TRAZHER

150 mg
i.v
ANTINEOPLASTIC

Composition
Each vial of Trazher 150 mg contains:
Active Ingredients:
Trastuzumab.....150 mg
Inactive Ingredients: L-Histidine Hydrochloride Monohydrate, L-Histidine, α,α -Trehalose Dihydrate, Polysorbate 20.
The reconstituted solution contains 21 mg/mL of trastuzumab.
Trazher is biosimilar to Herceptin®
Trazher is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion
exchange chromatography including specific viral inactivation and removal procedures

PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.
White to pale yellow lyophilised powder.

INDICATIONS
Trazher IV

Metastatic Breast Cancer (MBC)
Trazher is indicated for the treatment of patients with metastatic breast cancer who have tumors that overexpress HER2:
a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease
b) in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease
c) in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with Trazher. This indication is based on data from one Phase III trial which studied the use of Trazher in combination with anastrozole (see Clinical/ Efficacy Studies).
Experience with other aromatase inhibitors is limited.

Early Breast Cancer (EBC)
Trazher is indicated for the treatment of patients with HER2 positive early breast cancer.
- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see Clinical/ Efficacy Studies).
- 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 Trazher therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see Special Warnings and Precautions for Use, and Clinical/ Efficacy Studies).
Trazher should only be used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

Metastatic Gastric Cancer (MGC)
Trazher in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Trazher should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory FISH+ result, or IHC 3+, as determined by an accurate and validated assay.

DOSAGE AND ADMINISTRATION

General
HER2 testing is mandatory prior to initiation of Trazher therapy.

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

The safety and efficacy of alternating or switching between Herceptin and products that are biosimilar but not deemed interchangeable to Herceptin has not been established. Therefore, the benefit/risk of alternating or switching need to be carefully considered.

Trazher should be administered by a qualified health care professional.

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is Trazher (trastuzumab) and not another trastuzumab-containing product (eg. trastuzumab emtansine or trastuzumab deruxtecan).

Trazher IV (see Composition, Pharmaceutical Form, Presentations, and Conditions for Preservation and Storage):
Trazher IV is not to be used for subcutaneous administration and should be administered as intravenous infusion.

Do not administer as an intravenous push or bolus.

Metastatic Breast Cancer
Weekly schedule:
Loading dose: The recommended initial loading dose is 4 mg/kg body weight Trazher IV administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable effects). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses: The recommended weekly dose of Trazher IV is 2 mg/kg body weight. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable effects).

Administration in combination with an aromatase inhibitor
In the pivotal trial trastuzumab IV and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab IV and anastrozole at administration (for dose, see the Product Information for anastrozole or other aromatase inhibitors).

3-weekly schedule:
Alternatively the following loading and subsequent doses are recommended for monotherapy and in combination with paclitaxel or an aromatase inhibitor.

Initial Trazher IV loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 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.

Early Breast Cancer
3-weekly schedule:
As a three-weekly regimen the recommended initial loading dose of Trazher IV is 8 mg/kg body weight. The recommended maintenance dose of Trazher at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Alternative weekly schedule:
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.

Metastatic Gastric Cancer
3-weekly schedule:
Trazher IV is administered at an initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the initial loading dose is well tolerated, the subsequent doses can be administered as a 30-minute infusion (see Clinical/ Efficacy Studies for chemotherapy combination dosing).

Duration of Treatment
In clinical studies, patients with metastatic breast cancer or metastatic gastric cancer were treated with trastuzumab until progression of disease or unmanageable toxicity. Patients with early breast cancer should be treated for 1 year or until disease recurrence or unmanageable toxicity, whichever occurs first. Extending treatment in EBC beyond one year is not recommended (see Clinical/ Efficacy Studies).

For instructions for use and handling refer to Preparation, and Method of Administration.

Dose Modification
If the patient develops an infusion-related reaction (IRR), the infusion rate of Trazher IV may be slowed or interrupted (see Special Warnings and Precautions for Use).
No reductions in the dose of Trazher were made during clinical trials. Patients may continue Trazher 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.

Missed Doses
If the patient has missed a dose of Trazher IV 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 Trazher IV maintenance doses 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 Trazher IV by more than one week, a re-loading dose of Trazher IV should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; 3-weekly regimen: 8 mg/kg) as soon as possible. Subsequent Trazher IV 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 Dosage Instructions
Geriatric use
Data suggest that the disposition of Trazher is not altered based on age or serum creatinine (see Pharmacokinetics in Special Populations). In clinical trials, patients ≥ 65 years of age did not receive reduced doses of Trazher. Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. However in a population pharmacokinetic analysis, age and renal impairment were not shown to affect Trazher disposition.

Paediatric use
The safety and efficacy of Trazher in pediatric patients < 18 years of age have not been established.

PREPARATION
Use an appropriate aseptic technique, which ensures the sterility of the preparation.
Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.
The infusion preparation should be prepared in a laminar flow hood or biological safety cabinet and performed by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.

Instruction for aseptic reconstitution
1. Using sterile syringe, slowly inject 7.2 mL of sterile water for injection (not supplied) in the vial containing the lyophilised Trazher, directing the stream into the lyophilised cake. Use of other reconstitution solvents should be avoided.
2. Swirl the vial gently to aid reconstitution. DO NOT SHAKE!

Slight foaming of the product upon reconstitution is not usual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Trazher results in a colorless to pale yellow transparent solution and should be essentially free of visible particulates.

This yields a 7.5 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab at a pH of approximately 6.0.

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

Determine the dose (mg) of Trazher. Calculate the volume of the 21 mg/mL reconstituted Trazher solution needed. The required amount of Trazher (calculated according to specific indications and body weight) shall be withdrawn and added to an infusion bag containing 250 mL of 9 mg/ml (0.9%) sodium chloride solution. Do not use with glucose-containing solutions. The bag should be gently inverted to mix the solution in order to avoid foaming.

METHOD OF ADMINISTRATION
Trazher is for intravenous use only. Do not administer as an intravenous push or bolus.

The loading dose should be administered as a 90-minute intravenous infusion. Patients should be observed for at least 6 hours after the start of the first infusion. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minutes infusion.

Patients should be observed for at least 2 hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

CONTRAINDICATIONS
• Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients/inactive ingredients
• Severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Cardiac dysfunction
General
Patients treated with Trazher are at increased risk for 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 or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have been associated with death.

All candidate for treatment with Trazher, 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. 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 Trazher.

Trastuzumab may persist in the circulation for up to 7 months after stopping Trazher treatment based on population

pharmacokinetic analysis of all available data. Patients who receive anthracyclines after stopping Trazher may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping Trazher. If anthracyclines are used, the patient's cardiac function should be monitored carefully. In patients who receive anthracycline-containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administrations of Trazher, or longer if a continuous decrease of LVEF is observed.

Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequents monitoring (e.g. every 6-8 weeks). If patients have a continued decreased in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Trazher therapy has been seen.

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 Trazher should be strongly considered. If symptomatic cardiac failure develops during Trazher therapy, it should be treated with standard medicinal product for CHF. Most patients who develop CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker 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. All such patients should be referred for assessment by a cardiologist and followed up.

Metastatic breast cancer

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

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

Early breast cancer

Adjuvant treatment

Trazher 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 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, Trazher should be used concurrently with anthracyclines only in chemotherapy-naïve patients and only with low-dose anthracycline regiments i.e maximum cumulative doses of doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2.

In patients have been treated concurrently with a full course of low-dose anthracyclines and Trazher 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.

Infusion-related reactions (IRRs) and hypersensitivity

Serious IRRs to trastuzumab infusion including dyspnea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported. The majority of these events occur the infusion should be 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. 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 corticosteroid. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome.

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.

Patients experiencing dyspnea 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 Trazher.

Pulmonary events

Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting. 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 edema, and respiratory insufficiency have been reported.

Risk factor 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 dyspnea 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 Trazher.

Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes

Precaution

Caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age (>50 years), prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and 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.

In early breast cancer, 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 and cannot be recommended in such patients.

Interaction with other medicinal products and other forms of interactions

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

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents

Paclitaxel and Doxorubicin: Pharmacokinetic studies in women with HER2-positive MBC suggested that exposure to paclitaxel and doxorubicin was not altered in the presence of trastuzumab. 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.

Docetaxel: The concomitant administration of trastuzumab had no effect on the single dose pharmacokinetics of docetaxel in one study in Japanese women with HER2-positive MBC.

Capecitabine: 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 in patients with advanced gastric cancer. Capecitabine showed higher concentrations and a longer half-life when combined with trastuzumab. Cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab.

Carboplatin: Trastuzumab had no impact on the PK of carboplatin in patients with metastatic or locally advance inoperable HER2-positive cancer.

Effect of antineoplastic agents on trastuzumab pharmacokinetics

Docetaxel: No evidence of a PK effect of concurrent administration of docetaxel on the pharmacokinetic of trastuzumab was found in women with HER2-positive MBC.

Paclitaxel and Doxorubicin: There was no clear effect of the concomitant administration of paclitaxel on the pharmacokinetics of trastuzumab in women with HER2-positive MBC. No effect of doxorubicin and paclitaxel on the pharmacokinetic of trastuzumab in women with HER2-positive MBC.

Carboplatin: Carboplatin had no impact on the PK of trastuzumab.

Anastrozole: Anastrozole did not appear to influence the pharmacokinetics of trastuzumab.

Fertility, Pregnancy, and Lactation

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception during treatment with Trazher and for 7 months after treatment has concluded.

Pregnancy

Trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

In the post-marketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving trastuzumab. Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Trazher, or if a patient becomes pregnant while receiving Trazher or within 7 months following the last dose of Trazher, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

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 Trazher therapy and for 7 months after the last dose.

Fertility

There is no fertility data available.

Effect on ability to drive and use machines

Trazher has minor influence on the ability to drive or use machines.

Undesirable Effects

Clinical Trials

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

As trastuzumab is commonly used with other chemotherapeutic agents and radiotherapy it is often difficult to ascertain the causal relationship of an adverse event to a particular drug/radiotherapy.

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

Tabulated list of adverse reactions with the intravenous formulation

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 should be presented in order of decreasing seriousness.

Table 1 Summary of adverse drug reactions occurring in patients treated with trastuzumab in clinical trials

System organ class	Adverse reaction	Frequency
Infections and infestations	Nasopharyngitis	Very Common
	Infection	Very common
	Influenza	Common
	Neutropenic sepsis	Common
	Pharyngitis	Common
	Sinusitis	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	[+]Pneumonia	Common (<1 %)
	Cystitis	Common
	Herpes zoster	Common
	Skin infection	Common
	Erysipelas	Common
	Cellulitis	Common
	Sepsis	Uncommon
Blood and lymphaticsystem disorders	Anaemia	Very common
	Thrombocytopenia	Very common
	Febrile Neutropenia	Very common
	White blood cell count decreased/leukopenia	Very common
	Neutropenia	Very common
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Immune system disorders	Hypersensitivity	Common
	[+]Anaphylactic reaction	Not known
	[+]Anaphylactic shock	Rare
Metabolism and nutrition disorders	Weight Increased	Very common
	Weight Decreased/Weight Loss	Very common
	Decreased appetite	Very common
	Anorexia	Common
	Hyperkalaemia	Not known
Psychiatric disorders	Anxiety	Common
	Depression	Common
	Insomnia	Very common
	Thinking abnormal	Common
Nervous system disorders	[1]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Peripheral neuropathy	Common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Hypertonia	Very common
	Somnolence	Common
	Dysgeusia	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	[1] Blood pressure decreased	Very common
	[1] Blood pressure increased	Very common
	[1] Heart beat irregular	Very common
	[1]Palpitation	Common
	[1]Cardiac flutter	Very common
	+[1]Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	Ejection fraction decreased*	Very Common
	+Cardiac failure (congestive)	Common (2 %)
	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
	+[1] Hypotension	Common
	Hypertension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	+[1]Wheezing	Very common
	+Dyspnoea	Very common (14 %)
	Cough	Very Common
	Epistaxis	Very Common
	Oropharyngeal pain	Very Common
	Rhinorrhoea	Very Common
	Asthma	Common
	Lung disorder	Common
	Pneumonia	Common
	+Pleural effusion	Common
	Pneumonitis	Uncommon
	+Pulmonary fibrosis	Not known
	+Respiratory distress	Not known
	+Respiratory failure	Not known
	+Lung infiltration	Not known
	+Acute pulmonary oedema	Not known
	+Acute respiratory distress syndrome	Not known
	+Bronchospasm	Not known
	+Hypoxia	Not known
	+Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	Orthopnoea	Not known
	Pulmonary oedema	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	[1] Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Haemorrhoids	Common
	Constipation	Very common
	Stomatitis	Very 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
	[1] Swelling face	Very common
	Nail disorder	Very common
	Acne	Common
	Alopecia	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	[1]Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Pain in extremity	Common
	Neck pain	Common
Renal and urinary conditions	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal disorders	Oligohydramnios	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/Administration related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Peripheral oedema	Very common
	Malaise	Common
	Mucosal inflammation	Very common
	Oedema	Common
	Injection site pain**	Common
Injury, poisoning and procedural complications	Nail toxicity	Very common
	Contusion	Common

+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

** ADRs were added to the appropriate system organ class (SOC) category and are presented in a single table according to the highest incidence seen in any of the major clinical trials.

Note: Specific percentage frequencies have been provided in brackets for terms that have been reported in association with a fatal outcome with the frequency designation 'common' or 'very common'. The specific percentage frequencies relate to total number of these events, both fatal and non-fatal.

The following adverse reactions were reported in pivotal clinical trials with a frequency of ≥ 1/10 in either treatment arm (in HERA, BO16348 ≥ 1% at 1 year) and with no significant difference between the trastuzumab-containing arm and the comparator arm: lethargy, hypoaesthesia, pain in extremity, oropharyngeal pain, conjunctivitis, lymphoedema, weight increased, nail toxicity, musculoskeletal pain, pharyngitis, bronchitis, chest discomfort, abdominal pain upper, gastritis, stomatitis, vertigo, hot flush, hypertension, hiccups, palmar-plantar erythrodysaesthesia syndrome, breast pain, onychorrhexis, dyspnoea exertional and dysuria.

Additional information for selected adverse drug reactions Infusion/Administration-related reactions (IRRs) and Hypersensitivity

IRRs/ARRs 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 Special Warnings and Precautions for Use).

IRRs/ARRs may be clinically difficult to distinguish from hypersensitivity reactions.

The rate of IRRs/ARRs 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 MBC, 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 (grade 3 and above) ranged from 5% to 7% in the trastuzumab containing arm compared to 5 to 6% in the comparator arm.

In EBC, 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 (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.

Anaphylactoid reactions were observed in isolated cases.

Serious Pulmonary Events

Single cases of pulmonary infiltrates, pneumonia, pulmonary fibrosis, pleural effusion, respiratory distress, acute pulmonary oedema, acute respiratory distress syndrome (ARDS) and respiratory insufficiency have been reported rarely. These events have been reported rarely with fatal outcome (see Special Warnings and Precautions for Use).

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, S_3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with trastuzumab (see Special Warnings and Precautions for Use).

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 group, compared with 1% – 4% in the paclitaxel alone group. For trastuzumab monotherapy, the rate was 6% – 9%. The highest rate of cardiac dysfunction was seen in patients receiving concurrent trastuzumab + anthracycline/cyclophosphamide (27%), and was significantly higher than in the anthracycline/ cyclophosphamide alone group (7% – 10%). In a subsequent trial 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 CHF.

Early Breast Cancer (adjuvant setting)

In three pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy the incidence of grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone 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%). 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 (NCI-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 the 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 discernable 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 one-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.

Early Breast Cancer (neoadjuvant-adjuvant setting)

In the pivotal trial MO16432, 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.

Metastatic Gastric Cancer

In BO18255 study, at screening, the median LVEF value was 64% (range 48 %-90 %) in the Fluoropyrimidine/Cisplatin arm (FP) and 65 % (range 50 %-86 %) in the trastuzumab IV plus Fluoropyrimidine/Cisplatin arm (FP+H).

The majority of the LVEF decreases noted in BO18255 study were asymptomatic, with the exception of one patient in the trastuzumab-containing arm whose LVEF decrease coincided with cardiac failure.

Table 2 Summary of LVEF Change from baseline (BO18255 study)

LVEF Decrease: Lowest Post-screening Value	Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)	Fluoropyrimidine/ Cisplatin (N = 290) (% of patients in each treatment arm)
*LVEF decrease of ≥ 10% to a value of < 50%	4.6%	1.1%
Absolute Value < 50%	5.9%	1.1%
*LVEF decrease of ≥ 10% to a value of ≥ 50%	16.5%	11.8%

*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)

	Fluoropyrimidine/ Cissplatin (N = 290) (% of patients in each treatment arm)	Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)
Total Cardiac Events	6%	6%
≥ Grade 3 NCICTCAE v3.0	*3%	**1%

* 9 patients experienced 9 Events
** 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
Haematological toxicity was infrequent following the administration of trastuzumab as a single agent in the metastatic setting, WHO Grade 3 leucopenia, thrombocytopenia and anaemia occurring in < 1 % of patients. No WHO Grade 4 toxicities were observed.

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 % versus 21 %). Haematological toxicity was also increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32 % grade 3/4 neutropenia versus 22 %, using NCI-CTC criteria). Note that this is likely to be an underestimate since docetaxel alone at a dose of 100mg/m^2 is known to result in neutropenia in 97 % of patients, 76% grade 4, based on nadir blood counts. The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with trastuzumab plus docetaxel (23 % versus 17 % for patients treated with docetaxel alone).

Using NCI-CTC criteria, in the BO16348 study 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 (AGC)
The most frequently reported AEs, of Grade ≥ 3 occurring with an incidence rate of at least 1% by trial treatment, that were categorised under the Blood and Lymphatic System Disorders SOC are shown below:
Table 4 Frequently reported AEs grade ≥ 3 in blood and lymphatic system disorders SOC

	Fluoropyrimidine/ Cisplatin (N = 290) (% of patients in each treatment arm)	Trastuzumab/ Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)
Neutropenia	30%	27%
Anaemia	10%	12%
Febrile neutropenia	3%	5%
Thrombocytopenia	3%	5%

The total percentage of patients who experienced an AE of ≥ grade 3 NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) v3.0 that has been 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 IV 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 IV and paclitaxel than among patients receiving paclitaxel (7 % compared with 15 %). No WHO Grade 3 or 4 renal toxicity was observed.

Metastatic Gastric Cancer
In BO18255 study no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

NCI-CTCAE (version 3.0) grade ≥ 3 renal toxicity was not significantly higher in patients receiving trastuzumab IV + FP than those in the FP arm (3% and 2% respectively).

NCI-CTCAE (version 3.0) grade ≥ 3 adverse event in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported AE and was not significantly higher in patients receiving trastuzumab IV + FP than those in the FP arm (1% and < 1% respectively).

Diarrhoea
Breast Cancer
Of patients treated with trastuzumab IV as a single agent in the metastatic setting, 27 % experienced diarrhoea. An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has also been observed in patients receiving trastuzumab in combination with paclitaxel compared with patients receiving paclitaxel alone.

In the BO16348 study trial, 8 % of trastuzumab-treated patients experienced diarrhea during the first year of treatment.

Metastatic Gastric Cancer
In BO18255 study, 109 patients (37 %) participating in the trastuzumab-containing treatment arm versus 80 patients (28 %) in the comparator arm experienced any grade diarrhoea. Using NCI-CTCAE severity criteria, the percentage of patients experiencing grade ≥ 3 diarrhoea was 4 % in the FP arm vs 9 % in the FP+H arm.

Infection
An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections has been observed in patients treated with trastuzumab.

Laboratory Abnormalities
Febrile neutropenia occurs very commonly. Commonly occurring adverse reactions include anaemia, leukopenia, thrombocytopenia and neutropenia. The frequency of occurrence of hypoprothrombinemia is not known.

Postmarketing Experience
The following adverse drug reactions have been identified from postmarketing experience with trastuzumab (Table 5).

Table 5 Adverse Reactions reported in the post marketing setting

System organ class	Adverse reaction
Blood and lymphatic system disorders	Hypoprothrombinaemia Immune thrombocytopenia
Immune system disorders	Anaphylactoid reaction
	Anaphylactic reaction
Metabolism and nutrition disorders	Tumour lysis syndrome
Eye disorders	Madarosis
Cardiac disorders	Cardiogenic shock
	Tachycardia
Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Oxygen saturation decreased
	Respiratory failure
	Interstitial lung disease
	Lung infiltration
	Acute respiratory distress syndrome
	Respiratory distress
	Pulmonary fibrosis
	Hypoxia
	Laryngeal oedema
Renal and urinary disorders	Glomerulonephropathy
	Renal failure
Pregnancy, puerperium and perinatalconditions	Pulmonary hypoplasia
	Renal hypoplasia
	Oligohydramnios

Adverse Events
Table 6 below indicates adverse events that historically have been reported in patients who have received trastuzumab. As no evidence of a causal association has been found between trastuzumab and these events, these events are not considered expected for the purposes of regulatory reporting.

Table 6 Adverse Events

System organ class	Adverse Event
Infections and infestations	Meningitis
	Bronchitis
Blood and lymphatic system disorders	Leukaemia
Nervous system disorders	Cerebrovascular disorder
	Lethargy
	Coma
Ear and labyrinth disorders	Vertigo
Respiratory, Thoracic and Mediastinal system disorders	Hiccups
	Dyspnoea exertional
Gastrointestinal disorders	Gastritis
	Pancreatitis
Musculoskeletal and connective tissue disorders	Musculoskeletal pain
Renal and urinary disorders	Dysuria
Reproductive system and breast disorders	Breast pain
General disorders and administration site conditions	Chest discomfort

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies
ATC Codes: L01XC03

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (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% to 34% for IHC and 7.1% to 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 signaling 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
Trazher 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 immunohistochemistry (IHC)-based assessment of fixed tumour blocks. HER2 gene amplification should be detected using fluorescence *in situ* hybridisation (FISH) or chromogenic *in situ* hybridisation (CISH) of fixed tumour blocks. Patients are eligible for Trazher 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.

PHARMACOKINETIC PROPERTIES
Trastuzumab IV
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 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 the non-linear elimination, total clearance increased with decreasing concentrations. Linear clearance was 0.127 L/day for breast cancer (MBC/EBC) and 0.176 L/day for AGC. The nonlinear elimination parameters 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 (Cmax and Cmin) for breast cancer and AGC patients treated with the approved q1w and q3w (3-weekly) dosing regimens are shown in Table 7 (Cycle 1) and Table 8 (steady-state) below.

Table 7 Population Predicted Cycle 1 PK Exposure Values (with 5th - 95th Percentiles) for IV Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumor type	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC (µg.day/mL)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	29.4 (5.8 - 59.5)	178 (117 - 291)	1373 (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 8 Population Predicted Steady State PK Exposure Values (with 5th - 95th Percentiles) for trastuzumab IV Dosing Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumor type	N	Cmin,ss (µg/mL)	Cmax,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 trastuzumab administration using the 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 Cmin,ss, or about 97% washout) by 7 months after the last dose.

Pharmacokinetics in Special Populations
Detailed pharmacokinetic studies in the geriatric population and those with renal or hepatic impairment have not been carried out.

Renal Impairment
Detailed pharmacokinetic studies in patients with renal impairment have not been carried out. In a population pharmacokinetic analysis, renal impairment was shown not to affect trastuzumab disposition.

Geriatric Population
Age has been shown to have no effect on the disposition of trastuzumab (see Dosage and administration).

Clinical / Efficacy Studies
Efficacy
MBC
Trastuzumab monotherapy has been used in clinical trials for patients with metastatic breast cancer who have tumors 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 tumors that overexpress HER2.

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. 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 HER-2, results in an overall tumor 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 HER-2 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 trastuzumab and paclitaxel is 3.9 months (6.9 months vs. 3.0 months). Tumor response and one year survival rate are also increased for trastuzumab in combination with paclitaxel versus paclitaxel alone.

Combination treatment with trastuzumab and anastrozole
Trastuzumab has been studied in combination with anastrozole for first line treatment of metastatic breast cancer 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.

3-weekly dosing in MBC
The efficacy results from the non-comparative monotherapy and combination therapy studies are summarised in the following table:
Table 9

Parameter	Monotherapy		Combination Therapy
	Trastuzumab[1] N=105	Trastuzumab[2] N=72	Trastuzumab plus paclitaxel[3] N=32
Response rate (95%CI)	24% (15 - 35)	27% (14 - 43)	59% (41-76)
Median duration of response (months) (range)	10.1 (2.8-35.6)	7.9 (2.1-18.8)	10.5 (1.8-21)
Median TTP (months) (95%CI)	3.4 (2.8-4.1)	7.7 (4.2-8.3)	12.2 (6.2-ne)
Median Survival (months) (95%CI)	ne	ne	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 6mg/kg weekly x 3; followed by 6mg/kg 3-weekly schedule
3.BO15935

EBC
In the adjuvant treatment setting, trastuzumab was investigated in 4 large multicentre, randomised, phase 3 trials:
- Study BO16348 study was designed to compare one year and two years of three-weekly trastuzumab treatment versus observation in patients with HER2 positive early breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a 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.
- Studies NSABP B-31 and NCCTG N9831 that comprise the joint analysis were designed to investigate the clinical utility of combining trastuzumab IV treatment with paclitaxel following AC chemotherapy; additionally the NCCTG N9831 study investigated adding trastuzumab sequentially to AC-paclitaxel chemotherapy in patients with HER2 positive early breast cancer following surgery.
- Study BCIRG 006 study was designed to investigate combining trastuzumab IV treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2 positive early breast cancer following surgery.

Early breast cancer in the Study BO16348 was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative tumours of at least 1 cm in diameter.

The efficacy results from the BO16348 study are summarized in the following table:
Table 10 Efficacy Results BO16348 study: Results at 12 months* and 8 years of median follow-up**

	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 vs 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 vs. 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 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% 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 joint analysis of the NSABP B-31 and NCCTG N9831 studies, early breast cancer 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 (tumour size > 1 cm and ER negative or tumour size > 2 cm, regardless of hormonal status). Trastuzumab was administered in combination with paclitaxel, following AC chemotherapy. Paclitaxel was administered as follows:
- intravenous paclitaxel - 80 mg/m^2 as a continuous IV infusion, given every week for 12 weeks, or
- intravenous paclitaxel - 175 mg/m^2 as a continuous IV infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

Table 11 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 (n=1679)	AC→PH (n=1672)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Disease-free survival No. patients with event (%)	261 (15.5)	133 (8.0)	< 0.0001	0.48 (0.39, 0.59)
Distant Recurrence No. patients with event (%)	193 (11.5)	96 (5.7)	< 0.0001	0.47 (0.37, 0.60)
Death (OS event): No. patients with event (%)	92 (5.5)	62 (3.7)	0.014	0.67 (0.48, 0.92)

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 vs. AC→P
Source: Table 15 Clinical Study Report: Joint Analysis of B-31 and N9831, 04 February 2006, Genentech, Inc.

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 a 3-year disease-free survival rate, of 11.8 percentage points (87.2% versus 75.4%) in favour of the AC→PH (trastuzumab) arm.

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→P H 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→P H 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 the following table:

Table 12 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

In the BCIRG 006 study, HER-2 positive, early breast cancer was limited to either lymph node positive or high risk node negative patients, defined as negative (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, estrogen receptor and progesterone receptor negative, histologic and/or nuclear grade 2-3, or age < 35 years. 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:
- intravenously (100 mg/m^2 as an IV 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
- intravenously (75 mg/m^2 as an IV infusion over 1 hour) given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each cycle).

Docetaxel therapy was followed by carboplatin (at target AUC = 6 mg/mL/min) administered by IV infusion over 30-60 minutes repeated every 3 weeks for a total of 6 cycles.

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

Table 13 Overview of Efficacy Analyses AC→D versus AC →DH (BCIRG 006 study)

Parameter	AC→D (N=1073)	AC→DH (N=1074)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival No. patients with event	195	134	< 0.0001	0.61 (0.49, 0.77)
Distant recurrence No. patients with event	144	95	< 0.0001	0.59 (0.46, 0.77)
Overall Survival (Death) 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 14 Overview of Efficacy Analyses AC→D versus DCarbH (BCIRG 006 study)

Parameter	AC→D (N=1073)	DCarbH (N=1075)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival No. patients with event	195	145	0.0003	0.67 (0.54, 0.83)
Distant recurrence No. patients with event	144	103	0.0008	0.65 (0.50, 0.84)
Death (OS event) No. patients with event	80	56	0.0182	0.66 (0.47, 0.93)

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 a 3-year disease-free survival rate, 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.

For the secondary endpoint overall survival, treatment with AC→DH reduced the risk of death by 42% when compared to AC→D (hazard ratio 0.58 [95% CI: 0.40, 0.83] p = 0.0024, log-rank test) and the risk of death was reduced by 34% for patients treated with DCarbH compared to patients treated with AC→D (hazard ratio 0.66 [95% CI: 0.47, 0.93], p = 0.0182). In the BCIRG 006 study at the second interim analysis, 185 randomized patients had died: 80 patients (7.5%) in the AC→D arm, 49 patients (4.6%) in the AC→DH arm, and 56 patients (5.2%) in the DCarbH arm. The median duration of follow-up was 2.9 years in the AC→D arm and 3.0 years in both the AC→DH and DCarbH arms.

In the neoadjuvant-adjuvant treatment setting, trastuzumab was evaluated in two phase 3 trials.

Study MO16432, a multicenter randomised trial, was designed to investigated a total of 10 cycles of neoadjuvant chemotherapy [an anthracycline and a taxane (AP+H followed by P+H, followed by CMF+H] concurrently with neoadjuvant-adjuvant trastuzumab, or neoadjuvant chemotherapy alone, followed by adjuvant trastuzumab for up to a total treatment duration of 1 year) in newly diagnosed locally advanced (Stage III) or inflammatory HER2 positive breast cancer patients. The clinical utility of concurrent administration of trastuzumab with neoadjuvant chemotherapy including both an anthracycline and a taxane (AP+H followed by P+H, followed by CMF+H, followed by adjuvant trastuzumab, up to a total treatment duration of 1 year) as follow:

- Doxorubicin 60mg/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 study 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, or neoadjuvant chemotherapy alone.

Table 15 Overview of Efficacy Analyses MO16432 study

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
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

For the primary endpoint, EFS, the addition of trastuzumab to the 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.

Metastatic Gastric Cancer

Trastuzumab has been investigated in one randomised, open-label phase III trial 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 i.v. 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 the following table:

Table 16 Summary of Efficacy (from study BO18255 study)

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

In an exploratory subgroup analysis performed in the 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)].

Description of Comparative Study Conducted Using Trazher

Clinical Study of Trazher (Study HLX02 – HV01 and HLX02 – BC01)

The pharmacokinetic of Trazher were evaluated in a population pharmacokinetic (PopPK) using the data collected from phase I (Healthy volunteers received single dose of 6 mg/kg HLX02, or US or Germany sourced Herceptin®) and phase III study HLX02 – BC01 (Patient with HER2-positive, recurrent or previously untreated metastatic breast cancer, received HLX02 or EU – sourced Herceptin® 8 mg/kg on Day 1, Cycle 1, and then every 3 weeks for subsequent cycles at 6 mg/kg). The final PopPK model was developed based on a dataset of 754 subjects with 5.882 samples enrolled in two clinical studies. Trazher and Herceptin® PopPK was parameterized with clearance of the central compartment for HLX02 (CL_{HLX}) and Herceptin® (CL_{HER}), volume of the central compartment for HLX02 ($Vc_{,HLX}$) and Herceptin® ($Vc_{,HER}$), clearance of distribution from the central to the peripheral compartment for HLX02 (Q_{HLX}) and Herceptin® (Q_{HER}) and volume of the peripheral compartment for HLX02 ($Vp_{,HLX}$) and Herceptin® ($Vp_{,HER}$).

Body weight, health status and shed antigen were identified as significant covariates on the clearance. For a typical patient with body weight of 62 kg and shed antigen (SHED) of 10.93 ng/ml, the estimated CL were 0.0172 L/hr, 0.0155 L/hr, VcS were 3.23 L, 2.94 L, Qs were 0.0442 L/hr, 0.0480 L/hr, and VpS were 0.759 L, 0.839 L for Trazher and Herceptin®, respectively. Inter-individual variability on CL and Vc were 19.5% and 9.44%, respectively. Body weight associated drug exposure difference of Trazher and Herceptin® shows similar trend within a narrow (2%) range, e.g. 15.8 – 16.7% for AUCss, 13.9 – 14.4% for Cmax,ss, and 15.5 – 17.0% for Cmin,ss.

The steady state exposure in healthy volunteers were significantly lower than those in patients for both Trazher (11.3% for AUCss, 1.98% for Cmax,ss, and 25.7% for Cmin,ss) and EU-sourced Herceptin® (7.31% for AUCss, 0.572% for Cmax,ss and 18.4% for Cmin,ss). Less than 8% difference in Trazher and Herceptin® drug exposure was determined in patients with breast cancer and healthy volunteers, e.g. 7.31 – 11.3% for AUCss, 0.572 – 1.98% for Cmax,ss, 18.4 – 25.7% for Cmin,ss. Subjects with higher shed antigen demonstrated lower AUCss, Cmax,ss and Cmin,ss in both Trazher (13.4% for AUCss, 4.54% for Cmax,ss, and 33.1% for Cmin,ss) and Herceptin® (7.55% for AUCss, 2.12% for Cmax,ss, and 18.3% for Cmin,ss). Less than 15% difference in Trazher and Herceptin® drug exposure was determined in patients with higher shed antigen and lower shen antigen, e.g. 7.55 – 13.4% for AUCss, 2.12 – 4.54% for Cmax,ss, and 18.3 – 33.1% for Cmin,ss.

Phase III study Trazher was a multicenter, multinational, double-blind, randomized, parallel group, active-controlled to compare the efficacy and to evaluate the similarity of safety and immunogenicity of HLX02 and European-sourced Herceptin® in combination with docetaxel in patients with HER2 positive, recurrent or previously untreated metastatic breast cancer. The primary objective of the study was to compare objective response rate (ORR) at week 24, and secondary objectives were duration of response (DoR), disease control rate (DCR), clinical benefit rate (CBR), progression free survival (PFS) 12 months, overall survival (OS) 12, 24, 36 months.

Of 649 randomized patients, the ITT and SAS had 324 patients in Trazher group and 325 patients in Herceptin® group; the PP set had 310 patients in Trazher group and 306 patients in Herceptin® group; and the PK analysis set had 321 and 324 patients in Trazher and Herceptin® groups respectively. Patient demographics and key baseline characteristics were balanced between the Trazher and Herceptin® treatment groups.

Both Trazher and Herceptin® were administered as a loading dose of 8 mg/kg over 90 minutes on day 1, cycle 1, then 6 mg/kg every 3 weeks for subsequent cycles. Docetaxel dose was 75 mg/m^2 administered on day 2, cycle 1, then if well tolerated the same dose was given every 3 weeks on day 1 of each subsequent cycle always starting 60 minutes after the end of the HLX02 or European-sourced Herceptin® infusion. Dexamethasone was given as prophylactic drug either oral or intravenous (IV) in patients treated with docetaxel.

After up to 8 cycles of treatment at week 24, the proportions of patients with a best overall response (BOR) of complete response (CR) were 17/324 (5.2%) in the Trazher groups versus 12/325 (3.7%) in the Herceptin® groups. Similar proportions of patients in both groups had BOR of partial response (PR); 214 (66.0%) patients in Trazher group and 220 (67.7%) patients in Herceptin® group. The efficacy of the primary endpoint, ORR up to week 24 was 71.3% in Trazher treatment group and 71.4% in Herceptin® treatment group with no statistical difference observed between the 2 treatments group (P = 0.983). Therapeutic equivalence of Trazher and Herceptin® was statistically supported by the primary efficacy results of the ITT (P=0.983, risk difference in ORR = -0.1%) as well as the PP population (P=0.727, risk difference in ORR = 1.0%).

All secondary efficacy analysis (CBR, DCR, DoR, PFS, and OS) at week 24 supported the conclusion of therapeutic equivalence. The median DoR was from 10.61 to 10.71 and 10.12 to 11.60 months for Trazher and Herceptin®, respectively. The event free rate at 12 months for PFS ranged approximately between 41.8% and 55.5% for Trazher and 41.0% and 46.7% for Herceptin®. The event free rate at 12 months for OS ranged approximately between 86.4% and 89.5% for Trazher and 84.6% to 90.1% for Herceptin®.

For safety results, 98.8% of the patients reported at least 1 adverse event (AE) and treatment-emergent adverse events (TEAEs); similar number of AEs and TEAEs were reported between the Trazher and Herceptin® group. Similar incidence of AEs was noted for total Asian (99.0%) and non-Asian (98.0%) populations. Most commonly reported TEAEs by PT were white blood cell (WBC) decreased (82.4%), neutrophil count decreased (82.1%), alopecia (55.6%), and anemia (51.5%) in the Trazher treated patients; and WBC decreased (84.9%), neutrophil count decreased (82.5%), anemia (57.5%), and alopecia (53.5%) in Herceptin® treated patients. Asian and Chinese populations, 71.5% to 75.9% of patients reported TEAEs related to the study drug each treatment group and approximately 60.8% to 64.4% of patients in non-Asian and non-Chinese populations reported study drug-related TEAEs, with a similar incidence observed in Trazher and Herceptin®.

A total of 158 (24,3%) patients (Trazher: 77 [23.8%] patients; Herceptin®: 81 [24.9%] patients) reported 306 serious treatment-emergent adverse events (TEAEs), most commonly reported standard of care (SOC) being investigations, infections and infestations, and blood and lymphatic system disorders. Only 9.7% if the patients reported serious TEAEs related to study drug. Serious TEAEs related to study medication had similar incidence in the 2 treatment groups. The incidence and frequency of occurrence of serious TEAEs related to study drug were similar among 2 treatment groups in non-Asian (Trazher: 0%; Herceptin®: 1.4%) and Asian (Trazher: 12.9%; Herceptin®: 12.0%) patients as well as non-Chinese (Trazher: 2.3%; Herceptin®: 2.2%) and Chinese (Trazher: 12.7%; Herceptin®: 12.3%) patients. Nine of the 649 patients in the study dies due to TEAE, 3 (0.9%) in the Trazher group and 6 (1.8%) in the Herceptin® group.

The Trazher exposures in ADA (anti-drug antibody) and NADA (neutralizing anti-drug antibody) negative subjects were higher than that in ADA and NADA positive subjects (73.4%, 9.92%, and 419% for AUCss, Cmax,ss and Cmin,ss, respectively), as well as the Herceptin® exposures in ADA and NADA negative subjects were higher than that in ADA and NADA positive subjects (6.95%, 0.988%, and 18.5% for AUCss, Cmax,ss and Cmin,ss, respectively). Due to the low number of ADA and NADA positive patients (less than 1% ADA and NADA positive patients), these results should be interpreted with caution.

OVERDOSE

There is no experience with overdose in human clinical trials. Single doses of Trazher higher 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 clinical trial with metastatic gastric cancer patients. Doses up to this level were well tolerated.

Presentations:
Box of 1 vial of 150 mg presented in a Type I glass vial with bromobutyl rubber stopper and aluminium-plastic combination cap.

CONDITIONS FOR PRESERVATION AND STORAGE:
Shelf life:
Unopened vial: 3 years

Vials must be stored in a refrigerator between 2°C and 8°C.

After aseptic reconstitution with sterile water for injection, chemical and physical stability of the reconstituted solution has been demonstrated for 48 hours at 2°C and 8°C.

After aseptic dilution in polypropylene bag containing sodium chloride 9 mg/mL (0.9%) solution for injection, chemical and physical stability of Trazher has been demonstrated for up to 7 days at 2°C - 8°C, and subsequently for 24 hours at 30°C.

Do not freeze the reconstituted solution.

From a microbiological point of view, the product 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 2 to 8°C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

KEEP OUT OF REACH OF CHILDREN
ON MEDICAL PRESCRIPTION ONLY

Reg No.:

Manufactured by:
Shanghai Henlius Biopharmaceutical Co., Ltd., Shanghai - China

Registration holder:
Innogene Kalbiotech Pte. Ltd., Singapore

Current at October 2022

KALBE