NEW ZEALAND DATA SHEET
PHESGO (pertuzumab and trastuzumab)

1. PRODUCT NAME

Phesgo 600 mg/600 mg solution for injection
Phesgo 1200 mg/600 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Phesgo 600 mg/600 mg solution for injection
One vial of 10 mL solution contains 600 mg of pertuzumab and 600 mg of trastuzumab.
Each mL of solution contains 60 mg of pertuzumab and 60 mg of trastuzumab

Phesgo 1200 mg/600 mg solution for injection
One vial of 15 mL solution contains 1200 mg of pertuzumab and 600 mg of trastuzumab.
Each mL of solution contains 80 mg of pertuzumab and 40 mg of trastuzumab

Pertuzumab and trastuzumab are humanised immunoglobulin (Ig)G1 monoclonal antibodies produced in mammalian (Chinese hamster ovary) cells by recombinant deoxyribonucleic acid (DNA) technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for subcutaneous injection.

Clear to opalescent solution, colourless to slightly brownish, pH 5.2-5.8, osmolality of 270-370 and 275-375 mOsmol/kg for the 1200 mg/600 mg and 600 mg/600 mg solutions, respectively.

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

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Phesgo 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. Initiations should always occur in an environment where full resuscitation facilities are immediately available (see section 4.4).

Once pertuzumab-based therapy has been safely established, the prescribing physician may determine the suitability of administration of Phesgo outside of the clinical setting (e.g. at home) by a healthcare professional.

In order to prevent medication errors, it is important to check the vial label to ensure that the medicinal product being prepared and administered is Phesgo.

Patients currently receiving intravenous pertuzumab and trastuzumab can switch to Phesgo. Switching treatment from intravenous pertuzumab and trastuzumab to Phesgo (or vice versa) was investigated in study MO40628 (see sections 4.8 and 5.1).

Patient Selection

Patients treated with Phesgo should have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) 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 for subcutaneous (SC) use in the thigh only. Do not administer intravenously.

Metastatic and early breast cancer

For Phesgo dose recommendations in early and metastatic breast cancer refer to Table 1.

Table 1: Phesgo recommended dosing and administration

	Dose (irrespective of body weight)	Approximate duration of SC injection	Observation time[ab]
Loading dose	1200 mg pertuzumab/ 600 mg trastuzumab	8 minutes	30 minutes
Maintenance dose (every 3 weeks)	600 mg pertuzumab/ 600 mg trastuzumab	5 minutes	15 minutes

[a]Patients should be observed for injection-related and hypersensitivity reactions

[b]Observation period should start following administration of Phesgo and be completed prior to any subsequent administration of chemotherapy

The injection site should be alternated between the left and right thigh only. New injections should be given at least 1 inch/2.5 cm from the previous site on 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. During the treatment course with Phesgo, other medications for SC administration should preferably be injected at different sites.

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 and subsequently escalated to 100 mg/m^2 depending on the chosen regimen and tolerability of the initial dose. Alternatively, docetaxel can be given at 100 mg/m^2 on a 3-weekly schedule from the start, again depending on the chosen regimen. If a carboplatin-based regimen is used, the recommended dose for docetaxel is 75 mg/m^2 throughout (no dose escalation). When administered with Phesgo in the adjuvant setting, the recommended dose of paclitaxel is 80 mg/m^2 once weekly for 12 weekly cycles.

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

Early Breast Cancer (EBC)
In the neoadjuvant setting (before surgery), it is recommended that patients are treated with Phesgo for three to six cycles depending on the regimen chosen in combination with chemotherapy (see section 5.1).

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).

Patients who start Phesgo in the neoadjuvant setting should continue to receive adjuvant Phesgo to complete 1 year of treatment (maximum 18 cycles).

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 time between two sequential doses is less than 6 weeks, the 600 mg pertuzumab/ 600 mg trastuzumab maintenance dose of Phesgo should be administered as soon as possible. Thereafter, continue with the 3-weekly schedule.

If the time between two sequential injections is 6 weeks or more, the loading dose of 1200 mg pertuzumab/600 mg trastuzumab should be re-adminstered followed by the maintenance dose of 600 mg pertuzumab/ 600 mg trastuzumab every 3 weeks thereafter.

Dose modifications
Dose reductions are not recommended for Phesgo. Discontinuation of treatment with Phesgo may be needed at the discretion of the physician.

Patients may continue therapy during periods of reversible chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time.
For chemotherapy dose modifications, refer to the chemotherapy prescribinginformation.

Switching from intravenous pertuzumab and trastuzumab administration to Phesgo

- In patients receiving intravenous pertuzumab and trastuzumab with less than 6 weeks since their last dose, Phesgo should be administered as a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab and every 3 weeks for subsequent administrations.
- In patients receiving intravenous pertuzumab and trastuzumab with 6 weeks or more since their last dose, Phesgo should be administered as a loading dose of 1200 mg pertuzumab/600 mg trastuzumab, followed by a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab every 3 weeks for subsequent administrations.

Injection-related reactions
The injection should be slowed or paused if the patient experiences injection-related symptoms (see section 4.4). Treatment including oxygen, beta agonists, antihistamines, rapid intravenous fluids and antipyretics may also help alleviate systemic symptoms.

Hypersensitivity/anaphylaxis
The injection should be discontinued immediately and permanently if the patient experiences a NCI-CTCAE Grade 4 reaction (anaphylaxis), bronchospasm or acute respiratory distress syndrome (see section 4.4).

Left ventricular dysfunction
See section 4.4 for information on dose recommendations in the event of left ventricular dysfunction.

Special populations

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

Elderly
No dose adjustment of Phesgo is required in patients ≥65 years of age. Limited data are available in patients > 75 years of age.

Renal impairment
Dose adjustments of Phesgo are not needed 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 (PK) data available (see section 5.2).

Hepatic impairment
The safety and efficacy of Phesgo have not been studied in patients with hepatic impairment. Patients with hepatic impairment are unlikely to require Phesgo dose adjustment. No specific dose adjustment are recommended.

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

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Left ventricular dysfunction (including congestive heart failure)
Decreases in LVEF have been reported with drugs that block HER2 activity, including pertuzumab 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 section 4.8). 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.

Patients with history of serious cardiac illness or medical conditions, history of ventricular dysrhythmias or risk factors for ventricular dysrhythmias were excluded from the (neo-) adjuvant EBC pivotal trial FEDERICA with Phesgo.

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.

Assess LVEF prior to initiation of Phesgo and at regular intervals during treatment to ensure that LVEF is within normal limits (see Table 2 below). If the LVEF declines as indicated in Table 2 and has not improved, or has declined further at the subsequent assessment, discontinuation of Phesgo should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

Table 2: Dose recommendations for left ventricular dysfunction

	Pre-treatment LVEF:	**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:**	
Metastatic Breast Cancer[a]	≥ 50%	~12 weeks	Either		Either	
			<40%	40%-45% with a fall of ≥10%-points below pre-	>45%	40%-45% with a fall of <10%-points below pre-

				treatment value		treatment value
Early Breast Cancer	≥ 55%[b]	~12 weeks (once during neoadjuvant therapy)	<50% with a fall of ≥10%-points below pre-treatment value		Either	
					≥ 50%	< 10%-points below pre-treatment value

[a]based on intravenous pertuzumab data (CLEOPATRA study)
[b]for patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracyclines, before starting Phesgo.

Cardiac risk should be carefully considered and balanced against the medical need of the individual patient before use of Phesgo with an anthracycline. 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 Phesgo and anthracyclines than with sequential use.

Sequential use of Phesgo (in combination with a taxane) has been evaluated following the doxorubicin component of two anthracycline-based regimens in the FEDERICA study while sequential use of intravenous pertuzumab (in combination with trastuzumab and a taxane) has been evaluated following the epirubicin or doxorubicin component of many anthracycline-based regimens in the APHINITY and BERENICE studies. Only limited safety data are available on concurrent use of intravenous pertuzumab in combination with trastuzumab and an anthracycline. 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 sections 4.8 and 5.1). Only chemotherapy-naive patients were treated and they received low cumulative doses of epirubicin (up to 300 mg/m^2). In this study, cardiac safety was similar to that observed in patients given the same regimen but with pertuzumab administered sequentially (following FEC chemotherapy).

Injection-related reactions (IRRs)
Phesgo has been associated with injection-related reactions. Injection-related reactions were defined as any systemic reaction with symptoms such as fever, chills, headache, likely due to a release of cytokines occurring within 24 hours of administration of Phesgo. Close observation of the patient during and for 30 minutes after administration of the loading dose and during and for 15 minutes following the administration of the maintenance dose of Phesgo is recommended. If a significant injection-related reaction occurs, the injection should be slowed down or paused and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe injection-related reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction (see section 4.2). Although fatal outcomes resulting from injection-related reactions have not been observed with Phesgo, caution should be exercised as fatal infusion related-reactions have been associated with intravenous pertuzumab in combination with intravenous trastuzumab and chemotherapy.

Hypersensitivity reactions/anaphylaxis

Patients should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in patients treated with Phesgo, caution should be exercised as these have been associated with intravenous pertuzumab in combination with trastuzumab and chemotherapy see section 4.8. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Phesgo must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome (see section 4.2). Phesgo is contraindicated in patients with known hypersensitivity to pertuzumab, trastuzumab, or to any of its excipients (see section 4.3).

For administration outside of the clinical setting, appropriate medications for the management of hypersensitivity reactions in line with local standard clinical practice (depending on severity and type of reaction e.g. adrenaline, beta-agonists, antihistamines and corticosteroids) should be available for immediate use.

Febrile neutropenia
Patients treated with Phesgo in combination with a taxane are at increased risk of febrile neutropenia. Patients treated with intravenous pertuzumab in combination with trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel, especially during the first 3 cycles of treatment (see section 4.8). In the CLEOPATRA trial in metastatic breast cancer, nadir neutrophil counts were similar in pertuzumab-treated and placebo-treated patients. The higher incidence of febrile neutropenia in pertuzumab-treated patients was associated with the higher incidence of mucositis and diarrhoea in these patients. Symptomatic treatment for mucositis and diarrhoea should be considered. No events of febrile neutropenia were reported after cessation of docetaxel.

Diarrhoea
Phesgo may elicit severe diarrhoea. Diarrhoea is most frequent during concurrent administration with taxane therapy. Elderly patients (≥ 65 years) have a higher risk of diarrhoea compared with younger patients (< 65 years). Treat diarrhoea according to standard practice and guidelines. Early intervention with loperamide, fluids and electrolyte replacement should be considered, particularly in elderly patients, and in case of severe or prolonged diarrhoea. Interruption of treatment with Phesgo should be considered if no improvement in the patient's condition is achieved. When the diarrhoea is under control treatment with Phesgo may be reinstated.

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 oedema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Phesgo. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

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

Use in the elderly
No overall differences in efficacy and safety of Phesgo was 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 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, hypomagnesemia 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.
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
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug-drug interaction studies have been performed.

Phesgo
Based on the population pharmacokinetics analysis of FEDERICA study, there was no evidence of drug-drug interaction between pertuzumab and trastuzumb within Phesgo.

Pertuzumab
No PK interactions were observed between pertuzumab and trastuzumab, or between pertuzumab and docetaxel in a sub-study of 37 patients in the randomised, pivotal trial CLEOPATRA in metastatic breast cancer. In addition, in the population PK analysis, no evidence of a drug-drug interaction has been shown between pertuzumab and trastuzumab or between pertuzumab and docetaxel. This absence of drug-drug interaction was confirmed by PK data from the NEOSPHERE and APHINITY studies.

Five studies evaluated the effects of pertuzumab on the PK of co-administered cytotoxic agents, docetaxel, paclitaxel, gemcitabine, capecitabine, carboplatin and erlotinib. There was no evidence of any PK interaction between pertuzumab and any of these agents. The PK of pertuzumab in these studies was comparable to those observed in single-agent studies.

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

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents
PK data from studies BO15935 and M77004 in women with HER2-positive metastatic breast cancer suggested that exposure to paclitaxel and doxorubicin (and their major metabolites 6-α hydroxylpaclitaxel, POH, and doxorubicinol, DOL) was not altered in the presence of trastuzumab (8 mg/kg or 4 mg/kg intravenous loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w intravenous, respectively). However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite were unclear.

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

cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab.

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

Effect of antineoplastic agents on trastuzumab pharmacokinetics
By comparison of simulated serum trastuzumab concentrations after trastuzumab monotherapy (4 mg/kg loading/2 mg/kg q1w intravenous) and observed serum concentrations in Japanese women with HER2-positive metastatic breast cancer (study JP16003) no evidence of a PK effect of concurrent administration of docetaxel on the pharmacokinetics of trastuzumab was found. Comparison of PK results from two Phase II studies (BO15935 and M77004) and one Phase III study (H0648g) in which patients were treated concomitantly with trastuzumab and paclitaxel and two Phase II studies in which trastuzumab was administered as monotherapy (W016229 and MO16982), in women with HER2-positive MBC indicates that individual and mean trastuzumab trough serum concentrations varied within and across studies but there was no clear effect of the concomitant administration of paclitaxel on the pharmacokinetics of trastuzumab.

Comparison of trastuzumab PK data from Study M77004 in which women with HER2-positive metastatic breast cancer were treated concomitantly with trastuzumab, paclitaxel and doxorubicin to trastuzumab PK data in studies where trastuzumab was administered as monotherapy (H0649g) or in combination with anthracycline plus cyclophosphamide or paclitaxel (Study H0648g), suggested no effect of doxorubicin and paclitaxel on the pharmacokinetics of trastuzumab. Pharmacokinetic data from Study H4613g/GO01305 suggested that carboplatin had no impact on the PK of trastuzumab. The administration of concomitant anastrozole did not appear to influence the pharmacokinetics of trastuzumab.

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential/ contraception
Women of childbearing potential should use effective contraception while receiving Phesgo and for 7 months following the last dose.

Pregnancy – Category D
Phesgo should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

No clinical studies of Phesgo in pregnant women have been performed. Pertuzumab administered intravenously to cynomolgus monkeys during organogenesis led to oligohydramnios, delayed renal development and embryo foetal death. In the post-marketing setting for trastuzumab, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women.

Based on the aforementioned animal studies and post-marketing data, Phesgo has the potential to cause foetal harm when administered to a pregnant woman. Women who become pregnant should be advised of the possibility of harm to the foetus. 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.

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

Breastfeeding
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.

Fertility
No specific fertility studies in animals have been performed to evaluate the effects of pertuzumab or trastuzumab within Phesgo.

Intravenous pertuzumab
No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six month duration in cynomolgus monkeys (see section 5.3).

Intravenous trastuzumab
Reproduction studies of female fertility have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg intravenous trastuzumab and have revealed no evidence of impaired fertility. Additionally, no adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of up to six month duration in cynomolgus monkeys (see section 5.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Phesgo has a minor influence on the ability to drive and use machines. Injection-related reactions and dizziness may occur during treatment with Phesgo.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile
FEDERICA study in which HER2-positive early breast cancer patients were treated with either Phesgo (n=248) or intravenous pertuzumab and trastuzumab (n=252), in combination with chemotherapy (neoadjuvant) and without chemotherapy (adjuvant). See Table 3 for details of the adverse drug reactions (ADRs) reported on Phesgo.

The most common (≥5%) adverse drug reactions (ADRs) reported in patients treated with Phesgo were diarrhoea, injection site reaction, asthenia, fatigue, rash, dry skin, myalgia, arthralgia, neutropenia and anaemia.

The most common (≥1%) serious adverse events (SAEs) reported in patients treated with Phesgo were febrile neutropenia, cardiac failure, neutropenic sepsis and neutrophil count decreased.

SAEs were equally distributed between the Phesgo treatment arm and the intravenous pertuzumab in combination with trastuzumab treatment arm. The following adverse drug reactions were reported with a higher frequency (≥5%) with Phesgo compared to intravenous

pertuzumab in combination with trastuzumab: alopecia 79% vs 73%, myalgia 27.0% vs 20.6%, and dyspnoea 12.1% vs 6%

As pertuzumab and trastuzumab is used in combination with chemotherapy, it is difficult to ascertain the causal relationship of an adverse reaction to a particular drug.

Tabulated list of adverse drug reactions

In this section, the following categories of frequency have been used: 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), and unknown (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Summary of adverse drug reactions reported for Phesgo from the FEDERICA study

	N = 248					
	Phesgo + chemotherapy			Phesgo monotherapy		
ADR (MedDRA Preferred Term) System Organ Class	All grades	Grades 3-4%	Frequency category	All grades	Grades 3-4%	Frequency category
Blood and lymphatic system disorders						
Neutropenia	21.4	14.5	Very common	5.6	0.8	Common
Anaemia	33.5	1.2	Very common	6.9	0.4	Common
Febrile neutropenia	6.5	6.5	Common	0	0	Unknown
Leukopenia	8.1	2.8	Common	4.0	0	Common
Cardiac disorders						
Left ventricular dysfunction	0.4	0	Uncommon	0.8	0	Uncommon
Cardiac failure	0.8	0.4	Uncommon	1.2	0.8	Common
Eye disorders						
Lacrimation increased	5.2	0.4	Common	0.4	0	Uncommon
Gastrointestinal disorders						

Diarrhoea	59.7	6.5	Very common	17.3	0	Very common
Nausea	60.1	1.6	Very common	6.0	0	Common
Vomiting	19.0	0.8	Very common	2.4	0	Common
Stomatitis	24.6	0.8	Very common	1.6	0	Common
Constipation	21.8	0	Very common	2.4	0	Common
Dyspepsia	12.5	0	Very common	3.6	0	Common
Abdominal pain	7.3	0.4	Common	2.4	0	Common
General disorders and administration site conditions						
Fatigue	25.8	2.0	Very common	6.9	0	Common
Mucosal inflammation	15.7	0.8	Very common	0.4	0	Uncommon
Asthenia	29.4	0.8	Very common	10.9	0	Very common
Pyrexia	10.5	0	Very common	3.6	0	Common
Edema peripheral	6.0	0	Common	3.2	0	Common
Injection site reaction	6.9	0	Common	13.3	0	Very common
Immune system disorders						
Hypersensitivity	0.4	0	Uncommon	0	0	Unknown
Drug hypersensitivity	0.4	0	Uncommon	0.4	0	Uncommon
Infections and infestations						
Nasopharyngitis	6.9	0	Common	6.9	0	Common
Upper respiratory tract infection	8.9	0	Common	6.5	0	Common
Paronychia	5.6	0.4	Common	2.8	0	Common
Metabolism and nutrition disorders						

Decreased appetite	15.7	0.8	Very common	2.0	0	Common
Musculoskeletal and connective tissue disorders						
Arthralgia	13.3	0	Very common	19.4	0	Very common
Myalgia	20.2	0.4	Very common	8.5	0	Common
Pain in extremity	3.2	0	Common	6.5	0	Common
Nervous system disorders						
Dysgeusia	16.5	0	Very common	1.6	0	Common
Headache	14.1	0	Very common	7.3	0	Common
Peripheral sensory neuropathy	14.9	0.8	Very common	2.4	0	Common
Neuropathy peripheral	10.1	0.4	Very common	3.6	0	Common
Dizziness	6	0	Common	8.1	0	Common
Paraesthesia	7.7	0.8	Common	2.8	0	Common
Psychiatric disorders						
Insomnia	13.3	0	Very common	5.2	0	Common
Respiratory, thoracic and mediastinal disorders						
Epistaxis	10.9	0	Very common	2.4	0	Common
Cough	12.9	0.4	Very common	4.8	0	Common
Dyspnoea	9.3	0.4	Common	2.8	0.4	Common
Skin and subcutaneous tissue disorders						
Alopecia	78.6	0	Very common	0.4	0	Uncommon
Rash	10.9	0.4	Very common	8.1	0	Common

Nail disorder	5.2	0	Common	2.0	0	Common
Pruritus	2.4	0	Common	9.7	0	Common
Dry skin	12.5	0.4	Very common	3.2	0	Common
Vascular disorders						
Hot flush	5.2	0	Common	11.3	0	Very common

The safety profile of Phesgo was overall consistent to the known safety profile of intravenous pertuzumab in combination with trastuzumab and chemotherapy as seen in the pertuzumab and trastuzumab-treated arms of the following pivotal studies (n=3834):

- 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)
- FEDERICA, in which Phesgo (n= 243) or intravenous pertuzumab and trastuzumab (n= 247) was given in combination with chemotherapy to patients with early breast cancer

Description of selected adverse drug reactions from clinical trials

Left ventricular dysfunction

Phesgo in combination with chemotherapy

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% of Phesgo treated patients vs 0% of intravenous pertuzumab and trastuzumab-treated patients during neoadjuvant phase. All of the Phesgo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. The incidences of symptomatic heart failure with a LVEF decline of at least 10%-points from baseline and to <50% were similar in the adjuvant and in the follow- up phases. 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 not reported in Phesgo-treated patients and were reported in 0.4% of intravenous pertuzumab and trastuzumab-treated patients during the neoadjuvant phase, of whom none had recovered at the data cutoff. The incidences of 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 similar in the adjuvant phase. In the follow up phase, 3.6% of intravenous pertuzumab and trastuzumab-treated patients vs 1.6% of Phesgo treated patients had this type of cardiac events.

Injection/infusion-related reactions

Phesgo in combination with chemotherapy

In the pivotal trial FEDERICA, an injection/infusion-related reaction was defined as any systemic reaction reported within 24 hours of Phesgo or intravenous pertuzumab in combination with trastuzumab administration (see sections 4.2 and 4.4). Injection/infusion-related reactions were reported in 0.4% of Phesgo treated patients and 10.7% of intravenous pertuzumab and trastuzumab-treated patients in neoadjuvant phase. Injection/infusion-related reactions were reported in 0% of Phesgo-treated patients and in 1.6% of intravenous pertuzumab and trastuzumab-treated patients in adjuvant phase. Most of the systemic injection/infusion related reactions seen with Phesgo or intravenous pertuzumab and trastuzumab were chills, pyrexia or vomiting.

Injection site reactions were defined as any local reaction reported within 24 hours of Phesgo administration were reported in 6.9% and in 12.9% of Phesgo treated patients in the neoadjuvant phase and the adjuvant phase respectively, and were all grade 1 or 2 events. Most of the local injection site reactions seen with Phesgo were either injection site pain or injection site erythema.

Hypersensitivity reactions/anaphylaxis

Phesgo in combination with chemotherapy

In the pivotal trial FEDERICA, the overall frequency of hypersensitivity/anaphylaxis reported events related to HER2-targeted therapy was 1.2% in the Phesgo-treated patients vs. 0.8% in the intravenous pertuzumab and trastuzumab-treated patients, of which none were NCI-CTCAE (version 4.0) grade 3-4 (see section 4.4). One patient experienced a hypersensitivity/anaphylaxis event during or immediately after administration of Phesgo; at the first cycle which led to withdrawal from therapy (see sections 4.2 and 4.4). During neoadjuvant phase, 0.4% intravenous pertuzumab and trastuzumab-treated patients had drug hypersensitivity and 0.4% Phesgo treated patients had hypersensitivity. During adjuvant phase, 0.4% Phesgo-treated patients had drug hypersensitivity.

Febrile neutropenia

Phesgo in combination with chemotherapy

In the pivotal trial FEDERICA, febrile neutropenia occurred in 6.5% of Phesgo-treated patients and 5.6% of intravenous pertuzumab and trastuzumab-treated patients.

As in intravenous pertuzumab and trastuzumab pivotal trials, a higher incidence of febrile neutropenia was observed among intravenous pertuzumab and trastuzumab-treated Asian patients (13.0%), similarly, the incidence of febrile neutropenia in Phesgo-treated Asian patients was also higher (13.7%).

Pertuzumab intravenous in combination with trastuzumab and chemotherapy

In the pivotal trial CLEOPATRA, the majority of patients in both treatment groups experienced at least one leucopenic event (63.0% of patients in the pertuzumab-treated group and 58.3% of patients in the placebo-treated group), of which the majority were neutropenic events (see section 4.4). Febrile neutropenia occurred in 13.7% of pertuzumab-treated patients and 7.6% of placebo-treated patients. In both treatment groups, the proportion of patients experiencing febrile neutropenia was highest in the first cycle of therapy and declined steadily thereafter. An increased incidence of febrile neutropenia was observed among Asian patients in both treatment groups compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (25.8%) compared with the placebo-treated group (11.3%).

In the NEOSPHERE trial, 8.4% of patients treated with neoadjuvant pertuzumab, trastuzumab and docetaxel experienced febrile neutropenia compared with 7.5% of patients treated with trastuzumab and docetaxel. In the TRYPHAENA trial, febrile neutropenia occurred in 17.1% of patients treated with neoadjuvant pertuzumab + TCH, and 9.3% of patients treated with neoadjuvant pertuzumab, trastuzumab and docetaxel following FEC.In TRYPHAENA, the incidence of febrile neutropenia was higher in patients who received six cycles of pertuzumab compared with patients who received three cycles of pertuzumab, independent of the chemotherapy given. As in the CLEOPATRA trial, a higher incidence of neutropenia and febrile neutropenia was observed among Asian patients compared with other patients in both neoadjuvant trials. In NEOSPHERE, 8.3% of Asian patients treated with neoadjuvant pertuzumab, trastuzumab and docetaxel experienced febrile neutropenia compared with 4.0% of Asian patients treated with neoadjuvant trastuzumab and docetaxel.In the APHINITY trial, febrile neutropenia occurred in 12.1% of pertuzumab-treated patients and 11.1% of placebo-treated patients. As in the CLEOPATRA, TRYPHAENA, and NEOSPHERE trials, a higher incidence of febrile neutropenia was observed among pertuzumab-treated Asian patients compared with other races in the APHINITY trial (15.9% of pertuzumab-treated patients and 9.9% of placebo-treated patients).

Diarrhoea

Phesgo in combination with chemotherapy

In the pivotal trial FEDERICA diarrhoea occurred in 61.7% of Phesgo-treated patients and 59.1% of intravenous pertuzumab and trastuzumab-treated patients. Grade ≥ 3 diarrhoea was reported in 7.3% of patients in the Phesgo arm vs. 5.2% in the intravenous pertuzumab and trastuzumab arm. The majority of the reported events were Grade 1 or 2 in severity. The highest incidence of diarrhoea (all Grades) was reported during the targeted therapy and taxane chemotherapy period (57.7% of patients in the Phesgo-treated arm vs. 53.6% of patients in the intravenous pertuzumab and trastuzumab-treated arm) (see section 4.4).

Pertuzumab intravenous in combination with trastuzumab and chemotherapy

In the pivotal trial CLEOPATRA in metastatic breast cancer, diarrhoea occurred in 68.4% of pertuzumab-treated patients and 48.7% of placebo-treated patients (see section 4.4). Most events were mild to moderate in severity and occurred in the first few cycles of treatment. The incidence of NCI-CTCAE Grade 3-4 diarrhoea was 9.3% in pertuzumab-treated patients vs. 5.1% in placebo-treated patients. The median duration of the longest episode was 18 days in pertuzumab-treated patients and 8 days in placebo-treated patients. Diarrhoeal events responded well to proactive management with anti-diarrhoeal agents.

In the NEOSPHERE trial, diarrhoea occurred in 45.8% of patients treated with neoadjuvant pertuzumab, trastuzumab and docetaxel compared with 33.6% of patients treated with trastuzumab and docetaxel. In the TRYPHAENA trial, diarrhoea occurred in 72.3% of patients treated with neoadjuvant pertuzumab+TCH and 61.4% of patients treated with neoadjuvant pertuzumab, trastuzumab and docetaxel following FEC. In both studies most events were mild to moderate in severity.

In the APHINITY trial, a higher incidence of diarrhoea was reported in the pertuzumab-treated arm (71.2%) compared to the placebo arm (45.2%). Grade ≥ 3 diarrhoea was reported in 9.8% of patients in the pertuzumab arm vs. 3.7% in the placebo arm. The majority of the reported events were Grade 1 or 2 in severity. The highest incidence of diarrhoea (all Grades) was reported during the targeted therapy + taxane chemotherapy period (61.4% of patients in

the pertuzumab arm vs. 33.8% of patients in the placebo arm). The incidence of diarrhoea was much lower after chemotherapy cessation, affecting 18.1% of patients in the pertuzumab arm vs. 9.2% of patients in the placebo arm in the post-chemotherapy targeted therapy period.

Rash

Phesgo in combination with chemotherapy

In the pivotal trial FEDERICA rash occurred in 18.1% of Phesgo-treated patients and 21.8% of intravenous pertuzumab and trastuzumab-treated patients. The majority of rash events were Grade 1 or 2.

Pertuzumab intravenous in combination with trastuzumab and chemotherapy

In the pivotal trial CLEOPATRA in metastatic breast cancer, rash occurred in 51.7% of pertuzumab-treated patients, compared with 38.9% of placebo-treated patients. Most events were Grade 1 or 2 in severity, occurred in the first two cycles, and responded to standard therapies, such as topical or oral treatment for acne.

In the NEOSPHERE trial, rash occurred in 40.2% of patients treated with neoadjuvant pertuzumab, trastuzumab and docetaxel compared with 29.0% of patients treated with trastuzumab and docetaxel. In the TRYPHAENA trial, rash occurred in 36.8% of patients treated with neoadjuvant pertuzumab + TCH and 20.0% of patients treated with neoadjuvant pertuzumab, trastuzumab and docetaxel following FEC. The incidence of rash was higher in patients who received six cycles of pertuzumab compared with patients who received three cycles of pertuzumab, independent of the chemotherapy given.

In the APHINITY trial, the adverse reaction of rash occurred in 25.8% of patients in pertuzumab arm vs. 20.3% of patients in placebo arm. The majority of rash events were Grade 1 or 2.

Laboratory abnormalities

Phesgo in combination with chemotherapy

In the pivotal trial FEDERICA, the incidence of NCI-CTCAE v.4 Grade 3-4 neutropenia was balanced in the two treatment groups during the neoadjuvant phase (14.5% of Phesgo-treated patients and 13.9% of intravenous pertuzumab and trastuzumab-treated patients), and were significantly lower in the adjuvant phase.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response to pertuzumab and trastuzumab in patients treated with Phesgo.

In the FEDERICA study, the incidence of treatment-emergent anti-pertuzumab and anti-trastuzumab antibodies was 10.6% (26/245) and 0.4% (1/245), respectively, in patients treated with intravenous pertuzumab and trastuzumab. Among patients that tested positive to anti-pertuzumab antibodies, neutralising anti-pertuzumab antibodies were detected in three patients.

The incidence of treatment-emergent anti-pertuzumab, anti-trastuzumab, and anti-vorhyaluronidase alfa antibodies was 12.9% (31/241), 2.1% (5/241), and 6.3% (15/238), respectively, in patients treated with Phesgo. Among these patients, neutralising anti-pertuzumab antibodies were detected in two patients, and neutralising anti-trastuzumab antibodies were detected in one patient. Among patients that tested positive to anti-

pertuzumab antibodies, neutralising anti-pertuzumab antibodies were detected in one patient treated with intravenous pertuzumab and trastuzumab and in one patient treated with Phesgo. Among patients that tested positive to anti-trastuzumab antibodies, neutralising anti-trastuzumab antibodies were detected in one patient treated with Phesgo.
The incidence of anti-pertuzumab and anti-trastuzumab antibodies detected at any time point (including baseline) was 7.1% (18/252) and 1.2% (3/252), respectively, in patients treated with intravenous pertuzumab and trastuzumab.

The incidence of anti-pertuzumab, anti-trastuzumab, and anti-vorhyaluronidase alfa antibodies detected at any time point (including baseline) was 8.5% (21/248), 2.4% (6/248), and 6.7% (16/240), respectively, in patients treated with Phesgo. Among patients that tested positive to anti-pertuzumab antibodies, neutralising anti-pertuzumab antibodies were detected in two patients treated with intravenous pertuzumab and trastuzumab and in two patients treated with Phesgo. Among patients that tested positive to anti-trastuzumab antibodies, neutralising anti-trastuzumab antibodies were detected in one patient 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.

Switching treatment from intravenous pertuzumab and trastuzumab to Phesgo (or vice versa)
Study MO40628 investigated the safety of switching between intravenous pertuzumab and trastuzumab and Phesgo subcutaneous (Arm A) and vice versa (Arm B) with a primary objective to evaluate patient preference for Phesgo (see section 5.1 for study design details). Among the patients in Arm A, the incidence of AEs during Cycles 1-3 (intravenous treatment) was 77.5% (62/80 patients) compared to Cycles 4-6 (subcutaneous treatment) which was 72.5% (58/80 patients). Among the patients in Arm B, the incidence of AEs during Cycles 1-3 (subcutaneous treatment) was 77.5% (62/80 patients) compared to Cycles 4-6 (intravenous treatment) which was 63.8% (51/80 patients), mainly due to higher incidence of local injection site reactions (all grade 1 or 2) during Phesgo administration. Pre-switching rates (Cycles 1-3) for serious adverse events, grade 3 adverse events and treatment discontinuations due to adverse events were low (<6%) and similar to post-switching rates (Cycles 4-6). No grade 4 or grade 5 adverse events were reported.

Elderly patients
In FEDERICA, no overall differences in safety of Phesgo were observed in patients ≥ 65 and < 65 years of age. However, in the pivotal pertuzumab clinical trials with intravenous pertuzumab in combination with trastuzumab, decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhoea, occurred with an incidence of ≥ 5% higher in patients ≥ 65 years of age (n= 418) compared to patients < 65 years of age (n= 2926). Limited clinical trial data are available in patients > 75 years of age treated with Phesgo or intravenous pertuzumab and trastuzumab. Post-marketing data shows no differences in safety of pertuzumab in combination with trastuzumab in patients ≥ 65 and < 65 years of age.

Post-marketing setting
Tumour lysis syndrome (observed with pertuzumab IV only)
Interstitial lung disease (observed with trastuzumab IV only)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FY01

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 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

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, without competing and have complementary mechanisms for disrupting HER2 signaling:

- Pertuzumab specifically targets the extracellular dimerization domain (subdomain II) of HER2 and thereby blocks ligand-dependent heterodimerization of HER2 with other HER family members, including epidermal growth factor receptor (EGFR), HER3 and HER4. As a result, pertuzumab inhibits ligand-activated intracellular signalling through two major signalling pathways, mitogen-activated protein (MAP) kinase and

phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively
- Trastuzumab binds to sub-domain IV, of the extracellular domain of the HER2 protein to inhibit the ligand-independent, HER2 mediated proliferation and survival signals in human tumour cells that over express HER2.

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

Clinical trials

This section presents the clinical experience from Phesgo fixed dose combination of pertuzumab and trastuzumab and from intravenous pertuzumab in combination with trastuzumab patients with HER2 overexpressing early and metastatic breast cancer.

Clinical experience of Phesgo in patients with HER2 positive early breast cancer

The clinical experience of Phesgo is based on data from a Phase III clinical trial (FEDERICA WO40324) and a Phase II clinical trial (PHRANCESCA MO40628) in patients with HER2 overexpressing early breast cancer. HER2 overexpression was determined at a central laboratory and defined as a score of 3+ by IHC or an ISH amplification ratio ≥ 2.0 in the trial outlined below.

FEDERICA WO40324

FEDERICA is 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 4 as follows:

Table 4: 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). Key secondary endpoints at the time of primary analysis included non-inferiority of the Cycle 7 serum trastuzumab C_{trough} of trastuzumab within Phesgo compared with intravenous trastuzumab, efficacy (locally assessed [total pathological complete response (tpCR)]), and safety outcomes. Other secondary endpoints included long-term safety and clinical outcomes (iDFS, iDFS including second primary non-breast cancer [SPNBC], EFS, EFS including SPNBC, DRFI and OS). Demographics were well 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 refer to section 5.2. For safety profile refer to section 4.8. The analysis of secondary efficacy endpoint, tpCR (locally assessed), defined as an absence of invasive disease in the breast and axilla (ypT0/is, ypN0), is shown in Table 5. Analyses of secondary long term clinical outcomes are also shown in Table 5.

Table 5: Summary of efficacy (ITT population)

Parameter	**Phesgo (n=248)**	**Intravenous pertuzumab + trastuzumab (n=252)**
Total Pathological Complete Response (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	
Long term clinical outcomes[3]		
Invasive Disease Free Survival (iDFS)		
n	234	239
Patients with event (%)	26 (11.1%)	23 (9.6%)
Unstratified Hazard Ratio[4] (95% CI)	1.13 (0.64, 1.97)	
3 year event-free rate[5] (95% CI)	89.9 (85.9, 93.8)	90.7 (86.9, 94.5)
iDFS including second primary non-breast cancer (SPNBC)		
n	234	239
Patients with event (%)	28 (12.0%)	26 (10.9%)
Hazard Ratio[4] (95% CI)	1.08 (0.63, 1.84)	
3 year event-free rate[5] (95% CI)	88.5 (84.4, 92.7)	89.4 (85.4, 93.4)
Event Free Survival (EFS)		
n	248	252
Patients with event (%)	32 (12.9%)	29 (11.5%)
Hazard Ratio[4] (95% CI)	1.12 (0.68, 1.85)	
3 year event-free rate[5] (95% CI)	88.3 (84.2, 92.4)	89.8 (86.0, 93.6)
EFS including SNPBC		
n	248	252

Parameter	Phesgo (n=248)	Intravenous pertuzumab + trastuzumab (n=252)
Patients with event (%)	34 (13.7%)	32 (12.7%)
Hazard Ratio[4] (95% CI)	1.08 (0.67, 1.75)	
3 year event-free rate[5] (95% CI)	87.0 (82.8, 91.3)	88.5 (84.5, 92.5)
Disease Recurrence Free Interval (DRFI)		
n	248	252
Patients with event (%)	19 (7.7%)	18 (7.1%)
Hazard Ratio[4] (95% CI)	1.09 (0.57, 2.07)	
3 year event-free rate[5] (95% CI)	93.2 (90.0, 96.4)	93.8 (90.7, 96.8)
Overall Survival (OS)		
n	248	252
Patients with event (%)	14 (5.6%)	12 (4.8%)
Hazard Ratio[4] (95% CI)	1.20 (0.56, 2.60)	
3 year event-free rate[5] (95% CI)	95.8 (93.3, 98.4)	96.7 (94.5, 99.0)

[1] Confidence interval for one sample binomial using Pearson-Clopper method
[2] Hauck-Anderson continuity correction has been used in this calculation
[3] Final analysis, clinical cut off date 2 June 2023, median 51 months follow up
[4] All analyses stratified by central hormone receptor status, clinical stage and type of chemotherapy
[5] 3-year event-free rate derived from Kaplan-Meier estimates

Overall, results were comparable between the two treatment groups with respect to all efficacy parameters.

PHRANCESCA (MO40628)
Study MO40628 investigated the safety of switching between intravenous pertuzumab and trastuzumab and Phesgo subcutaneous and vice versa (see section 4.8) with a primary objective to evaluate patient preference for either the intravenous or the subcutaneous route of administration: 85% of patients preferred the subcutaneous route, whereas 13.8% preferred the IV administration, and 1.2% had no preference. A total of 160 patients were included in this 2-arm, cross-over study: 80 patients were randomised to Arm A (3 cycles of intravenous pertuzumab and trastuzumab followed by 3 cycles of Phesgo) and 80 patients were randomised to Arm B (3 cycles of Phesgo followed by 3 cycles intravenous pertuzumab and trastuzumab). At primary analysis, the median exposure to adjuvant pertuzumab and trastuzumab (both IV and SC administration) was 11 cycles (range: 6 to 15).

Clinical experience of intravenous pertuzumab in combination with trastuzumab in HER2 positive breast cancer
The clinical experience of intravenous pertuzumab in combination with trastuzumab is based on data from two randomised neoadjuvant phase II trials in early breast cancer (one controlled), a non-randomised neoadjuvant phase II trial, a randomised phase III trial in the adjuvant setting and a randomised phase III trial and a single-arm phase II trial in metastatic breast cancer. HER2 overexpression was determined at a central laboratory and defined as a score of 3+ by IHC or an ISH amplification ratio ≥ 2.0 in the trials outlined below.

Early breast cancer
Neoadjuvant treatment

In the neoadjuvant setting, locally advanced and inflammatory breast cancers are considered as high-risk irrespective of hormone receptor status. In early stage breast cancer, tumour size, grade, hormone receptor status and lymph node metastases should be taken into account in the risk assessment.

The indication in the neoadjuvant treatment of breast cancer is based on demonstration of an improvement in pathological complete response rate, and trends to improvement in disease-free survival (DFS) that nevertheless do not establish or precisely measure a benefit with regard to long-term outcomes, such as overall survival (OS) or DFS.

NEOSPHERE (WO20697)
NEOSPHERE is a multicentre, randomised Phase II clinical trial with pertuzumab and was conducted in 417 patients with newly diagnosed, early, inflammatory or locally advanced HER2-positive breast cancer (T2-4d; primary tumour > 2 cm in diameter) who had not received prior trastuzumab, chemotherapy or radiotherapy. Patients with metastases, bilateral breast cancer, clinically important cardiac risk factors (see section 4.4) or LVEF < 55% were not included. The majority of patients were less than 65 years old.

Patients were randomised to receive one of four neoadjuvant regimens for 4 cycles prior to surgery as follows:

- trastuzumab plus docetaxel
- pertuzumab plus trastuzumab and docetaxel
- pertuzumab plus trastuzumab
- pertuzumab plus docetaxel

Randomisation was stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen (ER) or progesterone (PgR) positivity.

Pertuzumab was given intravenously at an initial dose of 840 mg, followed by 420 mg every three weeks. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every three weeks. Docetaxel was given intravenously at an initial dose of 75 mg/m^2 followed by 75 mg/m^2 or 100 mg/m^2 (if tolerated) every 3 weeks. Following surgery all patients received 3 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 who only received pertuzumab plus trastuzumab prior to surgery subsequently received both FEC and docetaxel post-surgery.

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 well balanced [median age was 49-50 years old, the majority were Caucasian (71%) and all 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 6. 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. The difference in pCR rate is considered likely to translate into a clinically meaningful difference in long term outcomes and is supported by positive trends in PFS (hazard ratio [HR] = 0.69; 95% CI 0.34; 1.40) and DFS (HR = 0.60; 95% CI 0.28; 1.27).
The pCR rates as well as the magnitude of benefit with pertuzumab (pertuzumab plus trastuzumab and docetaxel compared to patients receiving trastuzumab and docetaxel) were lower in the subgroup of patients with hormone receptor-positive tumours (difference of 6% in pCR in the breast) than in patients with hormone receptor-negative tumours (difference of 26.4% in pCR in the breast).
pCR rates were similar in patients with operable versus locally advanced disease. There were too few patients with inflammatory breast cancer to draw any firm conclusions but the pCR rate was higher in patients who received pertuzumab plus trastuzumab and docetaxel.

TRYPHAENA (BO22280)
TRYPHAENA is a multicentre, randomised Phase ll clinical study conducted in 225 patients with HER2-positive locally advanced, operable, or inflammatory (T2-4d; primary tumour > 2 cm in diameter) breast cancer who had not received prior trastuzumab, chemotherapy or radiotherapy. Patients with metastases, bilateral breast cancer, clinically important cardiac risk factors (see section 4.4) or LVEF < 55% were not included. The majority of patients were less than 65 years old. 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
- 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 was given intravenously at an initial dose of 840 mg, followed by 420 mg every three weeks. Trastuzumab was given intravenously at an initial dose of 8 mg/kg, followed by 6 mg/kg every three weeks. FEC (5-Fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), cyclophosphamide (600 mg/m^2)) was 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 group treated with pertuzumab in combination with TCH, 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.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study (see section 4.8). Secondary efficacy endpoints were pCR rate in the breast (ypT0/is), DFS, PFS and OS.

Demographics were well balanced between arms (median age was 49-50 years old, 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.

Compared with published data for similar regimens without pertuzumab, highigh pCR rates were observed in all 3 treatment arms (see Table 6). 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). There were too few patients with inflammatory breast cancer to draw any firm conclusions. pCR rates were similar in patients with operable and locally advanced disease.

Table 6: NEOSPHERE (WO20697) and TRYPHAENA (BO22280): Overview of efficacy (Intent to treat 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 6): 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)
BERENICE is a non-randomised, open-label, multicentre, multinational, Phase II trial conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer (with primary tumours > 2 cm in diameter or node-positive disease).

The BERENICE study included two parallel groups of patients. 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 dose-dense doxorubicin and cyclophosphamide 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

Following surgery all patients received pertuzumab and trastuzumab intravenously every 3 weeks to complete 1 year of therapy.

The primary endpoint of the BERENICE trial was cardiac safety in the neoadjuvant period of the trial. 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 section 4.4 and 4.8). Key secondary endpoints at the time of primary analysis were neoadjuvant safety and pCR rate in the breast and nodes (i.e. ypT0/is ypN0). Other study secondary endpoints included long-term safety and clinical outcomes (iDFS, EFS and OS).

Adjuvant Treatment
In the adjuvant setting, based on data from the APHINITY study, HER2-positive early breast cancer patients at high risk of recurrence are defined as those with lymph node-positive or hormone receptor-negative disease.

APHINITY (BO25126)
APHINITY is 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 epirubicin and cyclophosphamide (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 (see section 4.2) starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (up to 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. Secondary efficacy endpoints were IDFS including second primary non-breast cancer, OS, DFS, recurrence-free interval (RFI) and distant recurrence-free interval (DRFI).

Demographics were well 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%).

After a median follow-up of 45.4 months, the APHINITY study showed 19% (hazard ratio [HR] = 0.81; 95% CI 0.66; 1.00 p-value 0.0446) reduction in risk of recurrence or death in patients randomised to receive pertuzumab compared with patients randomised to receive placebo.

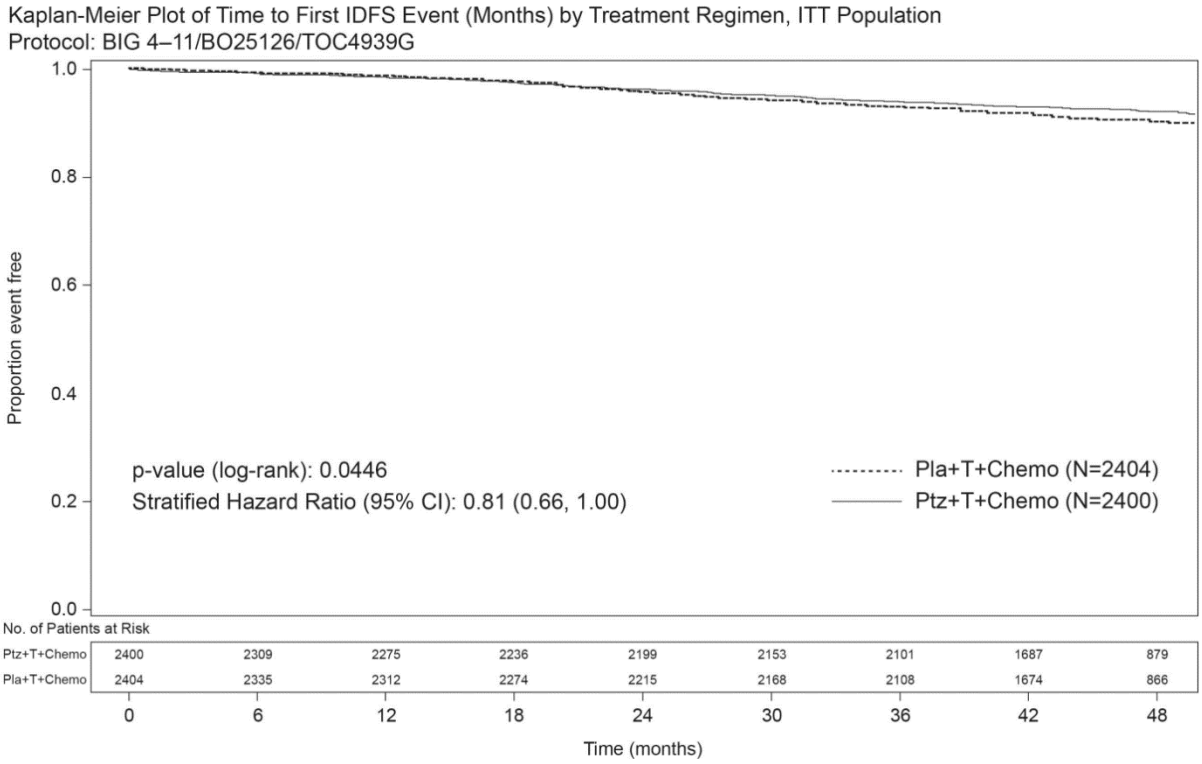
The efficacy results from the APHINITY trial are summarised in Table 7 and in Figures 1 and 2.

Table 7: Overall Efficacy (Intent to treat 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	205 (8.5%)	247 (10.3%)
HR [95% CI]	0.83 [0.69, 1.00]	
p-value (Log-Rank test, stratified[2])	0.0441	
10 year event-free rate[3] [95% CI]	91.6 [90.4, 92.7]	89.8 [88.5, 91.1]

Key to abbreviations (Table 7): HR: Hazard Ratio; CI: Confidence Intervals
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 and 10-year event-free rate derived from Kaplan-Meier estimates
4. Data from final analysis of OS; p-value boundary 0.0496

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



IDFS= invasive disease free survival; CI= confidence interval; 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.

Results of subgroup analysis
At the time of the primary analysis, the benefits of pertuzumab were more apparent in subgroups of patients a high risk of recurrence: patients with node-positive or hormone receptor-negative disease (see Table 8).

Table 8 Efficacy results in subgroups by nodal status and hormone receptor status[1]

Population	**Number of IDFS events/Total N (%)**		**Unstratified HR (95% CI)**
	Pertuzumab + trastuzumab + chemotherapy	**Placebo + trastuzumab + chemotherapy**	
Nodal status			
Positive	139/1503 (9.2%)	181/1502 (12.1%)	0.77 (0.62; 0.96)
Negative	32/897 (3.6%)	29/902 (3.2%)	1.13 (0.68; 1.86)
Hormone receptor status			

Negative	71/864 (8.2%)	91/858 (10.6%)	0.76 (0.56; 1.04)
Positive	100/1536 (6.5%)	119/1546 (7.7%)	0.86 (0.66; 1.13)

[1] Prespecified subgroup analyses without adjusting for multiple comparisons, therefore, results are considered descriptive.

Estimates of IDFS rates in the lymph node positive subgroup were 92.0% versus 90.2% at 3 years and 89.9% vs. 86.7% at 4 years in pertuzumab-treated patients versus the placebo-treated patients, respectively. In the lymph node negative subgroup estimates of IDFS rates were 97.5% versus 98.4% at 3 years and 96.2% versus 96.7% at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively.

In the hormone receptor-negative subgroup estimates of IDFS rates were 92.8% versus 91.2% at 3 years and 91.0% versus 88.7% at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively. In the hormone receptor-positive subgroup estimates of IDFS were 94.8% versus 94.4% at 3 years and 93.0% versus 91.6% at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively.

Patient Reported Outcomes (PRO)
Secondary endpoints included the assessment of patient-reported global health status, role and physical function, and treatment symptoms using the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires. In the analyses of patient-reported outcomes, a 10-point difference was considered clinically meaningful.

Patients' physical function, global health status and diarrhoea scores showed a clinically meaningful change during chemotherapy in both treatment arms. The mean decrease from baseline at that time for physical function was -10.7 (95% CI-11.4, -10.0) in the pertuzumab-arm and -10.6 (95% CI -11.4, -9.9) in the placebo arm; global health status was -11.2 (95% CI -12.2, -10.2) in the pertuzumab-arm and -10.2 (95% CI -11.1,-9.2) in the placebo arm. Change in diarrhoea symptoms increased to +22.3 (95% CI 21.0, 23.6) in the pertuzumab-arm versus +9.2 (9 5% CI 8.2, 10.2) in the placebo arm.

Thereafter in both arms, physical function and global health status scores returned to baseline levels during targeted treatment. Diarrhoea symptoms returned to baseline after HER2 therapy in the pertuzumab-arm. The addition of pertuzumab to trastuzumab plus chemotherapy did not affect patients' overall role function over the course of the study.

Metastatic Breast Cancer
Pertuzumab in combination with trastuzumab and docetaxel
CLEOPATRA (WO20698)
CLEOPATRA (WO20698) is a multicentre, randomised, double-blind, placebo-controlled phase III clinical trial conducted in 808 patients with HER2-positive metastatic or locally recurrent unresectable breast cancer. Patients with clinically important cardiac risk factors were not included (see section 4.4). Due to the exclusion of patients with brain metastases no data are available on pertuzumab activity on brain metastases. There is very limited data available in patients with unresectable locally recurrent disease. Patients were randomised 1:1 to receive placebo + trastuzumab + docetaxel or pertuzumab + trastuzumab + docetaxel.

Pertuzumab and trastuzumab were given at standard doses in a 3-weekly regimen. 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 as an intravenous infusion every three 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.

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), duration of response, and time to symptom progression according to the FACT B Quality of Life (QoL) questionnaire.

Approximately half the patients in each treatment group had hormone receptorpositive disease (defined as estrogen receptor [ER] positive and/or progesterone receptor [PgR] positive) and approximately half of the patients in each treatment group had received prior adjuvant or neo-adjuvant therapy. Most of these patients had received prior anthracycline therapy and 11% of all patients had received prior trastuzumab. A total of 43% of patients in both treatment groups had previously received radiotherapy. Patients' median LVEF at baseline was 65.0% (range 50% - 88%) in both groups.

The efficacy results from the CLEOPATRA study are summarised in Table 8. A statistically significant improvement in IRF-assessed PFS was demonstrated in the pertuzumab-treated group compared with the placebo-treated group. The results for investigator-assessed PFS were similar to those observed for IRF-assessed PFS. The efficacy results from the CLEOPATRA trial are summarised in Table 8 below.

Table 8: Summary of efficacy from CLEOPATRA study

Parameter	**Placebo + Trastuzumab + docetaxel n=406**	**Pertuzumab + Trastuzumab + docetaxel n=402**	**HR (95% CI)**	**p-value**
***Primary* Endpoint**				
Progression-Free Survival (IRF review)				
No. of patients with an event	242 (59%)	191 (47.5%)	0.62	
Median months	12.4	18.5	[0.51;0.75]	<0.0001
***Secondary* Endpoints**				
Overall Survival (Final analysis of OS)				
No. of patients with an event*	221 (54.4%)	168 (41.8%)	0.68	0.0002
Median months	40.8	56.5	[0.56;0.84]	
Progression-Free Survival (investigator assessment)				
No. of patients with an event	250 (61.6%)	201 (50.0%)	0.65	<0.0001
Median months	12.4	18.5	[0.54;0.78]	

Objective Response Rate (ORR)				
No. of patients with an event	336	343	Difference	0.0011
Responders**	233 (69.3%)	275 (80.2%)	in ORR:	
95% CI for ORR	[64.1; 74.2]	[75.6; 84.3]	10.8%	
Complete response (CR)	14 (4.2%)	19 (5.5%)	[4.2,17.5]%	
Partial Response (PR)	219 (65.2%)	256 (74.6%)		
Stable disease (SD)	70 (20.8%)	50 (14.6%)		
Progressive disease (PD)	28 (8.3%)	13 (3.8%)		
Duration of Response ^				
n=	233	275		
Median weeks	54.1	87.6		
95% CI for Median	[46;64]	[71;106]		

*Final analysis of overall survival, cutoff date 11 Feb 2014

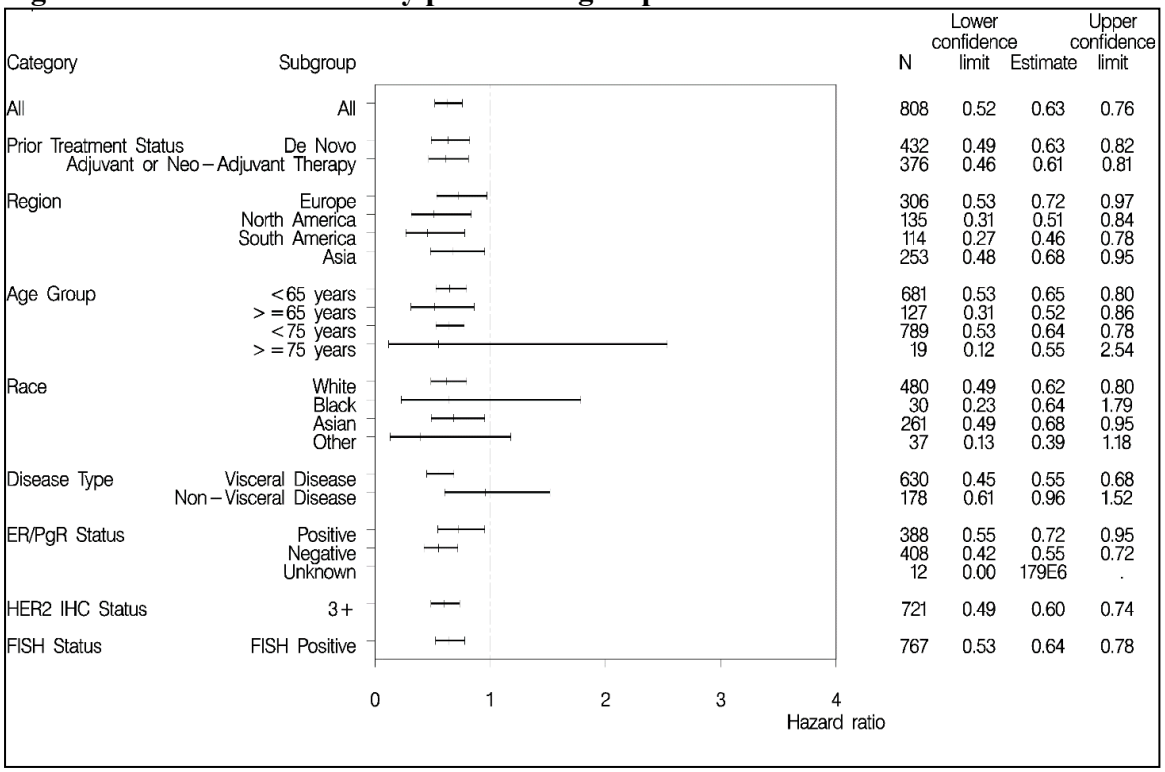
** Patients with best overall response of confirmed CR or PR by RECIST.

^ 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

Consistent results were observed across pre-specified patient subgroups including the subgroups based on stratification factors of geographic region and prior adjuvant/neoadjuvant therapy or de novo metastatic breast cancer (see Figure 2). A post hoc exploratory analysis revealed that for patients who had received prior trastuzumab (n= 88), the hazard ratio for IRF-assessed PFS was 0.62 (95% CI 0.35; 1.07), compared with 0.60 (95% CI 0.43; 0.83) for patients who had received prior therapy which did not include trastuzumab (n= 288).

Figure 2: IRF assessed PFS by patient subgroup

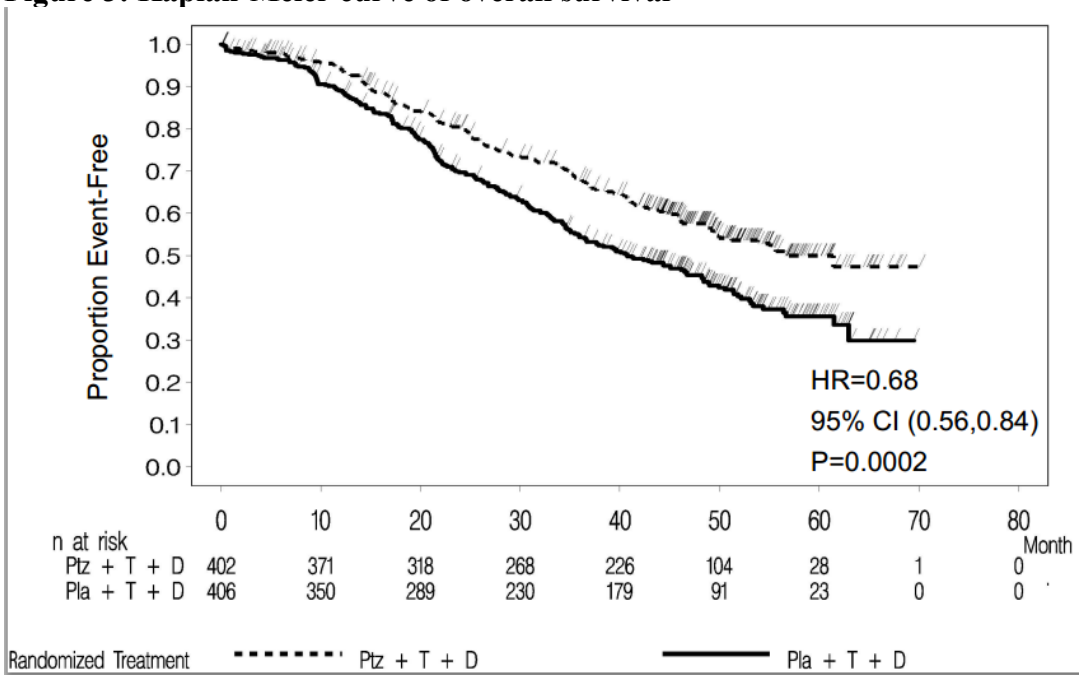


The event-driven final analysis of OS was performed when 389 patients had died (221 in the placebo-treated group and 168 in the pertuzumab-treated group). The statistically significant OS benefit in favour of the pertuzumab-treated group, previously observed at an interim

analysis of OS (performed one year after the primary analysis), was maintained (HR = 0.68; p= 0.0002 log-rank test). The median time to death was 40.8 months in the placebo-treated group and 56.5 months in the pertuzumab-treated group (see Table 8, Figure 3).

A descriptive analysis of OS performed at the end of the study when 515 patients had died (280 in the placebo-treated group and 235 in the pertuzumab-treated group) showed that the statistically significant OS benefit in favour of the pertuzumab-treated group was maintained over time after a median follow-up of 99 months (HR = 0.69; p < 0.0001 log-rank test; median time to death 40.8 months [placebo-treated group] versus 57.1 months [pertuzumab-treated group]). Landmark survival estimates at 8 years were 37% in the pertuzumab-treated group and 23% in the placebo-treated group.

Figure 3: Kaplan-Meier curve of overall survival



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

No statistically significant difference between the two treatment groups in Health Related Quality of Life as assessed by FACTB TOI-PFB scores.

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 10.6% (26/245) and 0.4% (1/245), respectively, in patients treated with intravenous pertuzumab and trastuzumab. Among patients that tested positive to

anti-pertuzumab antibodies, neutralising anti-pertuzumab antibodies were detected in three patients.

The incidence of treatment-emergent anti-pertuzumab, anti-trastuzumab, and anti-vorhyaluronidase alfa antibodies was 12.9% (31/241), 2.1% (5/241), and 6.3% (15/238), respectively, in patients treated with Phesgo. Among these patients, neutralising anti-pertuzumab antibodies were detected in two patients, and neutralising anti-trastuzumab antibodies were detected in one patient. 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

Pertuzumab and trastuzumab exposure following subcutaneous administration of Phesgo (1200 mg pertuzumab/600 mg trastuzumab loading dose followed by 600 mg pertuzumab/ 600 mg trastuzumab every 3 weeks) in the FEDERICA study is shown in Table 9. The PK results for the primary endpoint of 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 µg/mL) with a geometric mean ratio of 1.22 (90% CI: 1.14–1.31). The lower boundary of the two-sided 90% confidence interval for the geometric mean ratio of pertuzumab within Phesgo and intravenous pertuzumab was 1.14, i.e., greater than the predefined margin of 0.8.

The PK results for the secondary endpoint, trastuzumab Cycle 7 C_{trough} (i.e., predose Cycle 8), showed non-inferiority of trastuzumab within Phesgo (geometric mean 57.5 µg/mL) compared to intravenous trastuzumab (geometric mean 43.2 µg/mL) with a geometric mean ratio of 1.33 (90% CI: 1.24–1.43). A population PK model of pertuzumab with linear elimination from the central compartment was constructed using pooled pertuzumab within Phesgo and intravenous pertuzumab PK data from FEDERICA to describe the observed pertuzumab PK concentrations following subcutaneous Phesgo administration and intravenous pertuzumab administration.

A population PK model with parallel linear and nonlinear elimination from the central compartment was constructed using pooled trastuzumab PK data from the phase III study BO22227 (HANNAH) of subcutaneous trastuzumab vs. intravenous trastuzumab, to describe the observed PK concentrations following intravenous trastuzumab or subcutaneous trastuzumab administration in HER2 positive EBC patients. The PK analysis using the HANNAH population PK model demonstrated that there was no impact on the PK of trastuzumab within Phesgo from pertuzumab within Phesgo as consistent PK were observed between trastuzumab within Phesgo and subcutaneous trastuzumab. The population PK predicted pertuzumab and trastuzumab exposures are summarised in Table 9 below.

Table 9: Pertuzumab and trastuzumab exposure (median with 5th-95th Percentiles) following subcutaneous administration of Phesgo or intravenous pertuzumab or trastuzumab[a]

Parameter	Pertuzumab within Phesgo	Intravenous pertuzumab	Trastuzumab within Phesgo[b]	Intravenous trastuzumab[b]

C_{trough} (mcg/mL)	Cycle 5	85.1 (48.7 – 122.5)	74.9 (47.8 - 99.8)	27.7 (13.6 – 43.2)	31.4 (21.1 – 50.9)
	Cycle 7	88.9 (51.8 - 142.5)	78.5 (41.3 - 114.9)	57.5 (27.2-92.7)	44.9 (29.7-76.2)
C_{max} (mcg/mL)	Cycle 5	106.5 (62.9 - 152.6)	304.8 (191.1- 409.7)	44.6 (31.0-63.1)	172.9 (133.7- 238.9)
	Cycle 7	149.5 (88.5 - 218.5)	225.9 (158.5 - 301.8)	117.3 (72.2-166.6)	169.1 (130.6- 238.9)
$AUC_{0\text{-}21\ days}$ (mcg/mL•day)	Cycle 5	2306.9 (1388.4 - 3376.2)	2519.7 (1898.4 - 3138.9)	1023.8 (634.3- 1442.6)	1341.0 (1033.1- 2029.0)
	Cycle 7	2569.3 (1487.4 - 3786.1)	2454.3 (1561.4 - 3346.1)	1838.7 (1024.3- 2715.5)	1668.6 (1264.7- 2576.9)

[a]First dose of Phesgo, intravenous pertuzumab and trastuzumab administered at Cycle 5;
[b]Study BO22227 HANNAH population PK model used for trastuzumab PK simulation

Absorption

The median maximum serum concentration (C_{max}) of pertuzumab within Phesgo and time to maximal concentration (T_{max}) were 157 µg/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 114 µg/mL and 3.84 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.

Biotransformation

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

Elimination

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 PK 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) in at least 95% patients 7 months after the last dose.

Pharmacokinetics in Special Populations

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of Phesgo in the paediatric population.

Geriatric population
No studies have been conducted to investigate the pharmacokinetics of Phesgo in geriatric patients. In population PK analyses of pertuzumab within Phesgo and intravenous pertuzumab, age was not found to significantly affect PK of pertuzumab. In population PK analyses of subcutaneous or intravenous trastuzumab, age has been shown to have no effect on the disposition of trastuzumab.

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

Hepatic impairment
No formal pharmacokinetic study of Phesgo has been conducted in patients with hepatic impairment. Based on population PK analyses of pertuzumab within Phesgo, mild hepatic impairment was shown not to affect pertuzumab exposure. However, only limited data from patients with mild hepatic impairment were included in population PK analyses. IgG1 molecules such as pertuzumab and trastuzumab are catabolised by widely distributed proteolytic enzymes not restricted to hepatic tissue. Therefore, changes in hepatic function are unlikely to have an effect on the elimination of pertuzumab and trastuzumab.

5.3 PRECLINICAL SAFETY DATA

No dedicated studies were conducted with the combination of subcutaneous pertuzumab, trastuzumab and vorhyaluronidase alfa.

Subcutaneous and intravenous pertuzumab and trastuzumab
Subcutaneous pertuzumab (250 mg/kg/week for 4 weeks) and intravenous pertuzumab (up to 150 mg/kg weekly for up to 26 weeks) was well tolerated in cynomolgus monkeys (binding species), except for the development of diarrhoea. With intravenous pertuzumab doses of 15 mg/kg and higher, intermittent mild treatment-associated diarrhoea was noted. In a subset of monkeys, chronic dosing (26 weekly doses) resulted in episodes of diarrhoea-related dehydration which were managed with intravenous fluid replacement therapy. Trastuzumab was well tolerated in mice (non-binding species), rabbits (non-binding species) and Macaque (rhesus and cynomolgus) monkeys (binding species) in single-dose (IV) and repeat-dose toxicity (SC and IV) studies of up to 13 weeks (25 mg/kg twice weekly) or 26 weeks (25 mg/kg weekly) duration, respectively. No evidence of acute or chronic toxicity was identified.

Pertuzumab
No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. No definitive conclusion on adverse effects can be drawn on the male reproductive organs in cynomolgus monkey repeated dose toxicity.
Reproductive toxicology studies have been conducted in pregnant cynomolgus monkeys (Gestational Day (GD) 19 through to GD 50) at initial doses of 30 to 150 mg/kg 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 the recommended human subcutaneous dose, based on C_{max}. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-foetal death between GD25 to GD70. The incidences of embryo-foetal loss were 33, 50, and 85% for pregnant female monkeys treated with bi weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (4- to 35-fold greater than the recommended human dose, based on C_{max}). 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. In addition, consistent with foetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 in 30 mg/kg and 1 of 2 in 100 mg/kg groups), ventricular septal defects (1 of 6 in 30 mg/kg group), thin ventricular wall (1 of 2 in 100 mg/kg group) and minor skeletal defects (external - 3 of 6 in 30 mg/kg group) were also noted. Pertuzumab exposure was reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

Subcutaneous pertuzumab (250 mg/kg/week for 4 weeks) and intravenous pertuzumab (up to 150 mg/kg weekly for up to 26 weeks) was well tolerated in cynomolgus monkeys (binding species), except for the development of diarrhoea. With intravenous pertuzumab doses of 15 mg/kg and higher, intermittent mild treatment-associated diarrhoea was noted. In a subset of monkeys, chronic dosing (26 weekly doses) resulted in episodes of severe secretory diarrhoea. The diarrhoea was managed (with the exception of euthanasia of one animal, 50 mg/kg/dose) with supportive care including intravenous fluid replacement therapy.

Trastuzumab

Reproduction studies have been conducted in cynomolgus monkeys via the intravenous route at doses up to 16 times that of the human maintenance trastuzumab dose in Phesgo of 600 mg formulation and have revealed no evidence of impaired fertility or harm to the foetus. Placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (days 120-150 of gestation) foetal development period was observed.
There was no evidence of acute or multiple dose-related toxicity in studies of up to 6 months, or reproductive toxicity in teratology, female fertility or late gestational toxicity/placental transfer studies. Trastuzumab is not genotoxic. A study of trehalose, a major formulation excipient did not reveal any toxicities. No long-term animal studies have been performed to establish the carcinogenic potential of trastuzumab, or to determine its effects on fertility in males.

Lactation

A study conducted in cynomolgus monkeys that had received trastuzumab at doses 25 times that of the weekly human maintenance dose of 2 mg/kg intravenous trastuzumab from days 120 to 150 of pregnancy, demonstrated that trastuzumab is secreted in the milk postpartum. The exposure to trastuzumab in utero and the presence of trastuzumab in the serum of these infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age**.**

Hyaluronidase

Hyaluronidase is found in most tissues of the human body. Non-clinical data for recombinant human hyaluronidase reveal no special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints. Reproductive toxicology

studies with vorhyaluronidase alfa revealed embryofoetal toxicity in mice at high systemic exposure, but did not show teratogenic potential.
A single dose study in rabbits and a 13-week repeat dose toxicity study in cynomolgus monkeys were conducted with trastuzumab subcutaneous formulation. The rabbit study was performed to specifically examine local tolerance aspects. The 13-week study was performed to confirm that the change to the subcutaneous route of administration and the use of the excipient vorhyaluronidase alfa did not have an effect on the trastuzumab safety characteristics. Trastuzumab subcutaneous formulation was locally and systemically well tolerated.

Genotoxity
No studies have not been performed to evaluate the mutagenic potential of pertuzumab or trastuzumab within Phesgo.

Carcinogenicity
No carcinogenicity studies have been performed to establish the carcinogenic potential of pertuzumab or trastuzumab within Phesgo.

Other
Subcutaneous trastuzumab was well tolerated in a rabbit local tolerance study (non-binding species) and in a 13-week repeat dose toxicity study in cynomolgus monkeys (binding species).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Hyaluronidase
Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
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

18 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C - 8°C. Keep vial in the outer carton in order to protect 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 and 600 mg pertuzumab/600 mg trastuzumab solution are ready to use solutions for injection which does not need to be mixed with other drugs or diluted.

Phesgo should be inspected visually to ensure there is no particulate matter or discolouration prior to administration. Do not shake. Phesgo solution for injection is for single use only and should be prepared by a healthcare professional using aseptic technique.

From a microbiological point of view, the medicine should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial preservative. If the dose is not to be administered immediately, and the solution of Phesgo has been withdrawn from the vial into the syringe under aseptic conditions, replace the transfer needle with a syringe closing cap. Label the syringe with the peel-off sticker and store the syringe no longer than 7 days in the refrigerator (2°C - 8°C) protected from light, and no longer than 4 hours at 9°C - 25°C and avoid unnecessary storage. Once transferred from the vial to the syringe, the medicinal product is physically and chemically stable for 28 days at 2°C - 8°C protected from light or 24 hours at 9°C - 30°C.

After transfer of the solution to the syringe, it is recommended to replace the transfer needle by a syringe closing cap to avoid drying of the solution in the needle and not compromise the quality of the medicinal product. Label the syringe with the peel-off sticker. The hypodermic injection needle must be attached to the syringe immediately prior to administration followed by volume adjustment to 10 mL (600 mg pertuzumab/600 mg trastuzumab) or 15 mL (1200 mg pertuzumab/600 mg trastuzumab).

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

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)

Phesgo is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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

9. DATE OF FIRST APPROVAL

22 September 2022

10. DATE OF REVISION OF THE TEXT

14 August 2025

Summary table of changes

Section Changed	Summary of new information
4.2	Addition of guidance for dose administration outside of the hospital setting.
4.4	Addition of precaution for management of hypersensitivity reactions outside of the clinical setting.
4.8	Corrections of frequency of dyspnoea and of LVEF information.
5.1	Update of hazard ratio information presented in Table 5 ‘Summary of efficacy (ITT population)’ (FeDeriCa trial); update of Table 7 ‘Overall Efficacy (Intent to treat Population)’ (APHINITY trial) with 10-year results for overall survival.