AUSTRALIAN PRODUCT INFORMATION
Phesgo (pertuzumab and trastuzumab)

1. NAME OF THE MEDICINE
Pertuzumab and trastuzumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Phesgo is a clear to opalescent solution, colourless to slightly brownish solution supplied as:

- 1200 mg pertuzumab and 600 mg trastuzumab per 15 mL solution in a single dose vial with 30000 units of vorhyaluronidase alfa.
- 600 mg pertuzumab and 600 mg trastuzumab per 10 mL solution in a single dose vial with 20000 units of vorhyaluronidase alfa.

Vorhyaluronidase alfa (recombinant human hyaluronidase rHuPH20) is an enzyme used to increase the dispersion and absorption of co-formulated drugs when administered subcutaneously.

For the full list of excipients, see section *6.1 List of excipients*.

3. PHARMACEUTICAL FORM
Solution for subcutaneous injection.

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS

Early Breast Cancer (EBC)

Phesgo is indicated in combination with chemotherapy for the:

- neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either >2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer
- adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence

Select patients for therapy based on a validated test.

Metastatic Breast Cancer (MBC)

Phesgo is indicated in combination with docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Select patients for therapy based on a validated test.

4.2 DOSE AND METHOD OF ADMINISTRATION
Phesgo therapy should only be initiated under the supervision of a physician experienced in the use of anti-cancer agents.

Phesgo should always be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are immediately available (see section *4.4 Special warnings and precautions for use).*

Patient selection

To be eligible for treatment with Phesgo, patients must have a HER2-positive tumor status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of ≥ 2.0 by *in situ* hybridisation (ISH), assessed by a validated test.

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

For full instructions on assay performance and interpretation, please refer to the package inserts of validated HER2 testing assays.

Administration of Phesgo

Phesgo is only for subcutaneous (SC) administration in the thigh. **Do not administer intravenously (IV).**

When given SC, the doses of both trastuzumab and pertuzumab are different to those for IV administration. In order to prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is Phesgo (rather than a product containing either trastuzumab or pertuzumab alone, or for IV administration, or a trastuzumab or pertuzumab drug-antibody conjugate).

In patients receiving a taxane, Phesgo should be administered prior to the taxane. When administered with Phesgo, the recommended initial dose of docetaxel is 75 mg/m^2. The dose of docetaxel may be escalated to 100 mg/m^2 if the initial dose is well tolerated.

In patients receiving an anthracycline-based regimen, Phesgo should be administered following completion of the entire anthracycline regimen.

The recommended dosing and administration schedule for Phesgo is shown in Table 1.

Table 1: Recommended dosing and administration of Phesgo

	Dose (irrespective of body weight)	Approximate duration of SC injection	Observation time*
Initial (loading) dose	1200 mg pertuzumab/ 600 mg trastuzumab	8 minutes	30 minutes
Subsequent (maintenance) dose (once every 3 weeks thereafter)	600 mg pertuzumab/ 600 mg trastuzumab	5 minutes	15 minutes

* This is the minimum time that patients should be observed for injection-related and hypersensitivity reactions. The observation time starts when the Phesgo injection is finished, and must be completed prior to any subsequent administration of chemotherapy.

The injection site should always be located in the thigh, and should be alternated between the left thigh and the right thigh. New injections should be given at least 2.5 cm/1 inch from the previous site, into healthy skin and never into areas where the skin is red, bruised, tender, or hard.

Do not split the dose between two syringes or between two sites of administration. While a patient is continuing a treatment course with Phesgo, avoid giving other medications for subcutaneous administration in the thigh: inject them at different sites instead if possible.

Method of administration

For instructions on preparation of the medicine before administration, see section 6.6.

Duration of treatment

Early Breast Cancer (EBC)

In the neoadjuvant setting (before surgery), Phesgo should be administered for three to six cycles (depending on the regimen chosen) in combination with chemotherapy (see section *5.1 Pharmacodynamic properties - Clinical trials*). Patients who start Phesgo in the neoadjuvant setting should also receive adjuvant Phesgo, as described below.

In the adjuvant setting (after surgery), Phesgo should be administered for a total of one year (maximum 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first), as part of a complete regimen for early breast cancer, including standard anthracycline- and/or taxane-based chemotherapy. Phesgo treatment should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued (see section *5.1 Pharmacodynamic properties - Clinical trials*).

Metastatic Breast Cancer (MBC)

Phesgo should be administered in combination with docetaxel until disease progression or unmanageable toxicity. Treatment with Phesgo may continue even if treatment with docetaxel is discontinued.

Delayed or missed doses

If the last dose of Phesgo was less than 6 weeks ago, administer a maintenance dose of Phesgo (600 mg pertuzumab and 600 mg trastuzumab) as soon as possible. Do not wait until the next planned dose. Give another maintenance dose of Phesgo 3 weeks later, and every 3 weeks thereafter.

If it has been 6 weeks or longer since the last dose of Phesgo, administer a loading dose of Phesgo (1200 mg pertuzumab and 600 mg trastuzumab) as soon as possible. Do not wait until the next planned dose. Give a maintenance dose of Phesgo (600 mg pertuzumab and 600 mg trastuzumab) 3 weeks later, and every 3 weeks thereafter.

Dose modifications

Dose reductions are not recommended for Phesgo. For chemotherapy dose modifications, refer to the chemotherapy product information.

Adverse reactions

Injection-related reactions

The injection should be slowed or paused if the patient experiences injection-related symptoms (see *4.4 Special warnings and precautions for use).*

Hypersensitivity/anaphylaxis
Discontinue the injection immediately and permanently if the patient experiences a serious hypersensitivity reaction (e.g. anaphylaxis) (see *4.4 Special warnings and precautions for use)*.

Left ventricular dysfunction
Assess left ventricular ejection fraction (LVEF) prior to initiation of Phesgo and at regular intervals during treatment, and interrupt Phesgo as indicated in Table 2.

Table 2: Dose recommendations for left ventricular dysfunction

	Do not commence dosing unless pre-treatment LVEF is:	**Monitor LVEF every:**	**Withhold Phesgo for at least 3 weeks for an LVEF decrease to:**		**Resume Phesgo after 3 weeks if LVEF has recovered to:**	
Early Breast Cancer	≥ 55%*	~12 weeks (once during neoadjuvant therapy)	<50% with a fall of ≥10%-points below pre-treatment value		Either of	
					≥ 50%	< 10%-points below pre-treatment value
Metastatic Breast Cancer[a]	≥ 50%	~12 weeks	Either of		Either of	
			<40%	40%-45% with a fall of ≥10%-points below pre-treatment value	>45%	40%-45% with a fall of <10%-points below pre-treatment value

* For patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracyclines before starting Phesgo.

If Phesgo dosing is withheld due to a decrease in LVEF according to Table 2, and after a repeat assessment it has not improved, has declined further, and/or the patient is symptomatic, permanently discontinue Phesgo (see *4.4 Special warnings and precautions for use*).

Special populations

Paediatric patients
The safety and efficacy of Phesgo in children and adolescents (<18 years) has not been established.

Elderly patients
No dose adjustment of Phesgo is required in patients ≥65 years of age.

Renal impairment
No dose adjustment of Phesgo is required in patients with mild or moderate renal impairment. No dose recommendations can be made for patients with severe renal impairment because of the limited pharmacokinetic data available (see *5.2 Pharmacokinetic Properties*).

Hepatic impairment

The safety and efficacy of Phesgo have not been studied in patients with hepatic impairment. No dose recommendation can be made for this group of patients.

4.3 CONTRAINDICATIONS

Phesgo is contraindicated in patients with a known hypersensitivity to pertuzumab, trastuzumab or any of the excipients (see *6.1 List of excipients*).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Left ventricular dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including pertzumab and trastuzumab. The incidence of symptomatic left ventricular systolic dysfunction (LVD (congestive heart failure)) was higher in patients treated with pertuzumab in combination with trastuzumab and chemotherapy compared to trastuzumb and chemotherapy. In the adjuvant setting, the majority of cases of symptomatic heart failure reported were in patients who received anthracycline-based chemotherapy (see *4.8 Adverse Events (Undesirable effects)*). Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF decreases based on studies with intravenous pertuzumab in combination with trastuzumab and chemotherapy. Based on the pharmacological actions of HER2-targeted agents and anthracyclines, the risk of cardiac toxicity might be expected to be higher with concomitant use of pertuzumab and anthracyclines than with sequential use.

Sequential use of Phesgo (in combination with a taxane) following the doxorubicin component of two anthracycline-based regimens was evaluated in the FEDERICA study while sequential use of intravenous pertuzumab (in combination with trastuzumab and a taxane) following the epirubicin or doxorubicin component of many anthracycline-based regimens was evaluated in the APHINITY and BERENICE studies (see *4.8 Adverse effects (undesirable effects) – Further information on selected adverse drug reactions*). In the TRYPHAENA study, intravenous pertuzumab in combination with trastuzumab was given concurrently with epirubicin, as part of the FEC (5-fluorouracil, epirubicin, cyclophosphamide) regimen (see *5.1 Pharmacydynamic properties – Clinical trials*). Only chemotherapy-naive patients were treated and they received low cumulative doses of epirubicin (up to 300 mg/m2). In this study, cardiac safety was similar to that observed in patients given the same regimen but with pertuzumab administered sequentially (following FEC chemotherapy).

Phesgo and/or intravenous pertuzumab and trastuzumab have not been studied in patients with: a pretreatment LVEF value of <55% (EBC) or <50% (MBC); a prior history of congestive heart failure (CHF); conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to >360 mg/m^2 of doxorubicin or its equivalent. Intravenous pertuzumab in combination with trastuzumab and chemotherapy has not been studied in patients with decreases in LVEF <50% during prior trastuzumab adjuvant therapy.

Prior to initiation of Phesgo, conduct a thorough cardiac assessment, including history, physical examination, and determination of LVEF. Assess LVEF during Phesgo treatment, and interrupt treatment if it declines, as described in Table 2 (see *4.2 Dose and method of*

administration). Re-assess 3 weeks after interruption, and if the LVEF has not improved, has declined further, and/or the patient is symptomatic, permanently discontinue Phesgo. Following completion of Phesgo, continue to monitor for cardiomyopathy and assess LVEF measurements every 6 months for at least 2 years as a component of adjuvant therapy.

Hypersensitivity/anaphylaxis and administration-related reactions

Severe administration-related reactions, including hypersensitivity and anaphylaxis, can occur with pertuzumab and trastuzumab. No fatal injection-related reactions have occurred with Phesgo, however, caution should be exercised as fatal infusion related-reactions have occurred in patients treated with intravenous pertuzumab, trastuzumab and chemotherapy. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a severe or fatal administration-related reaction.

Closely monitor patients during and after administration of Phesgo as described in Table 1 (*4.2 Dose and method of administration*). If a significant injection-related reaction occurs, slow down or pause the injection and administer appropriate medical therapies, which may include adrenaline, corticosteroids, antihistamines, bronchodilators and oxygen. Evaluate and carefully monitor patients until complete resolution of signs and symptoms.

Permanently discontinue Phesgo in patients who experience anaphylaxis or severe injection-related reactions. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. For patients experiencing reversible Grade 1 or 2 hypersensitivity reactions, consider pre-medication with an analgesic, antipyretic, or an antihistamine prior to readministration of Phesgo. Phesgo is contraindicated in patients with known hypersensitivity to pertuzumab, trastuzumab, or to any of its excipients (*see 4.3 Contraindications*).

Exacerbation of chemotherapy-induced neutropenia

Phesgo may exacerbate chemotherapy-induced neutropenia.

In randomised controlled clinical trials with intravenous trastuzumab, Grade 3-4 neutropenia and febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab and those who did not.

In randomised controlled clinical trials, patients who received intravenous pertuzumab in combination with trastuzumab and docetaxel were at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel.

Pulmonary toxicity

Serious and fatal pulmonary toxicities have been reported with intravenous trastuzumab in the post-market setting. Pulmonary toxicity includes dyspnoea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary oedema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Patients with symptomatic intrinsic lung disease or with extensive tumour involvement of the lungs, resulting in dyspnoea at rest, appear to have more severe toxicity.

Tumour Lysis Syndrome

Cases of tumour lysis syndrome have been reported in patients treated with trastuzumab and pertuzumab in the post-market setting. Patients with significant tumour burden (e.g. bulky metastases) may be at a higher risk. Presentations may involve hyperuricaemia, hyperphosphataemia or acute renal failure.

Paediatric use

The safety and efficacy of Phesgo in patients below 18 years of age have not been established.

Use in the elderly

No overall differences in efficacy and safety of Phesgo were observed in patients ≥65 (n=26) and <65 years of age (n=222).

However, with intravenous pertuzumab in combination with trastuzumab, the incidence of the following all grade adverse events were at least 5% higher in patients ≥65 years of age (n=418) compared to patients <65 years of age (n=2926): decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesaemia and diarrhoea.

Use in renal impairment

No formal PK study of Phesgo has been conducted in patients with renal impairment.

Based on population PK analyses of pertuzumab within Phesgo and intravenous pertuzumab, renal impairment was shown not to affect pertuzumab exposure; however, only limited data from patients with severe renal impairment were included in population PK analyses (see *5.2 Pharmacokinetic properties*).

In a population pharmacokinetic analysis of subcutaneous and intravenous trastuzumab, renal impairment was shown not to affect trastuzumab disposition.

Use in hepatic impairment

The safety and efficacy of Phesgo in patients with hepatic impairment has not been studied.

Effect on laboratory tests

See *4.8 Adverse effects (undesirable effects).*

Traceability

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded in the patient file.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Patients who receive anthracycline after stopping Phesgo may be at increased risk of cardiac dysfunction because of Phesgo's long washout period (see *5.2 Pharmacodynamic properties – Excretion*). If possible, avoid anthracycline-based therapy for up to 7 months after stopping Phesgo. If anthracyclines are used, carefully monitor the patient's cardiac function.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No specific studies have been conducted into the effects of the pertuzumab/trastuzumab combination on fertility.

Pertuzumab

No adverse effects of IV pertuzumab on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six month duration in cynomolgus monkeys.

Trastuzumab

A study in female cynomolgus monkeys revealed no evidence of impaired fertility at IV trastuzumab doses up to 25 mg/kg twice weekly, corresponding to serum trough levels (serum C_{min}) about 22 times higher than that in humans receiving the recommended 600 mg SC dose every 3 weeks. Additionally, no adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six months duration in cynomolgus monkeys. .

Use in pregnancy - Category D

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

Based on animal studies and post-marketing data (see below), Phesgo has the potential to cause fetal harm when administered to a pregnant woman. Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Phesgo, or if a patient becomes pregnant while receiving Phesgo or within 7 months following the last dose of Phesgo, close monitoring by a multidisciplinary team is desirable.

No clinical studies of Phesgo, pertuzumab or trastuzumab in pregnant women have been performed. In the post-marketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women who received trastuzumab.

No studies of effects on embryofetal development have been conducted with the pertuzumab/trastuzumab combination.

The safe use of Phesgo during labour and delivery has not been established.

Animal data regarding use in pregnancy

Pertuzumab

Pregnant cynomolgus monkeys were treated on Gestational Day (GD) 19 with loading doses of 30 to 150 mg/kg pertuzumab, followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than exposures in humans receiving the recommended dose, based on C_{max}. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-fetal death between GD25 to GD70. The incidences of embryo-fetal loss were 33, 50, and 85%. At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights, and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups.

Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

Trastuzumab

In studies where intravenous trastuzumab was administered to pregnant cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (up to 25 times the recommended weekly human dose of 2 mg/kg), trastuzumab crossed the placental barrier during the early (Gestation Days 20 to 50) and late (Gestation Days 120 to 150) phases of gestation. The resulting concentrations of trastuzumab in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.

Vorhyaluronidase alfa

Phesgo contains vorhyaluronidase alfa (see *6.1 List of excipients*). In an embryo-fetal study, mice were dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase (recombinant human) at dose levels up to 2,200,000 U/kg, which is >2400 and 3600 times higher than the recommended human loading and maintenance doses, respectively. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is >400 and 600times higher than the human loading and maintenance doses, respectively.

In a peri-and post-natal reproduction study, mice were dosed daily by subcutaneous injection, with hyaluronidase (recombinant human) from implantation through lactation and weaning at dose levels up to 1,100,000 U/kg, which is >1,200 and 1,800, based on loading and maintenance doses, respectively, times higher than the human dose. The study found no adverse effects on sexual maturation, learning and memory or fertility of the offspring.

Contraception

Women of childbearing potential including those who are partners of male patients should use effective contraception during treatment with Phesgo and for 7 months following the last dose of Phesgo.

Use in lactation

As human IgG is excreted in human milk, and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue nursing during Phesgo therapy and for 7 months after the last dose of Phesgo.

A study conducted in lactating cynomolgus monkeys dosed with IV trastuzumab at 25 mg/kg twice weekly (serum C_{min} about 22 times higher than that in humans receiving the SC maintenance dose of 600 mg) demonstrated that trastuzumab is excreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with adverse effects on their growth or development from birth to 1 month of age.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Phesgo could influence the ability to drive and use machines as injection-related reactions and dizziness may occur during treatment with Phesgo.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of PHESGO was evaluated in an open-label, multicentre study (FEDERICA) in which 500 patients with HER2-overexpressing early breast cancer were randomised to receive either PHESGO or intravenous pertuzumab and trastuzumab in addition to neoadjuvant chemotherapy and as adjuvant therapy after surgery (see *5.1 Pharmacodynamic properties – Clinical trials*).

The median duration of treatment for PHESGO amongst the 248 patients who received it was 24 weeks (range: 0-42 weeks).

Serious adverse reactions occurred in 16% of patients who received PHESGO. Serious adverse reactions in >1% of patients included febrile neutropenia (4%), neutropenic sepsis (1%), and neutrophil count decreased (1%). One patient (0.4%) experienced a fatal adverse reaction (an acute myocardial infarction), but this occurred prior to the start of treatment with PHESGO.

Adverse reactions resulting in permanent discontinuation of any study drug occurred in 8% of patients in the PHESGO arm. Adverse reactions which resulted in permanent discontinuation of PHESGO were ejection fraction decreased (1.2%), cardiac failure (0.8%), and pneumonitis/pulmonary fibrosis (0.8%).

Dosage interruptions due to an adverse reaction occurred in 40% of patients who received PHESGO. Adverse reactions which required dosage interruption in >1% of patients who received PHESGO included neutropenia (8%), neutrophil count decreased (4%), and diarrhoea (7%).

Table 3 and Table 4 summarise the most common adverse events and laboratory abnormalities (worsening from baseline) seen in FEDERICA: those with incidence of at least 5%. Clinically relevant adverse events that occurred in less than 5% of patients who received PHESGO include ejection fraction decreased (3.6%) and pruritus (3.2%).

Table 3: Adverse events that occurred in at least 5% of patients who received PHESGO in FEDERICA

Body System/Adverse Reactions	**PHESGO (n=248)**		**Intravenous pertuzumab plus intravenous or subcutaneous trastuzumab (n=252)**	
	All Grades %	**Grades 3 – 4 %**	**All Grades %**	**Grades 3 – 4 %**
Skin and subcutaneous tissue disorders				
Alopecia	77	0	71	0.4
Dry skin	15	0.4	13	0
Rash	16	0.4	21	0

Body System/Adverse Reactions	**PHESGO (n=248)**		**Intravenous pertuzumab plus intravenous or subcutaneous trastuzumab (n=252)**	
	All Grades %	**Grades 3 – 4 %**	**All Grades %**	**Grades 3 – 4 %**
Nail discolouration	9	0	6	0
Erythema	9	0	5	0
Dermatitis	7	0	6	0
Nail disorder	7	0	7	0.4
Palmar-plantar erythrodysaesthesia syndrome	6	0.8	5	0.4
Gastrointestinal disorders				
Nausea	60	2	61	1.6
Diarrhoea	60	7	57	4.8
Stomatitis	25	0.8	24	0.8
Constipation	22	0	21	0
Vomiting	20	0.8	19	1.2
Dyspepsia	14	0	12	0
Haemorrhoids	9	0	4.0	0
Abdominal pain upper	8	0	6	0
Abdominal pain	9	0.4	6	0
Blood and lymphatic system disorders				
Anaemia	36	1.6	43	4.4
Neutropenia	22	14	27	14
Leukopenia	9	2.4	14	2
Febrile neutropenia	7	7	6	6
General disorders and administration site conditions				
Asthenia	31	0.4	32	2.4
Fatigue	29	2	24	2
Mucosal inflammation	15	0.8	20	1.2
Injection site reaction	15	0	0.8	0
Pyrexia	13	0	16	0.4
Oedema peripheral	8	0	10	0
Malaise	7	0	6	0.4
Influenza-like illness	5	0	3.6	0
Nervous system disorders				
Dysgeusia	17	0	14	0
Peripheral sensory neuropathy	16	0.8	14	0.4
Headache	17	0	25	0.8
Neuropathy peripheral	12	0.4	15	2
Paraesthesia	10	0.8	8	0
Dizziness	13	0	11	0

Body System/Adverse Reactions	**PHESGO (n=248)**		**Intravenous pertuzumab plus intravenous or subcutaneous trastuzumab (n=252)**	
	All Grades %	**Grades 3 – 4 %**	**All Grades %**	**Grades 3 – 4 %**
Investigations				
Weight decreased	11	0.8	6	0.8
Musculoskeletal and connective tissue disorders				
Myalgia	25	0.4	19	0.4
Arthralgia	24	0	28	0.4
Back pain	10	0	4.8	0
Bone pain	7	0	5	0
Pain in extremity	6	0	8	0
Muscle spasms	6	0	7	0
Musculoskeletal pain	6	0.4	8	0
Respiratory, thoracic and mediastinal disorder				
Cough	15	0.4	13	0
Epistaxis	12	0	14	0.4
Dyspnoea	10	1.2	5	0
Rhinorrhoea	7	0	4.4	0
Infections and infestations				
Upper respiratory tract infection	11	0	8	0.8
Nasopharyngitis	9	0	10	0
Paronychia	7	0.4	3.6	0
Urinary tract infection	7	0.4	5	0
Injury, poisoning and procedural complications				
Procedural pain	13	0	10	0
Radiation skin injury	19	0.4	19	0.4
Infusion-related reaction	3.6	0	15	0.8
Metabolism and nutrition disorders				
Decreased appetite	17	0.8	19	0.4
Hypokalaemia	7	1.6	8	0
Psychiatric disorders				
Insomnia	17	0	13	0.4
Eye disorders				
Lacrimation increased	5	0.4	6	0
Dry eye	5	0.4	3.2	0
Vascular disorders				
Hot flush	12	0	13	0

Table 4: Laboratory abnormalities that worsened from baseline in at least 5% of patients who received PHESGO in FEDERICA

	PHESGO (n=248)		**Intravenous pertuzumab plus intravenous or subcutaneous trastuzumab (n=252)**	
Laboratory Abnormality	**All Grades %**	**Grades 3 – 4 %**	**All Grades %**	**Grades 3 – 4 %**
Haematology				
Haemoglobin (low)	90	2.8	92	4.4
Lymphocytes, Absolute (low)	89	37	88	36
Total Leukocyte Count (low)	82	25	78	25
Neutrophils, Total Absolute (low)	68	30	67	33
Platelet (low)	27	0	28	0.4
Chemistry				
Creatinine (high)	84	0	87	0.4
Alanine aminotransferase (high)	58	1.6	68	2.4
Aspartate aminotransferase (high)	50	0.8	58	0.8
Potassium (low)	17	5.2	17	2.8
Albumin (low)	16	0	20	0.4
Potassium (high)	13	1.2	9	0
Sodium (low)	13	0.4	10	1.6
Bilirubin (high)	9	0	9	0.4
Glucose (low)	9	0	9	0.4
Sodium (high)	7	0.8	10	0.8

The safety profile of Phesgo seen in FEDERICA was broadly consistent with the established safety profile of intravenous pertuzumab in combination with trastuzumab and chemotherapy that was described in four pivotal randomised studies (n=3344):

- CLEOPATRA, in which pertuzumab was given in combination with trastuzumab and docetaxel to patients with MBC (n=453)
- NEOSPHERE (n=309) and TRYPHAENA (n=218), in which neoadjuvant pertuzumab was given in combination with trastuzumab and chemotherapy to patients with locally advanced, inflammatory or EBC
- APHINITY, in which adjuvant pertuzumab was given in combination with trastuzumab and anthracycline-based or non-anthracycline-based, taxane-containing chemotherapy to patients with EBC (n=2364)

Across these four randomised studies, the most common (≥5%) adverse reactions with pertuzumab in combination with trastuzumab were diarrhoea, infusion-related reactions, asthenia, fatigue, rash, ejection fraction decreased, and anaemia.

The most common (≥1%) serious adverse events (SAEs) reported in patients treated with Phesgo or intravenous pertuzumab in combination with trastuzumab were febrile neutropenia, pyrexia, neutropenia, neutropenic sepsis, infusion-related reaction and neutrophil count decreased.

Further information on selected adverse drug reactions

Left ventricular dysfunction

In FEDERICA, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10%-points from baseline and to <50% was 0.4% in the Phesgo arm and 0% in the comparator arm. All of the patients who experienced symptomatic heart failure recovered (defined as 2 consecutive LVEF measurements above 50%). Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10%-points from baseline and to <50% (confirmed by secondary LVEF) were reported in 0.4% of the Phesgo arm and 0.8% of the comparator arm. None of the cases of asymptomatic or mildly symptomatic declines in LVEF had recovered at the data cutoff.

In CLEOPATRA, the incidence of LVD during study treatment was higher in the placebo-treated group than the pertuzumab-treated group (8.6% and 6.6%, respectively). The incidence of symptomatic LVD was also lower in the pertuzumab-treated group (1.8% in the placebo-treated group vs. 1.5% in the pertuzumab-treated group) (*(see 4.4 Special warnings and precautions for use)*).

In NEOSPHERE, in which patients received four cycles of pertuzumab as neoadjuvant treatment, the incidence of LVD (during the overall treatment period) was higher in the pertuzumab, trastuzumab and docetaxel-treated group (7.5%) compared to the trastuzumab and docetaxel-treated group (1.9%). There was one case of symptomatic LVD in the pertuzumab and trastuzumab-treated group.

In TRYPHAENA, the incidence of LVD (during the overall treatment period*)* was 8.3% in the group treated with pertuzumab plus trastuzumab and 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by pertuzumab plus trastuzumab and docetaxel; 9.3% in the group treated with pertuzumab plus trastuzumab and docetaxel following FEC; and 6.6% in the group treated with pertuzumab in combination with TCH. The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with pertuzumab plus trastuzumab and docetaxel following FEC *(this excludes a patient that experienced symptomatic LVD during FEC treatment prior to receiving pertuzumab plus trastuzumab and docetaxel)* and was also 1.3% in the group treated with pertuzumab in combination with TCH. No patients in the group treated with pertuzumab plus trastuzumab and FEC followed by pertuzumab plus trastuzumab and docetaxel experienced symptomatic LVD.

In the BERENICE study, two non-randomised cohorts of patients with EBC (n=401) received neoadjuvant pertuzumab and trastuzumab in combination with one of two different neoadjuvant chemotherapy regimens, followed by surgery and then up to one year of adjuvant pertuzumab and trastuzumab, with a primary outcome of cardiac safety during neoadjuvant treatment (see also *5.1 Pharmacodynamic properties – Clinical trials*). In the neoadjuvant period of the BERENICE trial, the incidence of NYHA Class III/IV

symptomatic LVD (congestive heart failure according to NCI-CTCAE v.4) was 1.5% in the group treated with dose dense AC followed by pertuzumab plus trastuzumab and paclitaxel and none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by pertuzumab in combination with trastuzumab and docetaxel. The incidence of asymptomatic LVD (PT ejection fraction decrease according to NCI-CTCAE v.4) was 7% in the group treated with dose dense AC followed by pertuzumab plus trastuzumab and paclitaxel and 3.5% in the group treated with FEC followed by pertuzumab plus trastuzumab and docetaxel.

In APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10%-points from baseline and to <50% was <1% (0.6% of pertuzumab-treated patients vs 0.2% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 47% of pertuzumab-treated patients and 67% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. The majority of the events were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10%-points from baseline and to <50% were reported in 2.7% of pertuzumab-treated patients and 2.8% of placebo-treated patients, of whom 80% of pertuzumab-treated patients and 81% of placebo-treated patients had recovered at the data cutoff.

Injection/infusion-related reactions

Injection/infusion-related reactions were defined as events of hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome (or in FEDERICA, any systemic reaction) reported during or within 24 hours of administration of pertuzumab or trastuzumab.

In FEDERICA, injection-related reactions were reported in 1.2% of Phesgo-treated patients and infusion-related reactions were reported in 10.3% of the comparator arm. Injection site reactions (defined as any local reaction reported within 24 hours of Phesgo) were reported in 12.9% of Phesgo-treated patients and were all grade 1 or 2 events.

Infusion-related reaction was defined in the pivotal trials as any event reported as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the same day as the infusion. In CLEOPATRA, the initial dose of pertuzumab was given the day before trastuzumab and docetaxel to allow for the examination of pertuzumab-associated reactions. On the first day (when only pertuzumab was administered) the overall frequency of infusion-related reactions was 9.8% in the placebo-treated group and 13.2% in the pertuzumab-treated group, with the majority of reactions being mild or moderate. The most common infusion-related reactions (≥1%) in the pertuzumab-treated group were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting. During the second cycle when all drugs were administered on the same day, the most common infusion related reactions (≥1%) in the pertuzumab-treated group were fatigue, drug hypersensitivity, dysgeusia, hypersensitivity, myalgia, and vomiting.

In neoadjuvant and adjuvant trials, pertuzumab was administered on the same day as the other study treatment drugs. Infusion-related reactions occurred in 19% - 25% of patients on the first day of pertuzumab administration (in combination with trastuzumab and

chemotherapy). The type and severity of events were consistent with those observed in CLEOPATRA, with a majority of reactions being mild or moderate.

Hypersensitivity reactions/anaphylaxis
In FEDERICA, the overall frequency of hypersensitivity/anaphylaxis reported events related to HER2-targeted therapy was 1.6% in both the Phesgo arm and the comparator arm, with no events higher than NCI-CTCAE (version 4) Grade 2.

In CLEOPATRA, the overall frequency of hypersensitivity/anaphylaxis reported events was 9.3% in the placebo-treated patients and 11.3% in the pertuzumab-treated patients, of which 2.5% and 2.0% were NCI-CTCAE (version 3) grade 3-4, respectively. Overall, 2 patients in placebo-treated group and 4 patients in the pertuzumab-treated group experienced anaphylaxis (*(see 4.4 Special warnings and precautions for use)*).

In neoadjuvant and adjuvant trials, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NEOSPHERE, two patients in the pertuzumab and docetaxel-treated group experienced anaphylaxis. In both TRYPHAENA and APHINITY, the overall frequency of hypersensitivity/anaphylaxis was highest in the pertuzumab and TCH treated group (13.2% and 7.6% respectively), of which 2.6% and 1.3% of events, respectively were NCI-CTCAE Grade 3-4.

Diarrhoea
Diarrhoea is very common with pertuzumab treatment, more so with concurrent taxane therapy, and in patients older than 65 years. Management is standard, including early intervention for severe cases (which are common) or patients at higher risk of complications (including frail or elderly patients). In APHINITY, the rate of diarrhoea was 71% (10% grade 3-4 severity) in patients who received pertuzumab and 45% (4% grade 3-4) in those who did not.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE
There is no experience with overdose of Phesgo in human clinical trials. The highest Phesgo dose tested is 1200 mg pertuzumab/600 mg trastuzumab.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
ATC code: not yet assigned

Mechanism of action
Phesgo contains pertuzumab and trastuzumab, which provide the therapeutic effect of this medicinal product, and vorhyaluronidase alfa, which is an enzyme used to increase the dispersion and absorption of co-formulated substances when administered subcutaneously.

Pertuzumab and trastuzumab are recombinant humanized immunoglobulin (Ig)G1κ monoclonal antibodies that target the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2): a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Pertuzumab and trastuzumab bind to distinct HER2 epitopes, subdomains II and IV, respectively, with complementary mechanisms for disrupting HER2 signaling. The binding of pertuzumab and trastuzumab to two separate epitopes results in augmented anti-proliferative activity *in vitro* and *in vivo* when pertuzumab and trastuzumab are given in combination.

Both pertuzumab and trastuzumab mediate antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, ADCC are exerted preferentially on HER2-overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Clinical trials

This section presents clinical experience from studies investigating the use of pertuzumab in combination with trastuzumab in patients with HER2-positive early breast cancer (EBC) and metastatic breast cancer (MBC). With the exception of FEDERICA, all of the studies were conducted using intravenous pertuzumab with trastuzumab, and support the use of Phesgo for the studied indications based on the pharmacokinetic non-inferiority of Phesgo to intravenous pertuzumab plus trastuzumab, as demonstrated in FEDERICA (see *5.2 Pharmacokinetic properties*). Supporting efficacy data with Phesgo from FEDERICA is also included below.

HER2 overexpression in all trials described below was determined at a central laboratory and defined as a score of 3+ by IHC or an ISH amplification ratio ≥2.0.

Early Breast Cancer (EBC)

FEDERICA (WO40324)

FEDERICA was an open-label, multicentre, randomised study conducted in 500 patients with HER2-positive early breast cancer that is operable or locally advanced (including inflammatory) breast cancer with a tumour size >2 cm or node-positive in the neoadjuvant and adjuvant setting. Patients were randomised to receive 8 cycles of neoadjuvant chemotherapy with concurrent administration of 4 cycles of either Phesgo or intravenous pertuzumab and trastuzumab during cycles 5-8. Investigators selected one of two of the following neoadjuvant chemotherapy regimens for individual patients:

- 4 cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks followed by paclitaxel (80 mg/m^2) weekly for 12 weeks
- 4 cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks followed by 4 cycles of docetaxel (75 mg/m^2 for the first cycle and then 100 mg/m^2 at subsequent cycles at the investigator's discretion) every 3 weeks

Following surgery, patients continued therapy with Phesgo or intravenous pertuzumab and trastuzumab as treated prior to surgery, for an additional 14 cycles, to complete 18 cycles of HER2-targeted therapy. Patients also received adjuvant radiotherapy and endocrine therapy as per local practice. In the adjuvant setting, substitution of intravenous trastuzumab for subcutaneous trastuzumab SC was permitted at investigator discretion. HER2-targeted therapy was administered every 3 weeks according to Table 5 as follows:

Table 5: Dosing and administration of Phesgo, intravenous pertuzumab, intravenous trastuzumab, and subcutaneous trastuzumab

Medication	Administration	Dose	
		Loading	Maintenance
Phesgo	Subcutaneous injection	1200 mg/600 mg	600 mg/600 mg
pertuzumab	Intravenous infusion	840 mg	420 mg
trastuzumab	Intravenous infusion	8 mg/kg	6 mg/kg
trastuzumab	Subcutaneous injection	600 mg	

FEDERICA was designed to demonstrate non-inferiority of the pertuzumab Cycle 7 (i.e., pre-dose Cycle 8) serum C_{trough} of pertuzumab within Phesgo compared with intravenous pertuzumab (primary endpoint). Additional secondary endpoints included non-inferiority of the Cycle 7 serum trastuzumab C_{trough} of trastuzumab within Phesgo compared with intravenous trastuzumab, efficacy [total pathological complete response (tpCR)], and safety outcomes. Demographics were balanced between the two treatment arms and the median age of patients treated in the study was 51 years. The majority of patients had hormone receptor-positive disease (61.2%), node-positive disease (57.6%), and were Caucasian (65.8%).

Non-inferiority of the pertuzumab and trastuzumab exposure from Phesgo was demonstrated (*see 5.2 Pharmacokinetic properties*). The analysis of secondary efficacy endpoint, tpCR, defined as an absence of invasive disease in the breast and axilla (ypT0/is, ypN0), is shown in Table 6.

Table 6: Summary of total pathological Complete Response (tpCR)

	Phesgo (n=248)	Intravenous pertuzumab + trastuzumab (n=252)
tpCR (ypT0/is, ypN0)	148 (59.7%)	150 (59.5%)
Exact 95% CI for tpCR Rate[1]	(53.28, 65.84)	(52.18, 65.64)
Difference in tpCR rate (SC minus IV arm)	0.15	
95% CI for the difference in tpCR[2] rate	-8.67 to 8.97	

[1] Confidence interval for one sample binomial using Pearson-Clopper method
[2] Hauck-Anderson continuity correction has been used in this calculation

NEOSPHERE (WO20697) – neoadjuvant treatment of EBC

NEOSPHERE was a multicentre, randomised Phase II clinical trial conducted in 417 patients with operable, locally advanced, or inflammatory HER2-positive breast cancer (T2-4d) who were scheduled for neoadjuvant therapy. Patients were randomised to receive one of four neoadjuvant regimens prior to surgery as follows: trastuzumab plus docetaxel, pertuzumab plus trastuzumab and docetaxel, pertuzumab plus trastuzumab, or pertuzumab plus docetaxel. Randomization was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen (ER) or progesterone (PgR) positivity.

Pertuzumab and trastuzumab were administered intravenously as outlined in Table 5 for 4 cycles. Following surgery all patients received three cycles of 5-fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), cyclophosphamide (600 mg/m^2) (FEC) given intravenously every three weeks and trastuzumab administered intravenously every three weeks to complete one

year of therapy. Patients in the pertuzumab plus trastuzumab and docetaxel arm received docetaxel every three weeks for four cycles prior to FEC after surgery so that all patients received equivalent cumulative doses of the chemotherapeutic agents and trastuzumab.

The primary endpoint of the study was pathological complete response (pCR) rate in the breast (ypT0/is). Secondary efficacy endpoints were clinical response rate, breast conserving surgery rate (T2-3 only), disease-free survival (DFS), and PFS. Additional exploratory pCR rates included nodal status (ypT0/isN0 and ypT0N0).

Demographics were balanced between treatment arms. The median age was 49-50 years, the majority were Caucasian (71%) and all patients were female. Overall, 7% of patients had inflammatory breast cancer, 32% had locally advanced breast cancer and 61% had operable breast cancer. Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER positive and/or PgR positive).

The efficacy results are summarised in Table 7 (with the results of the TRYPHAENA study). A statistically significant and clinically meaningful improvement in pCR rate (ypT0/is) was observed in patients receiving pertuzumab plus trastuzumab and docetaxel compared to patients receiving trastuzumab and docetaxel (45.8% vs 29.0%, p value = 0.0141). A consistent pattern of results was observed regardless of pCR definition.

Pathological complete response (pCR) rates as well as the magnitude of improvement with pertuzumab were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors (5.9% to 26.0% and 27.3% to 63.2%, respectively).

TRYPHAENA (BO22280) – neoadjuvant treatment of EBC followed by adjuvant trastuzumab

TRYPHAENA was a multicentre, randomised, open-label Phase II clinical study conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d) breast cancer. Patients were randomised to receive one of three neoadjuvant regimens prior to surgery as follows: 3 cycles of FEC followed by 3 cycles of docetaxel all in combination with pertuzumab and trastuzumab, 3 cycles of FEC alone followed by 3 cycles of docetaxel and trastuzumab in combination with pertuzumab, or 6 cycles of TCH in combination with pertuzumab. Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and ER and /or PgR positivity.

Pertuzumab and trastuzumab were administered intravenously as outlined in Table 5. 5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), cyclophosphamide (600 mg/m^2) were given intravenously every three weeks for 3 cycles. Docetaxel was given as an initial dose of 75 mg/m^2 IV infusion every three weeks with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. However, in the pertuzumab in combination with TCH arm, docetaxel was given intravenously at 75 mg/m^2 and no escalation was permitted and carboplatin (AUC 6) was given intravenously every three weeks. Following surgery all patients received trastuzumab to complete one year of therapy, which was administered intravenously every 3 weeks.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study (see *4.4 Special warnings and precautions for use*). Secondary efficacy endpoints were pCR rate in the breast (ypT0/is), DFS, PFS and OS.

Demographics were balanced between treatment arms. The median age was 49-50 years, the majority were Caucasian (77%)) and all patients were female. Overall 6% of patients had inflammatory breast cancer, 25% had locally advanced breast cancer and 69% had operable breast cancer, with approximately half the patients in each treatment group had ER-positive and/or PgR-positive disease.

High pCR rates were observed in all 3 treatment arms (see Table 7). A consistent pattern of results was observed regardless of pCR definition. pCR rates were lower in the subgroup of patients with hormone receptor-positive tumours than in patients with hormone receptor-negative tumours (46.2% to 50.0% and 65.0% to 83.8% respectively).

Table 7: NEOSPHERE (WO20697) and TRYPHAENA (BO22280): summary of efficacy (ITT population)

	NEOSPHERE (WO20697)				**TRYPHAENA (BO22280)**		
Parameter	**T+D N=107**	**Ptz+T+D N=107**	**Ptz+T N=107**	**Ptz+D N=96**	**Ptz+T+FEC/ Ptz+T+D N=73**	**FEC/ Ptz+T+D N=75**	**Ptz+TCH N=77**
ypT0/is n (%) [95% CI][1]	31 (29.0%) [20.6; 38.5]	49 (45.8%) [36.1; 55.7]	18 (16.8%) [10.3; 25.3]	23 (24.0%) [15.8; 33.7]	45 (61.6%) [49.5; 72.8]	43 (57.3%) [45.4; 68.7]	51 (66.2%) [54.6; 76.6]
Difference in pCR rates[2] [95% CI][3]		+16.8 % [3.5; 30.1]	-12.2 % [-23.8; -0.5]	-21.8 % [-35.1; -8.5]	NA	NA	NA
p-value (with Simes corr. for CMH test)[4]		0.0141 (vs. T+D)	0.0198 (vs. T+D)	0.0030 (vs Ptz+T+D)	NA	NA	NA
ypT0/is N0 n (%) [95% CI]	23 (21.5%) [14.1; 30.5]	42 (39.3%) [30.3; 49.2]	12 (11.2%) [5.9; 18.8]	17 (17.7%) [10.7; 26.8]	41 (56.2%) [44.1; 67.8]	41 (54.7%) [42.7; 66.2]	49 (63.6%) [51.9; 74.3]
ypT0 N0 n (%) [95% CI]	13 (12.1%) [6.6; 19.9]	35 (32.7%) [24.0; 42.5]	6 (5.6%) [2.1; 11.8]	13 (13.2%) [7.4; 22.0]	37 (50.7%) [38.7; 62.6]	34 (45.3%) [33.8; 57.3]	40 (51.9%) [40.3; 63.5]
Clinical Response[5]	79 (79.8%)	89 (88.1%)	69 (67.6%)	65 (71.4%)	67 (91.8%)	71 (94.7%)	69 (89.6%)

Key to abbreviations (Table 7): T: Trastuzumab; D: docetaxel; Ptz: Pertuzumab; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin and trastuzumab.

1. 95% CI for one sample binomial using Pearson-Clopper method.
2. Treatment Ptz+T+D and Ptz+T are compared with T+D, while Ptz+D is compared with Ptz+T+D
3. Approximate 95% CI for difference of two rates using Hauck-Anderson method.
4. p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment
5. Clinical response represents patients with a best overall response of CR or PR during the neoadjuvant period (in the primary breast lesion)

BERENICE (WO29217) - neoadjuvant and adjuvant treatment of EBC

BERENICE was a non-randomised, open-label, multicentre, multinational, Phase II trial conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage HER2-positive breast cancer.

Patients considered suitable for neoadjuvant treatment with trastuzumab plus anthracycline/taxane-based chemotherapy were allocated to receive one of the two following regimens prior to surgery as follows:

- Cohort A - 4 cycles of two-weekly doxorubicin and cyclophosphamide (dose dense AC) followed by 4 cycles of pertuzumab in combination with trastuzumab and paclitaxel
- Cohort B - 4 cycles of FEC followed by 4 cycles of pertuzumab in combination with trastuzumab and docetaxel.

Pertuzumab and trastuzumab were administered intravenously as outlined in Table 5. Doxorubicin 60 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV were administered every 2 weeks (ddAC) for four cycles (Cycles 1-4) with G-CSF (granulocyte colony stimulating factor) support at investigator discretion, followed by paclitaxel 80 mg/m^2 IV weekly for 12 weeks (Cycles 5-8), with pertuzumab and trastuzumab every 3 weeks during Cycles 5-8 (from the start of paclitaxel; four cycles of pertuzumab and trastuzumab in total during the neoadjuvant period). 5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), cyclophosphamide (600 mg/m^2) were given intravenously every three weeks for 4 cycles. Docetaxel was given at an initial dose of 75 mg/m^2 IV infusion every three weeks with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. Following surgery all patients received pertuzumab and trastuzumab which were administered intravenously every 3 weeks, to complete one year of therapy.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study. A secondary endpoint was pCR rate (defined as eradication of invasive disease in the breast and axilla [i.e., ypT0/is ypN0], or total pathologic complete response [tpCR]), assessed by an external pathology expert.

The median age of enrolled patients was 49 years in both Cohort A (n=128) and Cohort B (n=124). The majority of patients were Caucasian (83%), female (all but one), and had hormone receptor-positive disease (64% of Cohort A and 62% of Cohort B).

The primary endpoint of cardiac safety, i.e. the incidence of NYHA Class III/IV LVD and LVEF declines, was consistent with previous data in the neoadjuvant setting (see *4.8 Adverse Events (Undesirable effects) – Further information on selected adverse drug reactions*).

The rate of pCR (tpCR or ypT0/is ypN0) was 62% in Cohort A and 61% in Cohort B. The pCR rates in Cohort A and Cohort B, respectively, were 52% and 57% for patients with hormone receptor-positive tumours, and 82% and 68% for patients with hormone receptor-negative tumours.

APHINITY (BO25126) – adjuvant treatment of EBC

APHINITY was a multicentre, randomised, double-blind, placebo-controlled Phase III trial conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumour excised prior to randomisation. Patients were then randomised to receive pertuzumab or placebo, in combination with adjuvant trastuzumab and chemotherapy. Investigators selected one of the following anthracycline-based or non-anthracycline-based chemotherapy regimens for individual patients:

- 3 or 4 cycles of FEC or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC), followed by 3 or 4 cycles of docetaxel or 12 cycles of weekly paclitaxel
- 4 cycles of AC or EC, followed by 3 or 4 cycles of docetaxel or 12 cycles of weekly paclitaxel
- 6 cycles of docetaxel in combination with carboplatin

Pertuzumab and trastuzumab were administered intravenously as outlined in Table 5, starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (maximum 18 cycles) or until recurrence, withdrawal of consent or unmanageable toxicity. Standard doses of 5-fluorouracil, epirubicin, doxorubicin, cyclophosphamide, docetaxel, paclitaxel and carboplatin were administered. After completion of chemotherapy, patients received radiotherapy and/or hormone therapy as per local clinical standard.

The primary endpoint of the study was invasive disease-free survival (IDFS), defined as the time from randomisation to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause.

Demographics were balanced between the two treatment arms. The median age was 51 years, and over 99% of patients were female. The majority of patients had node-positive (63%) and/or hormone receptor-positive disease (64%), and were Caucasian (71%).

Pertuzumab-treated patients and placebo-treated patients both received a median number of 18 cycles of anti-HER2 therapy. After a median follow-up to 45.4 months, the APHINITY study demonstrated a statistically significant improvement in IDFS in patients randomised to receive pertuzumab compared with patients randomised to receive placebo.

The efficacy results from the APHINITY trial are summarised in Table 8, Figure 1 and Table 9.

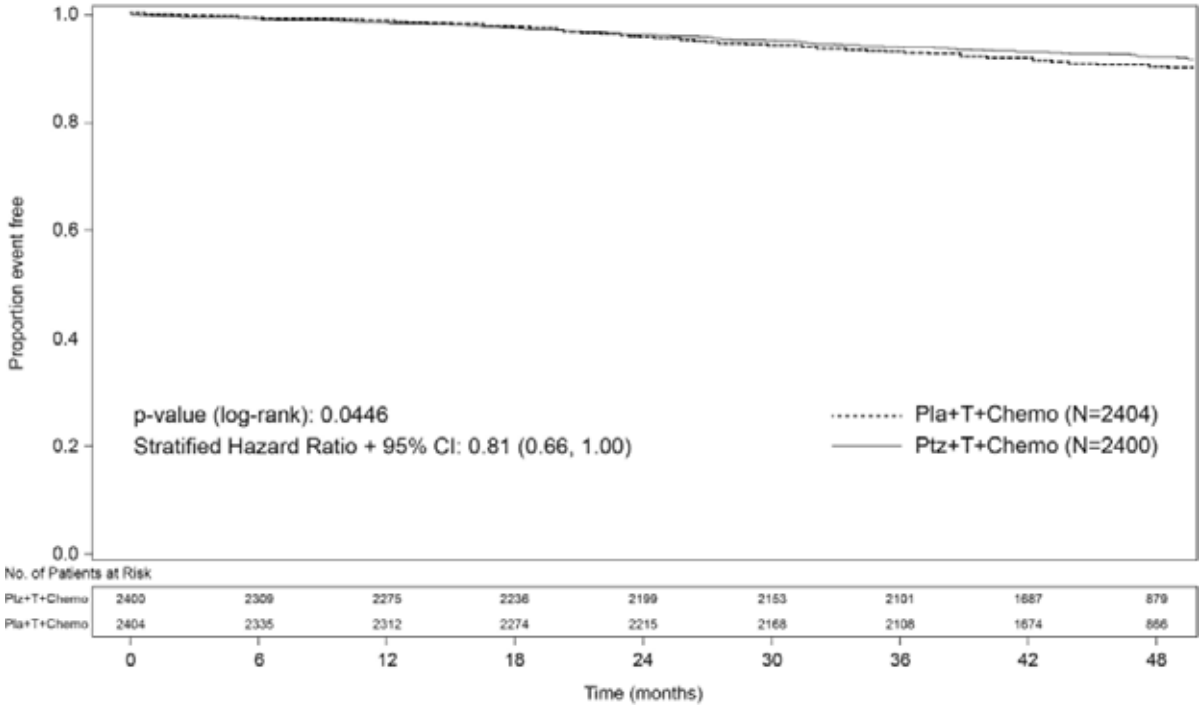
Table 8: Efficacy in the APHINITY trial (ITT population)

	Pertuzumab + trastuzumab + chemotherapy N=2400	**Placebo + trastuzumab + chemotherapy N=2404**
Primary endpoint		
Invasive disease-free survival (IDFS)		
Number (%) of patients with event	171 (7.1%)	210 (8.7%)
HR [95% CI]	0.81 [0.66, 1.00]	
p-value (Log-Rank test, stratified[2])	0.0446	
3 year event-free rate[3] [95% CI]	94.1 [93.1, 95.0]	93.2 [92.2, 94.3]
Secondary endpoints[1]		
IDFS including second primary non-breast cancer		
Number (%) of patients with event	189 (7.9%)	230 (9.6%)
HR [95% CI]	0.82 [0.68, 0.99]	
p-value (log-rank test, stratified[2])	0.0430	
3 year event-free rate[3] [95% CI]	93.5 [92.5, 94.5]	92.5 [91.4, 93.6]
Disease-free survival (DFS)		
Number (%) of patients with event	192 (8.0%)	236 (9.8%)
HR [95% CI]	0.81 [0.67, 0.98]	
p-value (log-rank test, stratified[2])	0.0327	
3 year event-free rate[3] [95% CI]	93.4 [92.4, 94.4]	92.3 [91.2, 93.4]
Overall survival (OS)[4]		
Number (%) of patients with event	80 (3.3%)	89 (3.7%)
HR [95% CI]	0.89 [0.66, 1.21]	
p-value (log-rank test, stratified[2])	0.4673	
3 year event-free rate[3] [95% CI]	97.7 [97.0, 98.3]	97.7 [97.1, 98.3]
Recurrence-free interval (RFI)		
Number (%) of patients with event	138 (5.8%)	173 (7.2%)
HR [95% CI]	0.79 [0.63, 0.99]	
p-value (log-rank test, stratified[2])	0.0430	
3 year event-free rate[3] [95% CI]	95.2 [94.3, 96.1]	94.3 [93.3, 95.2]
Distant recurrence-free interval (DRFI)		
Number (%) of patients with event	119 (5.0%)	145 (6.0%)
HR [95% CI]	0.82 [0.64, 1.04]	
p-value (log-rank test, stratified[2])	0.1007	
3 year event-free rate[3] [95% CI]	95.7 [94.9, 96.5]	95.1 [94.3, 96.0]

Key to abbreviations (Table 8): HR: Hazard Ratio; CI: Confidence Interval

1. Hierarchical testing applied for all secondary endpoints with the exception of RFI and DRFI.
2. All analyses stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.
3. 3-year event-free rate derived from Kaplan-Meier estimates
4. Data from first interim analysis

Figure 1: Kaplan-Meier curve of invasive disease free survival in APHINITY



Pla = placebo; Ptz = pertuzumab; T = trastuzumab

The estimate of IDFS at 4-years was 92.3% in the pertuzumab-treated group versus 90.6% in the placebo-treated group. At the time of the estimate the median follow-up was 45.4 months.

Consistent results were observed across the majority of pre-specified patient subgroups. The benefits of pertuzumab were more apparent for patients in certain high risk groups, notably patients with node-positive or hormone receptor-negative disease (Table 9).

Table 9: Efficacy results by baseline disease characteristics and adjuvant chemotherapy from APHINITY[1]

Population	Number of events/Total N (%)		IDFS at 3 year (%, 95% CI)		Unstratified HR (95% CI)
	PERJETA + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	PERJETA + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	
Hormone Receptor Status					
Negative	71/864 (8.2%)	91/858 (10.6%)	92.8 (90.8, 94.3)	91.2 (89.0, 92.9)	0.76 (0.56, 1.04)
Positive	100/1536 (6.5%)	119/1546 (7.7%)	94.8 (93.5, 95.8)	94.4 (93.1, 95.4)	0.86 (0.66, 1.13)
Nodal Status					
Negative	32/897 (3.6%)	29/902 (3.2%)	97.5 (96.3, 98.4)	98.4 (97.3, 99.0)	1.13 (0.68, 1.86)
Positive	139/1503 (9.2%)	181/1502 (12.1%)	92.0 (90.5, 93.3)	90.2 (88.5, 91.6)	0.77 (0.62, 0.96)
Adjuvant Chemotherapy Regimen					
Anthracycline	139/1865 (7.4%)	171/1877 (9.1%)	93.8 (92.6, 94.8)	93.0 (91.8, 94.1)	0.82 (0.66, 1.03)
Non-Anthracycline	32/535 (6.0%)	39/527 (7.4%)	94.9 (92.6, 96.6)	94.0 (91.5, 95.8)	0.82 (0.51, 1.31)

[1]Exploratory analyses without adjusting multiple comparisons, therefore, results are considered descriptive.

Estimates of IDFS rates in these subgroups of pertuzumab-treated patients versus placebo-treated patients were similar at 4 years: 89.9% vs. 86.7% in the node positive subgroup, 96.2% versus 96.7% in the node negative subgroup, 93.0% versus 91.6% in the hormone receptor-positive subgroup and 91.0% versus 88.7% in the hormone receptor-negative subgroup.

Metastatic Breast Cancer

CLEOPATRA (WO20698)
CLEOPATRA was a multicenter, randomised, double-blind, placebo-controlled Phase III clinical trial conducted in 808 patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who had not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Patients were randomised 1:1 to receive placebo plus trastuzumab and docetaxel (placebo-treated) or pertuzumab plus trastuzumab and docetaxel (pertuzumab-treated). Randomisation was stratified by prior treatment status (de novo or prior adjuvant / neoadjuvant therapy) and geographic region (Europe, North America, South America and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of at least 12 months before enrolment into the trial.

Pertuzumab and trastuzumab were administered intravenously as outlined in Table 5. Patients were treated with pertuzumab and trastuzumab until disease progression, withdrawal of consent or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m^2 IV infusion every 3 weeks for at least 6 cycles. The dose of docetaxel could be escalated to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated.

At the time of the primary analysis, the mean number of cycles of study treatment received was 16.2 in the placebo treatment group and 19.9 in the pertuzumab-treated group.

The primary endpoint of the study was progression-free survival (PFS) as assessed by an independent review facility (IRF) and defined as the time from the date of randomisation to the date of disease progression, or death (from any cause) if the death occurred within 18 weeks of the last tumour assessment. Secondary efficacy endpoints were overall survival (OS), PFS (investigator-assessed), objective response rate (ORR) and duration of response.

Demographics were balanced between treatment arms. The median age was 54 years, the majority were Caucasian (59%) and all patients were female with the exception of two. Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as estrogen receptor [ER] positive and/or progesterone receptor [PgR] positive), and prior adjuvant or neo-adjuvant therapy had been received by 47% of the placebo-treated group and 46% of the pertuzumab-treated group.

The results of the CLEOPATRA study are summarised in Table 10. Consistent results were observed across pre-specified patient subgroups including those based on stratification factors (geographic region and prior therapy).

Table 10: Summary of efficacy in the CLEOPATRA study

	Placebo + trastuzumab + docetaxel n=406	**Pertuzumab + trastuzumab + docetaxel n=402**
Primary endpoint		
Progression-free survival(IRF review)		
Number (%) of patients with event	242 (59%)	191 (47.5%)
Median, months	12.4	18.5
HR [95% CI] (p-value)	0.62 [0.51, 0.75] (<0.0001)	
Secondary endpoints		
Overall survival (final analysis)*		
Number (%) of patients with event	221 (54.4%)	168 (41.8%)
Median, months	40.8	56.5
HR [95% CI] (p-value)	0.68 [0.56, 0.84] (0.0002)	
Progression-free survival (investigator assessment)		
Number (%) of patients with event	250 (61.6%)	201 (50.0%)
Median, months	12.4	18.5
HR [95% CI] (p-value)	0.65 [0.54, 0.78] (<0.0001)	
Objective response rate (ORR)		
Patients with measurable disease at baseline	336	343
Number of responders (% of those with measurable disease at baseline)** [95% CI]	233 (69.3%) [64.1, 74.2]	275 (80.2%) [75.6, 84.3]
Number (%) with a complete response (CR)	14 (4.2%)	19 (5.5%)
Number (%) with a partial response (PR)	219 (65.2%)	256 (74.6%)
Number (%) with stable disease (SD)	70 (20.8%)	50 (14.6%)
Number (%) with progressive disease (PD)	28 (8.3%)	13 (3.8%)
Difference in ORR [95% CI] (p-value)	10.8% [4.2,17.5] (0.0011)	
Duration of response^		
Median, months	20.2	12.5

CI = confidence interval, HR = hazard ratio, IRF = independent review facility

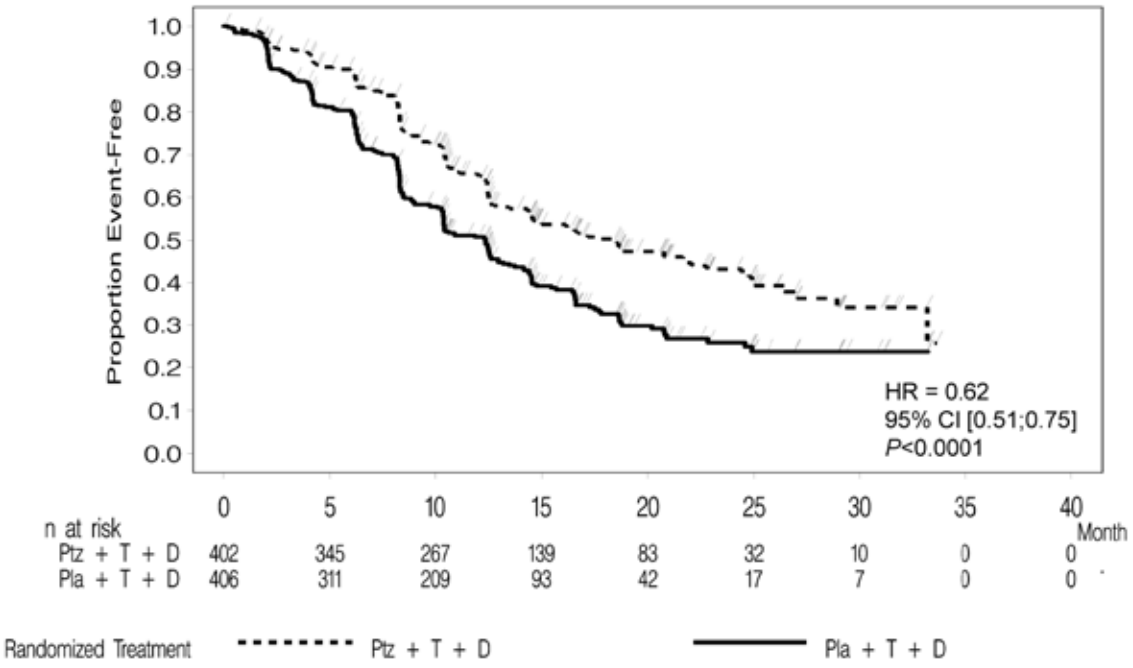
***** Cut-off date for final analysis of OS was 11 Feb 2014

** Patients with best overall response of confirmed CR or PR by RECIST

^ Evaluated in patients with best overall response of CR or PR

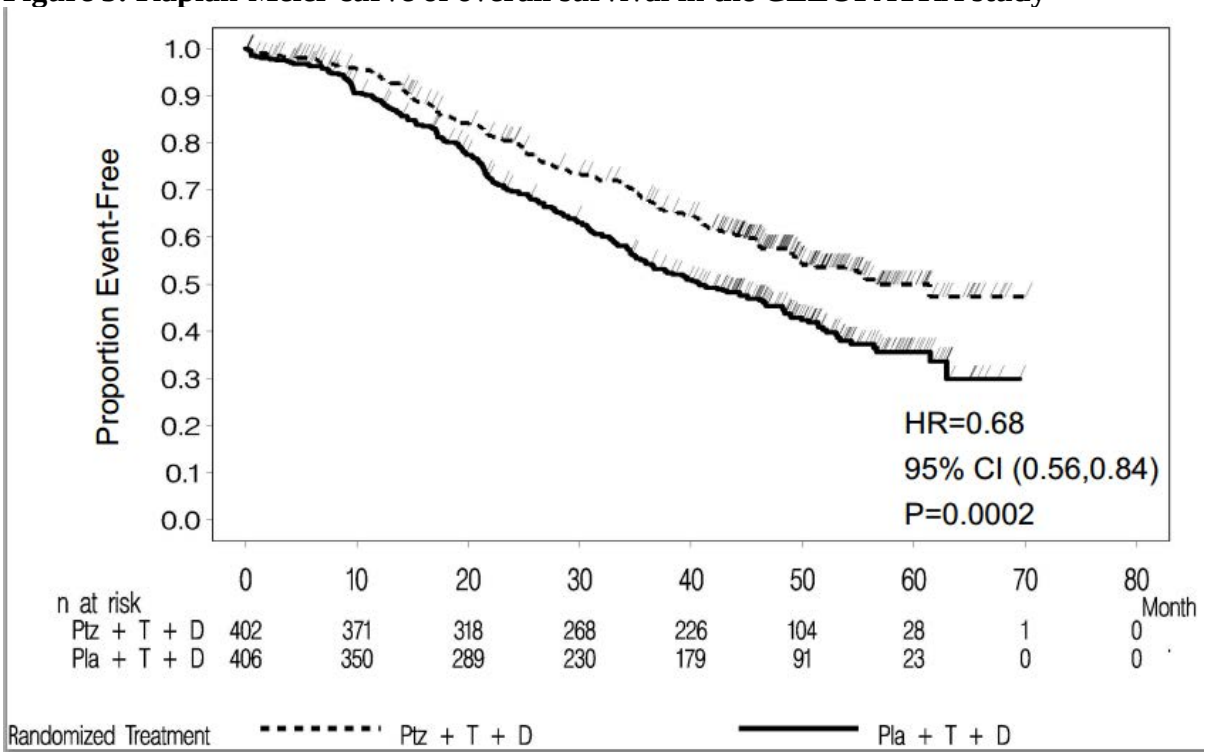
Objective response rate and duration of response are based on IRF-assessed tumour assessments

Figure 2: Kaplan-Meier curve of IRF-assessed progression-free survival in the CLEOPATRA study



D= docetaxel; HR= hazard ratio; Ptz= pertuzumab; T=trastuzumab

Figure 3: Kaplan-Meier curve of overall survival in the CLEOPATRA study



D= docetaxel; HR= hazard ratio; Ptz= pertuzumab; T=trastuzumab

Immunogenicity

As with all therapeutic proteins, there is the potential for immune response in patients treated with Phesgo.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of treatment-emergent antibodies to Phesgo with the incidence of antibodies to other products may be misleading.

In the FEDERICA study, the incidence of treatment-emergent anti-pertuzumab and anti-trastuzumab antibodies was 3% (7/237) and 0.4% (1/237), respectively, in patients treated with intravenous pertuzumab and trastuzumab.

The incidence of treatment-emergent anti-pertuzumab, anti-trastuzumab, and anti-vorhyaluronidase alfa antibodies was 4.8% (11/231), 0.9% (2/232), and 0.9% (2/225), respectively, in patients treated with Phesgo. The clinical relevance of the development of anti-pertuzumab, anti-trastuzumab or anti-vorhyaluronidase alfa antibodies after treatment with Phesgo is unknown.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of pertuzumab and trastuzumab were characterised in the FEDERICA study (see *5.1 Pharmacodynamic properties – Clinical trials*) following subcutaneous administration of Phesgo (1200 mg pertuzumab/600 mg trastuzumab loading dose followed by 600 mg pertuzumab/600 mg trastuzumab every 3 weeks) and intravenous administration of pertuzumab and trastuzumab (840 mg pertuzumab/8 mg/kg trastuzumab initial dose followed by 420 mg pertuzumab/6 mg/kg trastuzumab every 3 weeks). The PK parameters of pertuzumab and trastuzumab are described in Table 11.

The primary endpoint, pertuzumab cycle 7 C_{trough} (i.e. pre-dose cycle 8), showed non-inferiority of pertuzumab within Phesgo (geometric mean 88.7 mcg/mL) compared to intravenous pertuzumab (geometric mean 72.4 mcg/mL) with a geometric mean ratio of 1.22 (90% CI: 1.14–1.31).

The secondary endpoint, trastuzumab Cycle 7 C_{trough} (i.e., predose Cycle 8), showed non-inferiority of trastuzumab within Phesgo (geometric mean 58.7 mcg/mL) compared to intravenous trastuzumab (geometric mean 44.1 mcg/mL) with a geometric mean ratio of 1.33 (90% CI: 1.24–1.43).

A population PK analysis reported that, following subcutaneous administration of PHESGO, the mean cycle 7 C_{max} and $AUC_{0\text{-}21\ days}$ of pertuzumab were 34% lower and 5% higher, respectively, than that following intravenous administration of pertuzumab. The mean cycle 7 C_{max} and $AUC_{0\text{-}21\ days}$ of trastuzumab were 31% lower and 9% higher, respectively, than that following intravenous administration of trastuzumab. There was no evidence of drug-drug interaction between pertuzumab and trastuzumab within Phesgo.

Table 11: PK parameters of pertuzumab and trastuzumab following subcutaneous administration of Phesgo*

Table 5: PK parameters of pertuzumab and trastuzumab following subcutaneous administration of PHESGO *

	Pertuzumab[a]	**Trastuzumab**[b]
Absorption		
Absolute bioavailability	0.7 (18)	0.8 (13)
First-order absorption rate, ka (day^{-1})	0.4 (8) †	0.4 (2.9) †
T_{max} (day)	4 (1 – 21) ‡	4 (1– 22) ‡
Distribution		
Volume of central compartment (L)	2.8 (35)	2.9 (19)
Elimination		
Linear elimination clearance (L/day)	0.2 (24)	0.1 (30)
Non-linear elimination V_{max} (mg/day)	N/A	12 (20)
Non-linear elimination K_m (mg/L)	N/A	34 (39)

* Parameters represented as population mean (intersubject variability) unless otherwise specified
[a] Parameters obtained from FEDERICA population PK model unless otherwise specified
[b] Parameters obtained from subcutaneous trastuzumab population PK model unless otherwise specified
† Residual standard error
‡ Median (range) values from FEDERICA study

Absorption

The median maximum serum concentration (C_{max}) of pertuzumab within Phesgo and time to maximal concentration (T_{max}) were 157 ug/mL and 3.82 days, respectively. Based on population PK analysis, the absolute bioavailability was 0.712 and the first-order absorption rate (K_a) is 0.348 (1/day).

The median maximum serum concentration (C_{max}) of trastuzumab within Phesgo and time to maximal concentration (T_{max}) were 117 ug/mL and 3.85 days, respectively. Based on population PK analysis, the absolute bioavailability was 0.771 and the first-order absorption rate (K_a) is 0.404 (1/day).

Distribution

Based on population PK analysis, the volume of distribution of the central (Vc) compartment of pertuzumab within Phesgo in the typical patient, was 2.77 L.
Based on population PK analysis, the volume of distribution of the central (Vc) compartment of subcutaneous trastuzumab in the typical patient, was 2.91 L.

Metabolism

The metabolism of Phesgo has not been directly studied. Antibodies are cleared principally by catabolism.

Excretion

Based on population PK analysis, the clearance of pertuzumab within Phesgo was 0.163 L/day and the elimination half-life ($t_{1/2}$) was approximately 24.3 days.

Based on population pharmacokinetic analysis, the linear clearance of subcutaneous trastuzumab was 0.111 L/day. Trastuzumab is estimated to reach concentrations that are <1 µg/mL (approximately 3% of the population predicted $C_{min,ss}$, or about 97% washout) by 7 months after the last dose in at least 95% of patients.

Pharmacokinetics in special populations

Paediatric population

Phesgo has not been studied in paediatric patients.

Geriatric population

No dedicated studies have been conducted to investigate the pharmacokinetics (PK) of Phesgo in geriatric patients.

In population PK analyses, age did not significantly affect the PK of pertuzumab (whether subcutaneous [within Phesgo] or intravenous) or trastuzumab (whether subcutaneous or intravenous).

Renal impairment

No dedicated studies have been conducted to investigate the PK of Phesgo in patients with renal impairment.

Based on population PK analyses of pertuzumab within Phesgo and intravenous pertuzumab, renal impairment is not predicted to affect pertuzumab exposure; however, only limited data from patients with severe renal impairment (n=3) were included in population PK analyses.

In a population PK analysis of subcutaneous and intravenous trastuzumab, renal impairment did not affect trastuzumab disposition.

Hepatic impairment

No dedicated studies have been conducted to investigate the PK of Phesgo in patients with hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Trastuzumab is not genotoxic. No studies have been conducted to evaluate the mutagenic potential of pertuzumab alone or the pertuzumab/trastuzumab combination.

Carcinogenicity

No studies have been conducted to evaluate the carcinogenic potential of pertuzumab or trastuzumab alone or in combination.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Vorhyaluronidase alfa
Histidine
Histidine hydrochloride monohydrate
Trehalose dehydrate
Sucrose, polysorbate 20
Methionine
Water for injections

6.2 INCOMPATIBILITIES

No incompatibilities between Phesgo and polypropylene, polycarbonate, polyurethane, polyethylene, polyvinyl chloride and fluorinated ethylene polypropylene have been observed.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store between 2°C and 8°C. Keep vial in the outer carton to protect it from light.
Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

1200 mg pertuzumab/600 mg trastuzumab/15 mL solution in a vial.
600 mg pertuzumab/600 mg trastuzumab/10 mL solution in a vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

The 1200 mg pertuzumab/600 mg trastuzumab solution and the 600 mg pertzumab/600 mg trastuzumab solution are both ready-to-use solutions for injection, which should not need to be mixed with other drugs or diluted.

Prior to administration, inspect the vial visually to ensure there is no particulate matter or discolouration. Do not shake.

Product is for single use in one patient only. Discard any residual unused solution

Phesgo does not contain any antimicrobial preservatives, and if possible, should be used immediately once transferred from the vial to a syringe. If the syringe containing Phesgo cannot be used immediately and was prepared aseptically, the closed syringe can be stored in the refrigerator (2°C to 8°C) for up to 7 days protected from light and subsequently at room temperature (20°C to 25°C) for up to 4 hours in diffused daylight. After the solution of Phesgo is withdrawn from the vial into the syringe, replace the transfer needle with a syringe closing cap. Label the syringe with the peel-off sticker.

Immediately prior to administration, attach a 25G-27G (3/8”-5/8”) hypodermic injection needle to the syringe, and then adjust the volume to 10 mL (600 mg pertuzumab/600 mg trastuzumab) or 15 mL (1200 mg pertuzumab/600 mg trastuzumab).

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structures and CAS numbers

Pertuzumab

Pertuzumab is a recombinant, humanised monoclonal antibody. The antibody is based upon the human IgG_1 kappa framework sequence, with a molecular weight of ~ 148kDa and composed of two light chains consisting of 214 amino acid residues and two heavy chains consisting of 448 or 449 amino acid residues.

Pertuzumab CAS number: 380610-27-5

Trastuzumab

Trastuzumab is a recombinant, DNA-derived, humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG1 kappa that contains human framework regions with the complementarity determining regions of a murine anti-p185 HER2 antibody that binds to HER2. Trastuzumab is composed of 1,328 amino acids and has a molecular weight of ~148 kDa.

Trastuzumab CAS number: 180288-69-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

6 July 2021

10. DATE OF REVISION OF THE TEXT

6 July 2021

Summary table of changes

Section Changed	Summary of new information