clinical trials as monotherapy for patients with MBC who have tumours that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease (trastuzumab alone).

Trastuzumab has also been used in combination with paclitaxel or docetaxel for the treatment of patients who have not received chemotherapy for their metastatic disease. Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m^2 infused over 3 hours) with or without trastuzumab. In the pivotal trial of docetaxel (100 mg/m^2 infused over 1 hour) with or without trastuzumab, 60% of the patients had received prior anthracycline-based adjuvant chemotherapy. Patients were treated with trastuzumab until progression of disease.

The efficacy of trastuzumab in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been studied. However, trastuzumab plus docetaxel was efficacious in patients whether or not they had received prior adjuvant anthracyclines.

The test method for HER2 overexpression used to determine eligibility of patients in the pivotal trastuzumab monotherapy and trastuzumab plus paclitaxel clinical trials employed immunohistochemical staining for HER2 of fixed material from breast tumours using the murine monoclonal antibodies CB11 and 4D5. These tissues were fixed in formalin or Bouin's fixative. This investigative clinical trial assay performed in a central laboratory utilised a 0 to 3+ scale. Patients classified as staining 2+ or 3+ were included, while those staining 0 or 1+ were excluded. Greater than 70% of patients enrolled exhibited 3+ overexpression. The data suggest that beneficial effects were greater among those patients with higher levels of overexpression of HER2 (3+).

The main test method used to determine HER2 positivity in the pivotal trial of docetaxel, with or without trastuzumab, was immunohistochemistry. A minority of patients was tested using fluorescence *in-situ* hybridisation (FISH). In this trial, 87% of patients entered had disease that was IHC3+, and 95% of patients entered had disease that was IHC3+ and/or FISH-positive.

Weekly dosing in metastatic breast cancer

The efficacy results from the monotherapy and combination therapy studies are summarised in Table 4.

Table 4: Efficacy Results from the Monotherapy and Combination Therapy Studies

Parameter	Monotherapy	Combination Therapy			
	Trastuzumab[1] N=172	Trastuzumab plus paclitaxel[2] N=68	Paclitaxel[2] N=77	Trastuzumab plus docetaxel[3] N=92	Docetaxel[3] N=94
Response rate (95% CI)	18% (13-25)	49% (36-61)	17% (9-27)	61% (50-71)	34% (25-45)
Median duration of response (months) (95% CI)	9.1 (5.6-10.3)	8.3 (7.3-8.8)	4.6 (3.7-7.4)	11.7 (9.3-15.0)	5.7 (4.6-7.6)
Median TTP (months) (95% CI)	3.2 (2.6-3.5)	7.1 (6.2-12.0)	3.0 (2.0-4.4)	11.7 (9.2-13.5)	6.1 (5.4-7.2)
Median Survival (months) (95% CI)	16.4 (12.3-ne)	24.8 (18.6-33.7)	17.9 (11.2-23.8)	31.2 (27.3-40.8)	22.74 (19.1-30.8)

TTP=time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

1 Study H0649g: IHC3+ patient subset

2 Study H0648g: IHC3+ patient subset

3 Study M77001: Full analysis set (intent-to-treat), 24 months results

Combination treatment with trastuzumab and anastrozole

Trastuzumab has been studied in combination with anastrozole for first line treatment of MBC in HER2 overexpressing, hormone-receptor (i.e., estrogen-receptor (ER) and/or progesterone-receptor (PR)) positive postmenopausal patients. Progression free survival was doubled in the trastuzumab plus anastrozole arm compared to anastrozole (4.8 months versus 2.4 months). For the other parameters the improvements seen for the combination were for overall response (16.5% versus 6.7%); clinical benefit rate (42.7% versus 27.9%); time to progression (4.8 months versus 2.4 months). For time to response and duration of response no difference could be recorded between the arms. The median overall survival was extended by 4.6 months for patients in the combination arm. The difference was not statistically significant, however more than half of the patients in the anastrozole alone arm crossed over to a

trastuzumab containing regimen after progression of disease.

Three weekly dosing in metastatic breast cancer

The efficacy results from the non-comparative monotherapy and combination therapy studies are summarised in Table 5.

Table 5: Efficacy Results from the Non-Comparative Monotherapy and Combination Therapy Studies

Parameter	Monotherapy		Combination Therapy	
	Trastuzumab[1] N=105	Trastuzumab[2] N=72	Trastuzumab plus paclitaxel[3] N=32	Trastuzumab plus docetaxel[4] N=110
Response rate (95% CI)	24% (15-35)	27% (14-43)	59% (41-76)	73% (63-81)
Median duration of response (months) (range)	10.1 (2.8-35.6)	7.9 (2.1-18.8)	10.5 (1.8-21)	13.4 (2.1-55.1)
Median TTP (months) (95% CI)	3.4 (2.8-4.1)	7.7 (4.2-8.3)	12.2 (6.2-ne)	13.6 (11-16)
Median Survival (months) (95% CI)	ne	ne	ne	47.3 (32-ne)

TTP=time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

1 Study WO16229: loading dose 8 mg/kg, followed by 6 mg/kg 3 weekly schedule

2 Study MO16982: loading dose 6 mg/kg weekly x 3; followed by 6 mg/kg 3-weekly schedule

3 Study BO15935

4 Study MO16419

Sites of progression

The frequency of progression in the liver was significantly reduced in patients treated with the combination of trastuzumab and paclitaxel, compared to paclitaxel alone (21.8% versus 45.7%; p=0.004). More patients treated with trastuzumab and paclitaxel progressed in the central nervous system than those treated with paclitaxel alone (12.6% versus 6.5%; p=0.377).

Early breast cancer (adjuvant setting)

Early breast cancer is defined as non-metastatic primary invasive carcinoma of the breast.

In the adjuvant treatment setting, trastuzumab was investigated in 4 large multicentre, randomised trials.

- Study BO16348 was designed to compare one and two years of three-weekly trastuzumab treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). In addition, comparison of two years of trastuzumab treatment versus one year of 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 three weeks for either one or two years.
- The NSABP B-31 and NCCTG N9831 studies that comprise the joint analysis were designed to investigate the clinical utility of combining trastuzumab treatment with paclitaxel following AC chemotherapy, additionally the NCCTG N9831 study also investigated adding trastuzumab sequentially to AC⟶P chemotherapy in patients with HER2 positive EBC following surgery.
- The BCIRG 006 study was designed to investigate combining trastuzumab treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2 positive EBC following surgery.

Early breast cancer in the HERA trial was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative if tumors at least 1 cm in diameter.

In the joint analysis of the NSABP B-31 and NCCTG N9831 studies, EBC was limited to women with operable breast cancer at high risk, defined as HER2-positive and axillary lymph node positive or HER2 positive and lymph node negative with high risk features (tumor size >1 cm and ER negative or tumor size >2 cm, regardless of hormonal status).

In the BCIRG 006 study HER2 positive, EBC was defined as either lymph node positive or high risk node negative patients with no (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, estrogen receptor and progesterone receptor negative, histological and/or nuclear grade 2-3, or age <35 years.

The efficacy results from the BO16348 trial following 12 months* and 8 years** median follow-up are summarized in Table 6.

Table 6: Efficacy Results from Study BO16348

	Median follow-up 12 months*		Median follow-up 8 years**	
Parameter	**Observation N=1693**	**Trastuzumab 1 Year N=1693**	**Observation N=1697*** **	**Trastuzumab 1 Year N=1702*** **
Disease-free survival				
- No. patients with event	219 (12.9%)	127 (7.5%)	570 (33.6%)	471 (27.7%)
- No. patients without event	1474 (87.1%)	1566 (92.5%)	1127 (66.4%)	1231 (72.3%)
P-value versus Observation	<0.0001		<0.0001	
Hazard Ratio versus Observation	0.54		0.76	
Recurrence-free survival				
- No. patients with event	208 (12.3%)	113 (6.7%)	506 (29.8%)	399 (23.4%)
- No. patients without event	1485 (87.7%)	1580 (93.3%)	1191 (70.2%)	1303 (76.6%)
P-value versus Observation	<0.0001		<0.0001	
Hazard Ratio versus Observation	0.51		0.73	
Distant disease-free survival				
- No. patients with event	184 (10.9%)	99 (5.8%)	488 (28.8%)	399 (23.4%)
- No. patients without event	1508 (89.1%)	1594 (94.6%)	1209 (71.2%)	1303 (76.6%)
P-value versus Observation	<0.0001		<0.0001	
Hazard Ratio versus Observation	0.50		0.76	
Overall survival (death)				
- No. patients with event	40 (2.4%)	31 (1.8%)	350 (20.6%)	278 (16.3%)
- No. patients without event	1653 (97.6%)	1662 (98.2%)	1347 (79.4%)	1424 (83.7%)
P-value versus Observation	0.24		0.0005	
Hazard Ratio versus Observation	0.75		0.76	

* Co-primary endpoint of DFS of 1 year versus observation met the pre-defined statistical boundary.

** Final analysis (including crossover of 52% of patients from the observation arm to trastuzumab).

*** There is a discrepancy in the overall sample size due to a small number of patients who were randomized

after the cut-off date for the 12-month median follow-up analysis.

The efficacy results from the interim efficacy analysis crossed the protocol pre-specified statistical boundary for the comparison of 1-year of trastuzumab versus observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 0.54 (95% CI 0.44, 0.67) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8% versus 78.2%) in favour of the trastuzumab arm.

A final analysis was performed after a median follow-up of 8 years, which showed that 1 year trastuzumab treatment is associated with a 24% risk reduction compared to observation only (HR=0.76, 95% CI 0.67, 0.86). This translates into an absolute benefit in terms of an 8 year disease free survival rate of 6.4 percentage points in favour of 1 year trastuzumab treatment.

In this final analysis, extending trastuzumab treatment for a duration of two years did not show additional benefit over treatment for 1 year [DFS HR in the intent to treat (ITT) population of 2 years versus 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% versus 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%).

In the NSABP B-31 and NCCTG N9831 studies trastuzumab was administered in combination with paclitaxel, following AC chemotherapy.

Doxorubicin and cyclophosphamide were administered concurrently as follows:
- intravenous push doxorubicin, at 60 mg/m^2, given every 3 weeks for 4 cycles.
- intravenous cyclophosphamide, at 600 mg/m^2 over 30 minutes, given every 3 weeks for 4 cycles.

Paclitaxel, in combination with trastuzumab, was administered as follows:
- intravenous paclitaxel - 80 mg/m^2 as a continuous intravenous infusion, given every week for 12 weeks.

or

- intravenous paclitaxel - 175 mg/m^2 as a continuous intravenous infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

The efficacy results from the joint analysis of the NSABP B-31 and NCCTG 9831 trials at the time of the definitive analysis of DFS* are summarized in Table 7. The 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.

Table 7: Summary of Efficacy results from the joint analysis of the NSABP B-31 and NCCTG N9831 trials at the time of the definitive DFS analysis*

Parameter	AC⟶P (n=1679)	AC⟶PH (n=1672)	Hazard Ratio versus AC⟶P (95% CI) p-value
Disease-free survival			
No. patients with event (%)	261 (15.5)	133 (8.0)	0.48 (0.39, 0.59) p<0.0001
Distant Recurrence			
No. patients with event	193 (11.5)	96 (5.7)	0.47 (0.37, 0.60) p<0.0001
Death (OS event)			
No. patients with event	92 (5.5)	62 (3.7)	0.67 (0.48, 0.92) p=0.014**

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

* At median duration of follow up of 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 versus 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⟶PH 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 summarized in Table 8 below.

Table 8: 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 versus AC⟶P**	**Hazard Ratio versus AC⟶P (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.

In the BCIRG 006 study trastuzumab was administered either in combination with docetaxel, following AC chemotherapy (AC⟶DH) or in combination with docetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- intravenous docetaxel - 100 mg/m^2 as an intravenous infusion over 1 hour, given every 3 weeks for 4 cycles (day 2 of first docetaxel cycle, then day 1 of each subsequent cycle)

or

- intravenous docetaxel - 75 mg/m^2 as an intravenous infusion over 1 hour, given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each subsequent cycle)

which was followed by:

- carboplatin - at target AUC=6 mg/mL/min administered by intravenous infusion over 30-60 minutes repeated every 3 weeks for a total of six cycles

Trastuzumab was administered weekly with chemotherapy and 3 weekly thereafter for a total of 52 weeks.

The efficacy results from the BCIRG 006 are summarized in Tables 9 and 10. The median duration of follow up was 2.9 years in the AC⟶D arm and 3.0 years in each of the AC⟶DH and DCarbH arms.

Table 9: Overview of Efficacy Analyses BCIRG 006 AC⟶D versus AC⟶DH

Parameter	**AC⟶D (n=1073)**	**AC⟶DH (n=1074)**	**Hazard Ratio versus AC⟶D (95% CI) p-value**
Disease-free survival No. patients with event	195	134	0.61 (0.49, 0.77) p<0.0001
Distant recurrence No. patients with event	144	95	0.59 (0.46, 0.77) p<0.0001
Death (OS event) No. patients with event	80	49	0.58 (0.40, 0.83) p=0.0024

AC⟶D=doxorubicin plus cyclophosphamide, followed by docetaxel; AC⟶DH=doxorubicin plus

cyclophosphamide, followed by docetaxel plus trastuzumab; CI=confidence interval

Table 10: Overview of Efficacy Analyses BCIRG 006 AC⟶D versus DCarbH

Parameter	AC⟶D (n=1073)	DCarbH (n=1074)	Hazard Ratio versus AC⟶D (95% CI)
Disease-free survival No. patients with event	195	145	0.67 (0.54, 0.83) p=0.0003
Distant recurrence No. patients with event	144	103	0.65 (0.50, 0.84) p=0.0008
Death (OS event) No. patients with event	80	56	0.66 (0.47, 0.93) p=0.0182

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

In the BCIRG 006 study for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 5.8 percentage points (86.7% versus 80.9%) in favour of the AC⟶DH (trastuzumab) arm and 4.6 percentage points (85.5% versus 80.9%) in favour of the DCarbH (trastuzumab) arm compared to AC⟶D.

In study BCIRG 006, 213/1075 patients in the DCarbH (TCH) arm, 221/1074 patients in the AC⟶DH (AC⟶TH) arm, and 217/1073 in the AC⟶D (AC⟶T) arm had a Karnofsky performance status ≤90 (either 80 or 90). No disease-free survival (DFS) benefit was noticed in this subgroup of patients (hazard ratio=1.16, 95% CI [0.73, 1.83] for DCarbH (TCH) versus AC⟶D (AC⟶T); hazard ratio=0.97, 95% CI [0.60, 1.55] for AC⟶DH (AC⟶TH) versus AC⟶D).

In addition a post-hoc exploratory analysis was performed on the data sets from the joint analysis (JA) NSABP B-31/NCCTG N9831* and BCIRG006 clinical studies combining DFS events and symptomatic cardiac events and summarised in Table 11.

Table 11: Post-Hoc Exploratory Analysis Results from the Joint Analysis NSABP B-31/NCCTG N9831* and BCIRG006 Clinical Studies Combining DFS Events and Symptomatic Cardiac Events

	AC⟶PH (versus AC⟶P) (NSABP B-31 and NCCTG N9831)*	AC⟶DH (versus AC⟶D) (BCIRG 006)	DCarbH (versus AC⟶D) (BCIRG 006)
Primary efficacy analysis			
DFS Hazard ratios	0.48	0.61	0.67
(95% CI)	(0.39, 0.59)	(0.49, 0.77)	(0.54, 0.83)
p-value	p<0.0001	p<0.0001	p=0.0003
Long term follow-up efficacy analysis**			
DFS Hazard ratios	0.61	0.72	0.77
(95% CI)	(0.54, 0.69)	(0.61, 0.85)	(0.65, 0.90)
p-value	p<0.0001	p<0.0001	p=0.0011
Post-hoc exploratory analysis with DFS and symptomatic cardiac events			
Long term follow-up** Hazard ratios	0.67	0.77	0.77
(95% CI)	(0.60, 0.75)	(0.66, 0.90)	(0.66, 0.90)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; D: docetaxel; Carb: carboplatin; H: trastuzumab

CI=confidence interval

* At the time of the definitive analysis of DFS. Median duration of follow up was 1.8 years in the AC⟶P arm and 2.0 years in the AC⟶PH arm

** Median duration of long term follow-up for the Joint Analysis clinical studies was 8.3 years (range: 0.1 to 12.1) for the AC⟶PH arm and 7.9 years (range: 0.0 to 12.2) for the AC⟶P arm; Median duration of long term follow-up for the BCIRG 006 study was 10.3 years in both the AC⟶D arm (range: 0.0 to 12.6) arm and the DCarbH arm (range: 0.0 to 13.1), and was 10.4 years (range: 0.0 to 12.7) in the AC⟶DH arm

Early breast cancer (neoadjuvant-adjuvant setting)

So far, no results are available which compare the efficacy of trastuzumab administered with chemotherapy in the adjuvant setting with that obtained in the neo-adjuvant/adjuvant setting.

In the neoadjuvant-adjuvant treatment setting, study MO16432, a multicentre randomised trial, was designed to investigate the clinical efficacy of 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 study recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory EBC. Patients with HER2+ tumours were randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant trastuzumab, or neoadjuvant chemotherapy alone.

In study MO16432, trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg maintenance every 3 weeks) was administered concurrently with 10 cycles of neoadjuvant chemotherapy as follows:

- Doxorubicin 60 mg/m^2 and paclitaxel 150 mg/m^2, administered 3-weekly for 3 cycles,

which was followed by

- Paclitaxel 175 mg/m^2 administered 3-weekly for 4 cycles,

which was followed by

- CMF on day 1 and 8 every 4 weeks for 3 cycles

which was followed after surgery by

- additional cycles of adjuvant trastuzumab (to complete 1 year of treatment)

The efficacy results from Study MO16432 are summarized in Table 12. The median duration of follow-up in the trastuzumab arm was 3.8 years.

Table 12: Efficacy Results from MO16432

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

Parameter	Chemo + trastuzumab (n=115)	Chemo only (n=116)	
Overall survival No. patients with event	22	33	Hazard Ratio (95% CI) 0.59 (0.35, 1.02) p=0.0555

* Defined as absence of any invasive cancer both in the breast and axillary nodes.

An absolute benefit of 13 percentage points in favour of the trastuzumab arm was estimated in terms of 3-year event-free survival rate (65% versus 52%).

Advanced gastric cancer

Trastuzumab has been investigated in one randomised, open-label phase III trial ToGA (BO18255) in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:

- capecitabine - 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles (evening of day 1 to morning of day 15 of each cycle)

or

- intravenous 5-fluorouracil - 800 mg/m^2/day as a continuous intravenous infusion over 5 days, given every 3 weeks for 6 cycles (days 1 to 5 of each cycle)

Either of which was administered with:

- cisplatin - 80 mg/m^2 every 3 weeks for 6 cycles on day 1 of each cycle.

The efficacy results from study BO18225 are summarized in Table 13.

Table 13: Efficacy Results from BO18225

Parameter	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

Parameter	FP N=290	FP + H N=294	HR (95% CI)	p-value
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 + H: Fluoropyrimidine/cisplatin + trastuzumab

FP: Fluoropyrimidine/cisplatin

[a] Odds ratio

Patients were recruited to the trial who were previously untreated for HER2-positive inoperable locally advanced or recurrent and/or advanced adenocarcinoma of the stomach or gastro-oesophageal junction not amenable to curative therapy. The primary endpoint was overall survival which was defined as the time from the date of randomization to the date of death from any cause. At the time of the analysis, a total of 349 randomized 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.

Post-hoc subgroup analyses indicate that positive treatment effects are limited to targeting tumours with higher levels of HER2 protein (IHC 2+/FISH+ or IHC 3+). 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 versus 7.6 months, HR 0.64 (95% CI 0.51-0.79) for FP versus FP + H, respectively. For overall survival, the HR was 0.75 (95% CI 0.51-1.11) in the IHC 2+/FISH+ group and the HR was 0.58 (95% CI 0.41-0.81) in the IHC 3+/FISH+ group.

In an exploratory subgroup analysis performed in the TOGA (BO18255) trial there was no apparent benefit on overall survival with the addition of trastuzumab in patients with ECOG PS 2 at baseline [HR 0.96 (95% CI 0.51-1.79)], non-measurable [HR 1.78 (95% CI 0.87-3.66)] and locally advanced disease [HR 1.20 (95% CI 0.29-4.97)].

TRAZIMERA clinical studies

The biosimilar clinical development program for TRAZIMERA included a total of two randomized,

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.

5.2 Pharmacokinetic properties

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects, including patients with HER2 positive MBC, EBC, AGC or other tumor types, and healthy volunteers, in 18 Phase I, II and III trials receiving trastuzumab IV. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to non-linear elimination, total clearance increased with decreasing concentration. Therefore, no constant value for half-life of trastuzumab can be deduced. The $t_{1/2}$ decreases with decreasing concentrations within a dosing interval (see Table 16). MBC and EBC patients had similar PK parameters (e.g., clearance (CL), the central compartment volume (V_c)) and population-predicted steady-state exposures (C_{min}, C_{max} and AUC). Linear clearance was 0.136 L/day for MBC, 0.112 L/day for EBC and 0.176 L/day for AGC. The non-linear elimination parameter values were 8.81 mg/day for the maximum elimination rate (V_{max}) and 8.92 µg/mL for the Michaelis-Menten constant (K_m) for the MBC, EBC, and AGC patients. The central compartment volume was 2.62 L for patients with MBC

and EBC and 3.63 L for patients with AGC.

In the final population PK model, in addition to primary tumor type, body-weight, serum aspartate aminotransferase and albumin were identified as a statistically significant covariates affecting the exposure of trastuzumab. However, the magnitude of effect of these covariates on trastuzumab exposure suggests that these covariates are unlikely to have a clinically meaningful effect on trastuzumab concentrations.

The population predicted PK exposure values (median with 5th-95th Percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for MBC, EBC and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 14 (Cycle 1), Table 15 (steady-state), and Table 16 (PK parameters).

Table 14: Population Predicted Cycle 1 PK Exposure Values (median with 5th-95th Percentiles) for trastuzumab IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumor type	N	C_{min} (µg/mL)	C_{max} (µg/mL)	$AUC_{0\text{-}21\ days}$ (µg.day/mL)
8 mg/kg + 6 mg/kg q3w	MBC	805	28.7 (2.9-46.3)	182 (134-280)	1376 (728-1998)
	EBC	390	30.9 (18.7-45.5)	176 (127-227)	1390 (1039-1895)
	AGC	274	23.1 (6.1-50.3)	132 (84.2-225)	1109 (588-1938)
4 mg/kg + 2 mg/kg qw	MBC	805	37.4 (8.7-58.9)	76.5 (49.4-114)	1073 (597-1584)
	EBC	390	38.9 (25.3-58.8)	76.0 (54.7-104)	1074 (783-1502)

Table 15: Population Predicted Steady State PK Exposure Values (median with 5th-95th Percentiles) for trastuzumab IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumor type	N	$C_{min,ss}$* (µg/mL)	$C_{max,ss}$** (µg/mL)	$AUC_{ss, 0\text{-}21 days}$ (µg.day/mL)	Time to steady-state*** (week)
8 mg/kg + 6 mg/kg q3w	MBC	805	44.2 (1.8-85.4)	179 (123-266)	1736 (618-2756)	12
	EBC	390	53.8 (28.7-85.8)	184 (134-247)	1927 (1332-2771)	15
	AGC	274	32.9 (6.1-88.9)	131 (72.5-251)	1338 (557-2875)	9
4 mg/kg + 2 mg/kg qw	MBC	805	63.1 (11.7-107)	107 (54.2-164)	1710 (581-2715)	12
	EBC	390	72.6 (46-109)	115 (82.6-160)	1893 (1309-2734)	14

* $C_{min,ss}=C_{min}$ at steady state

** $C_{max,ss}=C_{max}$ at steady state

*** Time to 90% of steady-state

Table 16: Population Predicted PK Parameter Values at Steady State for trastuzumab IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumor type	N	Total CL range from $C_{max,ss}$ to $C_{min,ss}$ (L/day)	$t_{1/2}$ range from $C_{max,ss}$ to $C_{min,ss}$ (day)
8 mg/kg + 6 mg/kg q3w	MBC	805	0.183-0.302	15.1-23.3
	EBC	390	0.158-0.253	17.5-26.6
	AGC	274	0.189-0.337	12.6-20.6
4 mg/kg + 2 mg/kg qw	MBC	805	0.213-0.259	17.2-20.4
	EBC	390	0.184-0.221	19.7-23.2

Trastuzumab washout

Trastuzumab washout period was assessed following q1w or q3w intravenous administration using the population PK model. The results of these simulations indicate that at least 95% of patients will reach concentrations that are <1 µg/mL (approximately 3% of the population predicted $C_{min,ss}$, or about 97% washout) by 7 months.

Circulating shed HER2 ECD

The exploratory analyses of covariates with information in only a subset of patients suggested that patients with greater shed HER2-ECD level had faster nonlinear clearance (lower K_m) (P<0.001). There was a correlation between shed antigen and SGOT/AST levels; part of the impact of shed antigen on clearance may have been explained by SGOT/AST levels.

Baseline levels of the shed HER2-ECD observed in MGC patients were comparable to those in MBC and EBC patients and no apparent impact on trastuzumab clearance was observed.

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, randomized, (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.

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) >20 µg/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}>20 µg/mL of TRAZIMERA and Herceptin-EU.

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 with trastuzumab. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine, L-histidine hydrochloride monohydrate, Polysorbate 20, Sucrose

6.2 Incompatibilities

This medicinal product must not be mixed or diluted with other medicinal products except those mentioned under section 6.6.

Do not dilute with dextrose or glucose solutions.

6.3 Shelf life

48 months

6.4 Special precautions for storage

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

Unopened vials of TRAZIMERA should be stored under refrigeration (2°C-8°C) until expiry shown on the vial.

Unopened vials of TRAZIMERA may be stored up to 30°C for a single period of up to 3 months. Upon removal from refrigerated storage, TRAZIMERA must not be returned to refrigerated storage. Discard at the end of this 3-month period or by the expiry date on the vial, whichever occurs first. Record the “discard by” date in the date field provided on the carton.

For storage conditions of the opened medicinal product, see section 6.6.

6.5 Nature and contents of container

15 mL (150 mg) and 30 mL (440 mg) Type I clear glass vial with a chlorobutyl stopper and crimp seal having a flip-off cap.

6.6 Special precautions for disposal and other handling

150 mg presentation

Appropriate aseptic technique should be used. Each 150 mg vial of TRAZIMERA is reconstituted with 7.2 mL of SWFI (not supplied). Use of other reconstitution solvents should be avoided.

This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. A volume overfill of 4% ensures that the labelled dose of 150 mg can be withdrawn from each vial.

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

The reconstituted solution should not be frozen.

Instructions for reconstitution:

1) Using a sterile syringe, slowly inject 7.2 mL of SWFI in the vial containing the lyophilised trastuzumab.
2) Swirl the 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 trastuzumab results in a clear to slightly opalescent and colourless to pale yellow-brown solution and should be essentially free of visible particulates.

After reconstitution with SWFI, the reconstituted solution is physicochemically stable for 48 hours at 2°C-8°C, however, from a microbiological point of view, the product should be used immediately. Any remaining reconstituted solution should be discarded.

Determine the volume of the solution required:

- based on a loading dose of 4 mg trastuzumab/kg body weight, or a subsequent weekly dose of 2 mg trastuzumab/kg body weight:

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

- based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent 3-weekly dose of 6 mg trastuzumab/kg body weight:

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

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with dextrose- or glucose-containing solutions (see section 6.2). The bag should be gently inverted to mix the solution in order to avoid foaming.

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

Solutions for intravenous infusion are physicochemically stable in polyvinylchloride, polyethylene, polypropylene, or ethylene vinyl acetate bags or glass IV bottles containing sodium chloride 9 mg/mL (0.9%) solution for injection for 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and infusion solution should be used immediately. The product is not intended to be stored after reconstitution and dilution unless this has taken place under controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

TRAZIMERA is for single-use only, as the product contains no preservatives. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

440 mg presentation

Appropriate aseptic technique should be used. Each 440 mg vial of TRAZIMERA is reconstituted with 20 mL of bacteriostatic water for injection (BWFI), containing 1.1% benzyl alcohol as a preservative (supplied). This yields a multi-dose solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.0.

In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative (not supplied) to yield a single use solution.

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

The reconstituted solution should not be frozen.

Instructions for reconstitution:

1) Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized TRAZIMERA.
2) Swirl the 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 trastuzumab results in a clear to slightly opalescent and colourless to pale yellow-brown solution and should be essentially free of visible particulates.

Store reconstituted TRAZIMERA at 2°C-8°C.

- If TRAZIMERA is reconstituted with BWFI, discard unused TRAZIMERA after 28 days.
- If TRAZIMERA is reconstituted with SWFI without preservative, the reconstituted solution is physicochemically stable for 48 hours at 2°C-8°C. However, from a microbiological point of view, the product should be used immediately. Any remaining reconstituted solution should be discarded.

Determine the volume of the solution required:

- based on a loading dose of 4 mg trastuzumab/kg body weight, or a subsequent weekly dose of 2 mg trastuzumab/kg body weight:

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

- based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent 3-weekly dose of 6 mg trastuzumab/kg body weight:

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

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with dextrose- or glucose-containing solutions (see section 6.2). The bag should be gently inverted to mix the solution in order to avoid foaming.

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

Solutions for intravenous infusion are physicochemically stable in polyvinylchloride, polyethylene, polypropylene, or ethylene vinyl acetate bags or glass IV bottles containing sodium chloride 9 mg/mL (0.9%) solution for injection for 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution (if SWFI is used) and infusion solution should be used immediately. The product is not intended to be stored after dilution unless this has taken place under controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Pfizer (Thailand) Limited

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT

8 May 2020

Warning (based on the Ministry of Public Health's Announcement)

This drug may cause serious harm, should be used under the supervision of physician.