**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Phesgo 600 mg/600 mg solution for injection
Phesgo 1 200 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 1 200 mg/600 mg solution for injection

One vial of 15 mL solution contains 1 200 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.

Excipient with known effect
Each 15 mL vial of Phesgo contains 6 mg of polysorbate 20.
Each 10mL vial of Phesgo contains 4 mg of polysorbate 20.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for 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 1 200 mg/600 mg and 600 mg/600 mg solutions, respectively.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Early breast cancer (EBC)

Phesgo is indicated for use in combination with chemotherapy in:
- the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence (see section 5.1)
- the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence (see section 5.1)

Metastatic breast cancer (MBC)

Phesgo is indicated for use in combination with docetaxel in adult 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 Posology and method of administration

Phesgo should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. Phesgo should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are immediately available. Once pertuzumab-based therapy has been safely established, the physician may determine the suitability of administration of Phesgo outside of the clinical setting (e.g. at home) by a healthcare professional (see section 4.4).

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).

Posology

Patients treated with Phesgo must have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of ≥ 2 by *in situ* hybridization (ISH), assessed by a validated test.

To ensure accurate and reproducible results, the testing must be performed in a specialized laboratory, which can ensure validation of the testing procedures. For full instructions on assay performance and interpretation, please refer to the package leaflet of validated HER2 testing assays.

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

**Table 1: Phesgo recommended dosing and administration**

| | Dose (irrespective of body weight) | Approximate duration of subcutaneous injection | Observation time [ab] |
|---|---|---|---|
| Loading dose | 1 200 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 reactions and hypersensitivity reactions
[b]Observation period should start following administration of Phesgo and be completed prior to any subsequent administration of chemotherapy

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 (see section 4.4).

*Metastatic breast cancer*

Phesgo should be administered in combination with docetaxel. Treatment with Phesgo may continue until disease progression or unmanageable toxicity even if treatment with docetaxel is discontinued (see section 4.4).

*Early breast cancer*

In the neoadjuvant setting, Phesgo should be administered for 3 to 6 cycles in combination with chemotherapy, as part of a complete treatment regimen for early breast cancer (see section 5.1).

In the adjuvant setting, Phesgo should be administered for a total of one year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first), as part of a complete regimen for early breast cancer and regardless of the timing of surgery. Treatment should include standard anthracycline- and/or taxane-based chemotherapy. Phesgo should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued.

*Delayed or missed doses*

If the time between two sequential injections is:

- less than 6 weeks, the maintenance dose of Phesgo 600 mg/600 mg should be administered as soon as possible. Thereafter, continue with the 3-weekly schedule.
- 6 weeks or more, a loading dose of Phesgo 1 200 mg/600 mg should be re-administered followed by maintenance dose of Phesgo 600 mg/600 mg 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 docetaxel and other chemotherapy dose modifications, see relevant summary of product characteristics (SmPC).

*Left ventricular dysfunction*

Phesgo should be withheld for at least 3 weeks for any signs and symptoms suggestive of congestive heart failure. Phesgo should be discontinued if symptomatic heart failure is confirmed (see section 4.4 for more details).

*Patients with metastatic breast cancer*

Patients should have a pre-treatment left ventricular ejection fraction (LVEF) of ≥ 50 %. Phesgo should be withheld for at least 3 weeks for:

- a drop in LVEF to less than 40 %
- a LVEF of 40 %-45 % associated with a fall of ≥ 10 % points below pre-treatment value.

Phesgo may be resumed if the LVEF has recovered to > 45 %, or to 40-45 % associated with a difference of < 10 % points below pre-treatment values.

*Patients with early breast cancer*

Patients should have a pre-treatment LVEF of ≥ 55 % (≥ 50 % after completion of the anthracycline component of chemotherapy, if given).

Phesgo should be withheld for at least 3 weeks for a drop in LVEF to less than 50 % associated with a fall of ≥ 10 % points below pre-treatment values.

Phesgo may be resumed if the LVEF has recovered to ≥ 50 % or to a difference of < 10 % points below pre-treatment values.

*Special populations*

*Elderly*

No overall differences in efficacy of Phesgo were observed in patients ≥ 65 and < 65 years of age. No dose adjustment of Phesgo is required in patients ≥ 65 years of age. Limited data are available in patients > 75 years of age.

Please see section 4.8 for assessment of safety in elderly patients.

*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 (see section 5.2).

*Paediatric population*

The safety and efficacy of Phesgo in children and adolescents below 18 years of age have not been established. There is no relevant use of Phesgo in the paediatric population in the indication of breast cancer.

*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 1 200 mg pertuzumab/600 mg trastuzumab, followed by a maintenance dose of 600 mg pertuzumab/600 mg trastuzumab every 3 weeks for subsequent administrations.

Method of administration

Phesgo should be administered as a subcutaneous injection only. Phesgo is not intended for intravenous administration.

The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. The dose should not be split between two syringes or between two sites of administration. During the treatment course with Phesgo, other medicinal products for subcutaneous administration should preferably be injected at different sites.

The loading dose and maintenance dose should be administered over 8 and 5 minutes, respectively.

An observation period of 30 minutes after completion of Phesgo loading dose and 15 minutes after completion of the maintenance dose is recommended for injection-related reactions (see sections 4.4 and 4.8).

*Injection-related reactions*

The injection may be slowed or paused if the patient experiences injection-related symptoms (see section 4.4 and section 4.8). Treatment including oxygen, beta agonists, antihistamines, rapid intravenous fluids and antipyretics may also help alleviate systemic symptoms.

*Hypersensitivity reactions /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 and section 4.8).

For instructions on use and handling of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Traceability

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

Left ventricular dysfunction (including congestive heart failure)

Decreases in LVEF have been reported with medicinal products 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 trastuzumab 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 declines 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 has not been studied in patients with: a pre-treatment 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. In addition, pertuzumab in combination with trastuzumab and chemotherapy has not been studied in patients with decreases in LVEF < 50 % during prior trastuzumab adjuvant therapy.

LVEF should be assessed prior to initiation of Phesgo and at regular intervals during treatment (e.g. once during neoadjuvant treatment and every 12 weeks in the adjuvant and metastatic setting) to ensure that LVEF is within normal limits. If the LVEF has declined as indicated in section 4.2 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.

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/infusion-related reactions (IRRs)

Phesgo has been associated with injection-related reactions (see section 4.8). 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 hour 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. Severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have been observed with pertuzumab in combination with trastuzumab and chemotherapy (see section 4.8). The majority of anaphylactic reactions occurred within the first 6-8 cycles of treatment when pertuzumab and trastuzumab were given in combination with chemotherapy. Medicinal products to treat such reactions, as well as emergency equipment, should be available for immediate use.

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. epinephrine, beta-agonists, antihistamines and corticosteroids) 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).

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 also 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 with known effect

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

This medicinal product contains polysorbate 20. Each vial of 15 mL solution contains 6 mg of polysorbate 20. Each vial of 10mL solution contains 4 mg of polysorbate 20. Polysorbates may cause allergic reactions.

## 4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed.

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

In animal studies pertuzumab has shown reproductive toxicity. There is only a limited amount of data from the use of pertuzumab in pregnant women.

From animal studies, it is not known whether trastuzumab can affect reproductive capacity (see section 5.3). However, in the post-marketing setting, 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 receiving trastuzumab.

Based on the aforementioned animal studies and post-marketing data, Phesgo should therefore be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. 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.

Breast-feeding

As human IgG is secreted into human milk and the potential for absorption and harm to the infant is unknown, women should not breast-feed during Phesgo therapy and for at least 7 months following the last dose.

Fertility

*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 pertuzumab for up to six-month duration in cynomolgus monkeys (see section 5.3).

*Trastuzumab*

Reproduction studies conducted in cynomolgus monkeys with trastuzumab revealed no evidence of impaired fertility in female cynomolgus monkeys (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Phesgo has minor influence on the ability to drive and use machines (see section 4.8). Patients experiencing injection-related reactions or dizziness (see section 4.4) should be advised not to drive and use machines until symptoms abate.

## 4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (ADRs) (≥ 30 %) reported in patients treated with Phesgo or intravenous pertuzumab in combination with trastuzumab and chemotherapy were alopecia, diarrhoea, nausea, anemia, asthenia and arthralgia.

The most common serious adverse events (SAE) (≥ 1 %) reported in patients treated with Phesgo or intravenous pertuzumab in combination with trastuzumab were febrile neutropenia, cardiac failure, pyrexia, neutropenia, neutropenic sepsis, neutrophil count decreased and pneumonia.

The safety profile of Phesgo was overall consistent to the known safety profile of intravenous pertuzumab in combination with trastuzumab, with an additional ADR of injection site reaction (15.3 % vs. 0.4 %).

In the pivotal trial FEDERICA, 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 % vs 20.6 %, and dyspnea 12.1 % vs 6 %.

Tabulated list of adverse reactions

The safety of pertuzumab in combination with trastuzumab has been evaluated in 3 834 patients with HER2-positive breast cancers in the pivotal trials CLEOPATRA, NEOSPHERE, TRYPHAENA APHINITY and FEDERICA. It was generally consistent across studies, although the incidence and most common ADRs varied depending on whether pertuzumab in combination with trastuzumab were administered with or without concomitant anti-neoplastic agent.

Table 2 presents, in the first column, ADRs that have been reported in association with the use of pertuzumab in combination with trastuzumab and chemotherapy in the below mentioned pivotal clinical trials (n= 3 834) and in the post-marketing setting. As pertuzumab is used in combination with trastuzumab and chemotherapy, it is difficult to ascertain the causal relationship of an adverse reaction to a particular medicinal product. The last two columns detail ADRs reported in the Phesgo arm of FEDERICA study (n=243) when Phesgo is administered with chemotherapy agent and as monotherapy.

- CLEOPATRA, in which pertuzumab was given in combination with trastuzumab and docetaxel to patients with metastatic breast cancer (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 early breast cancer
- APHINITY, in which adjuvant pertuzumab was given in combination with trastuzumab and anthracycline-based or non-anthracycline-based, taxane-containing chemotherapy to patients with early breast cancer (n= 2 364)
- FEDERICA, in which Phesgo (n= 243) or intravenous pertuzumab and trastuzumab (n= 247) was firstly administered in combination with chemotherapy (neoadjuvant phase) and subsequently as monotherapy (adjuvant phase) to patients with early breast cancer.

These ADRs are listed below by MedDRA system organ class (SOC) and categories of frequency:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1 000 to < 1/100)
- Rare (≥ 1/10 000 to < 1/1 000)
- Very rare (< 1/10 000)

- Not known (cannot be estimated from the available data)

Within each frequency grouping and SOC, ADRs are presented in the order of decreasing seriousness.

**Table 2 Summary of ADRs in patients treated with pertuzumab, trastuzumab in pivotal clinical trials^, ^^, and in the post-marketing setting†**

| | N = 3 834^ | N = 243^^ | |
|---|---|---|---|
| | Pertuzumab+trastuzumab | Phesgo with chemotherapy | Phesgo monotherapy |
| **ADR (MedDRA preferred term) System Organ Class** | Frequency category | Frequency category | Frequency category |
| **Blood and lymphatic system disorders** | | | |
| Neutropenia | Very common | Very common | Common |
| Anemia | Very common | Very common | Common |
| Febrile neutropenia* | Very common | Common | Not known |
| Leukopenia | Very common | Common | Common |
| **Cardiac disorders** | | | |
| Left ventricular dysfunction** | Common | Uncommon | Uncommon |
| Cardiac failure** | Common | Uncommon | Common |
| **Eye disorders** | | | |
| Lacrimation increased | Very common | Common | Uncommon |
| **Gastrointestinal disorders** | | | |
| Diarrhea | Very common | Very common | Very common |
| Nausea | Very common | Very common | Common |
| Vomiting | Very common | Very common | Common |
| Stomatitis | Very common | Very common | Common |
| Constipation | Very common | Very common | Common |
| Dyspepsia | Very common | Very common | Common |

| | N = 3 834^ | N = 243^^ | |
|---|---|---|---|
| | Pertuzumab+trastuzumab | Phesgo with chemotherapy | Phesgo monotherapy |
| Abdominal pain | Very common | Common | Common |
| **General disorders and administration site conditions** | | | |
| Fatigue | Very common | Very common | Common |
| Mucosal inflammation | Very common | Very common | Uncommon |
| Asthenia | Very common | Very common | Very common |
| Pyrexia | Very common | Common | Common |
| Edema peripheral | Very common | Common | Common |
| Injection site reaction°°° | Very common | Common | Very common |
| **Immune system disorders** | | | |
| Hypersensitivity*° | Common | Uncommon | Not known |
| Drug hypersensitivity*° | Common | Uncommon | Uncommon |
| Anaphylactic reaction*° | Uncommon | Not known | Not known |
| Cytokine release syndrome° | Rare | Not known | Not known |
| **Infections and infestations** | | | |
| Nasopharyngitis | Very common | Common | Common |
| Upper respiratory tract infection | Common | Common | Common |
| Paronychia | Common | Common | Common |
| **Metabolism and nutrition disorders** | | | |
| Decreased appetite | Very common | Very common | Common |
| Tumour lysis syndrome† | Rare | Not known | Not known |

| | N = 3 834^ | N = 243^^ | |
|---|---|---|---|
| | Pertuzumab+trastuzumab | Phesgo with chemotherapy | Phesgo monotherapy |
| **Musculoskeletal and connective tissue disorders** | | | |
| Arthralgia | Very common | Very common | Very common |
| Myalgia | Very common | Very common | Common |
| Pain in extremity | Very common | Common | Common |
| **Nervous system disorders** | | | |
| Dysgeusia | Very common | Very common | Common |
| Headache | Very common | Very common | Common |
| Peripheral sensory neuropathy | Very common | Very common | Common |
| Neuropathy peripheral | Very common | Very common | Common |
| Dizziness | Very common | Common | Common |
| Paraesthesia | Very common | Common | Common |
| **Psychiatric disorders** | | | |
| Insomnia | Very common | Very common | Common |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Epistaxis | Very common | Very common | Common |
| Cough | Very common | Very common | Common |
| Dyspnea | Very common | Common | Common |
| Interstitial lung disease°° | Uncommon | Not known | Not known |

| | N = 3 834^ | N = 243^^ | |
|---|---|---|---|
| | Pertuzumab+trastuzumab | Phesgo with chemotherapy | Phesgo monotherapy |
| **Skin and subcutaneous tissue disorders** | | | |
| Alopecia | Very common | Very common | Uncommon |
| Rash | Very common | Very common | Common |
| Dry skin | Very common | Very common | Common |
| Nail disorder | Very common | Common | Common |
| Pruritus | Very common | Common | Common |
| **Vascular disorders** | | | |
| Hot flush | Very common | Common | Very common |

^ Shows pooled data from the overall treatment period in CLEOPATRA (data cut off 11 February 2014; median number of cycles of pertuzumab was 24); and from the neoadjuvant treatment period in NEOSPHERE (median number of cycles of pertuzumab was 4, across all treatment arms) and TRYPHAENA (median number of cycles of pertuzumab was 3-6 across treatment arms); from the treatment period of APHINITY (median number of cycles of pertuzumab was 18) and from the overall treatment period of FEDERICA (median number of cycles of Phesgo was 18).

^^Shows Phesgo data from the overall treatment period of FEDERICA (median number of cycles of Phesgo was 18)

* Including ADRs with a fatal outcome have been reported.

** For the overall treatment period across the 5 studies (CLEOPATRA, NEOSPHERE, TRYPHAENA, APHINITY, FEDERICA). The incidence of left ventricular dysfunction and cardiac failure congestive reflect the MedDRA Preferred Terms reported in the individual studies.

° Terms that are the most frequently reported in the medical concepts of Anaphylactic reaction and Injection/Infusion-related Reaction which are further described in the Description of selected adverse reactions section.

°° No events of Interstitial lung disease were reported in the FeDeriCa study but these events have been observed with trastuzumab.

°°°Observed with Phesgo only (subcutaneous administration related). The higher frequency observed in the adjuvant phase is related to a longer period of treatment when Phesgo is administered as monotherapy.

† ADRs reported in the post marketing setting of pertuzumab and trastuzumab IV.

Description of selected adverse reactions

*Left ventricular dysfunction*

*Phesgo*

In the pivotal trial 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 (when concomitantly administered with chemotherapy). Of the patients who experienced symptomatic heart failure, none of the Phesgo-treated patients had recovered at the data cut-off and one patient was withdrawn from Phesgo due to an event of symptomatic heart failure. 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 (when Phesgo was administered alone) 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 (see sections 4.2 and 4.4). There was no report 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) in both arms in the adjuvant phase. In the follow up phase, 1.6 % of Phesgo treated patients and 3.6 % of intravenous pertuzumab and trastuzumab-treated patients had this type of cardiac event.

*Pertuzumab intravenous in combination with trastuzumab and chemotherapy*

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

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

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

In the neoadjuvant period of the BERENICE trial, the incidence of NYHA Class III/IV symptomatic LVD (congestive heart failure according to NCI-CTCAE v.4) was 1.5 % in the group treated with dose dense doxorubicin and cyclophosphamide (AC) followed by pertuzumab plus trastuzumab and paclitaxel and none of the patients (0 %) experienced symptomatic LVD in the group treated with FEC followed by pertuzumab in combination with trastuzumab and docetaxel. The incidence of asymptomatic LVD (ejection fraction decrease according to NCI-CTCAE v.4) was 7 % in the group treated with dose dense AC followed by pertuzumab plus trastuzumab and paclitaxel and 3.5 % in the group treated with FEC followed by pertuzumab plus trastuzumab and docetaxel.

In APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10 % points from baseline and to < 50 % was < 1 % (0.6 % of pertuzumab-treated patients vs 0.3 % of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 46.7 % of pertuzumab-treated patients and 57.1 % of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50 %) at the data cutoff. The majority of the events were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10 % points from baseline and to < 50 % were reported in 2.7 % of pertuzumab-treated patients and 2.8 % of placebo-treated patients, of whom 79.7 % of pertuzumab-treated patients and 80.6 % of placebo-treated patients had recovered at the data cutoff.

*Injection/infusion-related reactions*

*Phesgo*

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-related reactions were reported in 0.4 % of Phesgo treated patients and infusion related reactions were reported in 10.7 % of intravenous pertuzumab and trastuzumab-treated patients in the neoadjuvant phase. In the adjuvant phase, there were no injection-related reactions reported in Phesgo -treated patients, and infusion related reactions were reported in 1.6 % of intravenous pertuzumab and trastuzumab-treated patients. Most of the systemic injection/infusion related reactions seen with Phesgo or intravenous pertuzumab and trastuzumab were chills, nausea or vomiting.

Injection site reactions 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.

*Pertuzumab* intravenous *in combination with trastuzumab and chemotherapy*

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

During the second cycle when all medicinal products were administered on the same day, the most common infusion related reactions (≥ 1 %) in the pertuzumab-treated group were fatigue, drug hypersensitivity, dysgeusia, hypersensitivity, myalgia, and vomiting (see section 4.4).

In neoadjuvant and adjuvant trials, pertuzumab was administered on the same day as the other study treatment. Infusion-related reactions occurred in 18.6 %-25 % of patients on the first day of pertuzumab administration (in combination with trastuzumab and chemotherapy). The type and severity of events were consistent with those observed in CLEOPATRA, with a majority of reactions being mild or moderate in severity.

*Hypersensitivity reactions/anaphylaxis*

*Phesgo*

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 the neoadjuvant phase, 0.4 % of Phesgo treated patients and 0.4 % of intravenous pertuzumab and trastuzumab-treated patients had drug hypersensitivity. During the adjuvant phase, 0.4 % of Phesgo treated patients had drug hypersensitivity, and none of the intravenous pertuzumab and trastuzumab-treated patients had hypersensitivity or drug hypersensitivity.

*Pertuzumab intravenous in combination with trastuzumab and chemotherapy*

In the pivotal trial CLEOPATRA in metastatic breast cancer, the overall frequency of investigator reported hypersensitivity/anaphylaxis events during the entire treatment period was 9.3 % in the placebo-treated group and 11.3 % in the pertuzumab-treated group, of which 2.5 % and 2 % were NCI-CTCAE Grade 3-4, respectively. Overall, 2 patients in the placebo-treated group and 4 patients in the pertuzumab-treated group experienced events described as anaphylaxis by the investigator (see section 4.4).

Overall, the majority of hypersensitivity reactions were mild or moderate in severity and resolved upon treatment. Based on modifications made to the study treatment, most reactions were assessed as secondary to docetaxel infusions.

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

*Febrile neutropenia*

*Phesgo*

In the pivotal trial FEDERICA, febrile neutropenia (Grade 3 or 4) occurred in 6.6 % of Phesgo -treated patients and 5.6 % of intravenous pertuzumab and trastuzumab-treated patients during the neoadjuvant phase. No febrile neutropenia events (Grade 3 or 4) occurred during the adjuvant phase.
As in intravenous pertuzumab and trastuzumab pivotal trials, a higher incidence of febrile neutropenia (Grade 3 or 4) was observed among intravenous pertuzumab and trastuzumab -treated Asian patients (13 %), similarly, the incidence of febrile neutropenia in Phesgo-treated Asian patients was also higher (13.7 %) during the neoadjuvant phase. During the adjuvant phase, no events of febrile neutropenia (Grade 3 or 4) were observed in either arm.

*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 % 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 % 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 the pivotal trial FEDERICA during the neoadjuvant phase, diarrhoea occurred in 60.5 % of Phesgo-treated patients and 54.8 % of intravenous pertuzumab and trastuzumab-treated patients. Grade ≥ 3 diarrhoea was reported in 6.6 % of patients in the Phesgo arm vs. 4 % in the intravenous pertuzumab and trastuzumab arm (see section 4.4).

During the adjuvant phase, diarrhoea occurred in 17.7 % of Phesgo-treated patients and 20.6 % of intravenous pertuzumab and trastuzumab-treated patients. Grade ≥ 3 diarrhoea was reported in 0 % of patients in the Phesgo arm vs. 1.2 % in the intravenous pertuzumab and trastuzumab arm.

*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 the pivotal trial FEDERICA rash occurred in 10.7 % of Phesgo-treated patients and 15.5 % of intravenous pertuzumab and trastuzumab-treated patients during the neoadjuvant phase. During the adjuvant phase, rash occurred in 8.2 % of Phesgo-treated patients and 8.7 % 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 % 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 % 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 the pivotal trial FEDERICA, the incidence of NCI-CTCAE v.4 Grade 3-4 neutropenia was balanced in the two treatment groups (13.6 % of Phesgo -treated patients and 13.9 % of intravenous pertuzumab and trastuzumab-treated patients) during the neoadjuvant phase and were significantly lower during the adjuvant phase (0.8% of Phesgo -treated patients and 0 % of intravenous pertuzumab and trastuzumab-treated patients).

*Pertuzumab intravenous in combination with trastuzumab and chemotherapy*

In the pivotal trial CLEOPATRA in metastatic breast cancer, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was balanced in the two treatment groups (86.3 % of pertuzumab-treated patients and 86.6 % of placebo-treated patients, including 60.7 % and 64.8 % Grade 4 neutropenia, respectively).

In the NEOSPHERE trial, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 74.5 % in patients treated with neoadjuvant pertuzumab, trastuzumab and docetaxel compared with 84.5 % in patients treated with trastuzumab and docetaxel, including 50.9 % and 60.2 % Grade 4 neutropenia, respectively. In the TRYPHAENA trial, the incidence of NCI-CTCAE v.3 Grade 3-4 neutropenia was 85.3 % in patients treated with neoadjuvant pertuzumab+ TCH and 77 % in patients treated with neoadjuvant pertuzumab, trastuzumab and docetaxel following FEC, including 66.7 % and 59.5 % Grade 4 neutropenia, respectively.

In the APHINITY trial, the incidence of NCI-CTCAE v.4 Grade 3-4 neutropenia was 40.6 % in patients treated with pertuzumab, trastuzumab and chemotherapy compared with 39.1 % in patients treated with placebo, trastuzumab and chemotherapy, including 28.3 % and 26.5 % Grade 4 neutropenia, respectively.

*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, neutralizing 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, neutralizing anti-pertuzumab antibodies were detected in two patients, and neutralizing 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.

*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= 2 926).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

The highest Phesgo dose tested is 1 200 mg pertuzumab/600 mg trastuzumab. In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

Mechanism of action

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

Pertuzumab and trastuzumab are recombinant humanised IgG1 monoclonal antibodies which target the human epidermal growth factor receptor 2 (HER2). Both substances bind to distinct HER2 subdomains without competing and have complementary mechanisms for disrupting HER2 signalling:

- 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 efficacy and safety

This section is presenting the clinical experience from Phesgo fixed dose combination of pertuzumab and trastuzumab and from intravenous pertuzumab in combination with trastuzumab in 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 in the trial outlined below.

*FEDERICA (WO40324)*

FEDERICA was an open-label, multicenter, randomized study conducted in 500 patients with HER2-positive early breast cancer that was operable or locally advanced (including inflammatory) with a tumour size > 2 cm or node-positive in the neoadjuvant and adjuvant settings. Patients were randomized 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 the two following neoadjuvant chemotherapy 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 adjuvant period, substitution of intravenous trastuzumab for subcutaneous trastuzumab was permitted at investigator discretion. HER2-targeted therapy was administered every 3 weeks according to Table 3 as follows:

**Table 3: Dosing and administration of Phesgo, intravenous pertuzumab, intravenous trastuzumab, and subcutaneous trastuzumab**

| Medicinal products | Administration | Dose | |
|---|---|---|---|
| | | Loading | Maintenance |
| Phesgo | Subcutaneous injection | 1 200 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 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 %).

For non-inferiority of the pertuzumab and trastuzumab exposures 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 4. Results from the final analysis of iDFS and OS with clinical cut-off date of 2 June 2023 and a median follow up of 51 months is also shown in Table 4.

**Table 4: Summary of efficacy**

| | Phesgo (n= 248) | Intravenous pertuzumab + trastuzumab (n= 252) |
|---|---|---|
| **Total pathological complete response (tpCR)** | | |
| n | 248 | 252 |
| **tpCR (ypT0/is, ypN0)** | 148 (59.7 %) | 150 (59.5 %) |
| 95 % CI [1] | (53.28; 65.84) | (53.18; 65.64) |
| **Invasive disease free survival (iDFS)** | | |
| n | 234 | 239 |
| Patients with event (%) | 26 (11.1 %) | 23 (9.6 %) |
| Unstratified Hazard Ratio (95% CI) | 1.13 (0.64, 1.97) | |
| **Overall survival (OS)** | | |
| n | 248 | 252 |
| Patients with event (%) | 14 (5.6 %) | 12 (4.8 %) |
| Hazard ratio[2] (95% CI) | 1.26 (0.58, 2.72) | |

[1] Confidence interval for one sample binomial using Pearson-Clopper method
[2] Analysis stratified by central hormone receptor status, clinical stage and type of chemotherapy

*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 randomized to Arm A (3 cycles of intravenous pertuzumab and trastuzumab followed by 3 cycles of Phesgo) and 80 patients were randomized 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 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 phase II, multicentre, multinational randomised controlled trial with pertuzumab and was conducted in 417 adult female 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 the following neoadjuvant regimens for 4 cycles prior to surgery:

- 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 oestrogen receptor (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 tumours only), DFS, and progression-free survival (PFS). Additional exploratory pCR rates included nodal status (ypT0/isN0 and ypT0N0).

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

The efficacy results are presented in Table 5. A statistically significant 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 %, 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 II clinical trial conducted in 225 adult female patients with HER2-positive locally advanced, operable, or inflammatory 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 three neoadjuvant regimens prior to surgery as follows:

- 3 cycles of FEC followed by 3 cycles of docetaxel, all given concurrently with pertuzumab and trastuzumab
- 3 cycles of FEC alone followed by 3 cycles of docetaxel, with trastuzumab and pertuzumab given concurrently
- 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$^2$]) were given intravenously every three weeks for 3 cycles. Docetaxel was given as an initial dose of 75 mg/m$^2$ intravenous 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$^2$ (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. 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, 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. 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, high pCR rates were observed in all 3 treatment arms (see Table 5). A consistent pattern of results was observed regardless of pCR definition used. The pCR rates were lower in the subgroup of patients with hormone receptor-positive tumours (range 46.2 % to 50 %) than in patients with hormone receptor-negative tumours (range 65 % to 83.8 %).

pCR rates were similar in patients with operable and locally advanced disease. There were too few patients with inflammatory breast cancer to draw any firm conclusions.

**Table 5 NEOSPHERE (WO20697) and TRYPHAENA (BO22280): Overview of efficacy (Intent to treat population)**

| | NEOSPHERE (WO20697) | | | | TRYPHAENA (BO22280) | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Trastuzumab +docetaxel N= 107** | **Pertuzumab+ trastuzumab+ docetaxel N= 107** | **Pertuzumab+ trastuzumab N= 107** | **Pertuzumab +docetaxel N= 96** | **Pertuzumab+ trastuzumab+ FEC→ pertuzumab+ trastuzumab+ docetaxel N= 73** | **FEC→ Pertuzumab + trastuzumab+ docetaxel N= 75** | **Pertuzumab +TCH N= 77** |
| pCR rate in the breast (ypT0/is) n (%) [95 % CI][1] | 31 (29 %) [20.6; 38.5] | 49 (45.8 %) [36.1; 55.7] | 18 (16.8 %) [10.3; 25.3] | 23 (24 %) [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. trastuzumab +docetaxel) | 0.0198 (vs. trastuzumab +docetaxel) | 0.0030 (vs. pertuzumab+ trastuzumab+ docetaxel) | NA | NA | NA |
| pCR rate in the breast and lymph node (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; 42.5] | 6 (5.6 %) [2.1; 11.8] | 13 (13.2 %) [7.4; 22] | 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 %) |

FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin and trastuzumab, CMH: Cochran–Mantel–Haenszel

1. 95% CI for one sample binomial using Pearson-Clopper method.

2. Treatment pertuzumab+trastuzumab+docetaxel and pertuzumab+trastuzumab are compared to Trastuzumab+ Docetaxel while pertuzumab+docetaxel is compared to pertuzumab+trastuzumab+docetaxel.

3. Approximate 95 % CI for difference of two response 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-randomized, 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 is 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 sections 4.4. and 4.8).

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) every 3 weeks 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 a 19 % (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 6 and in Figure 1.

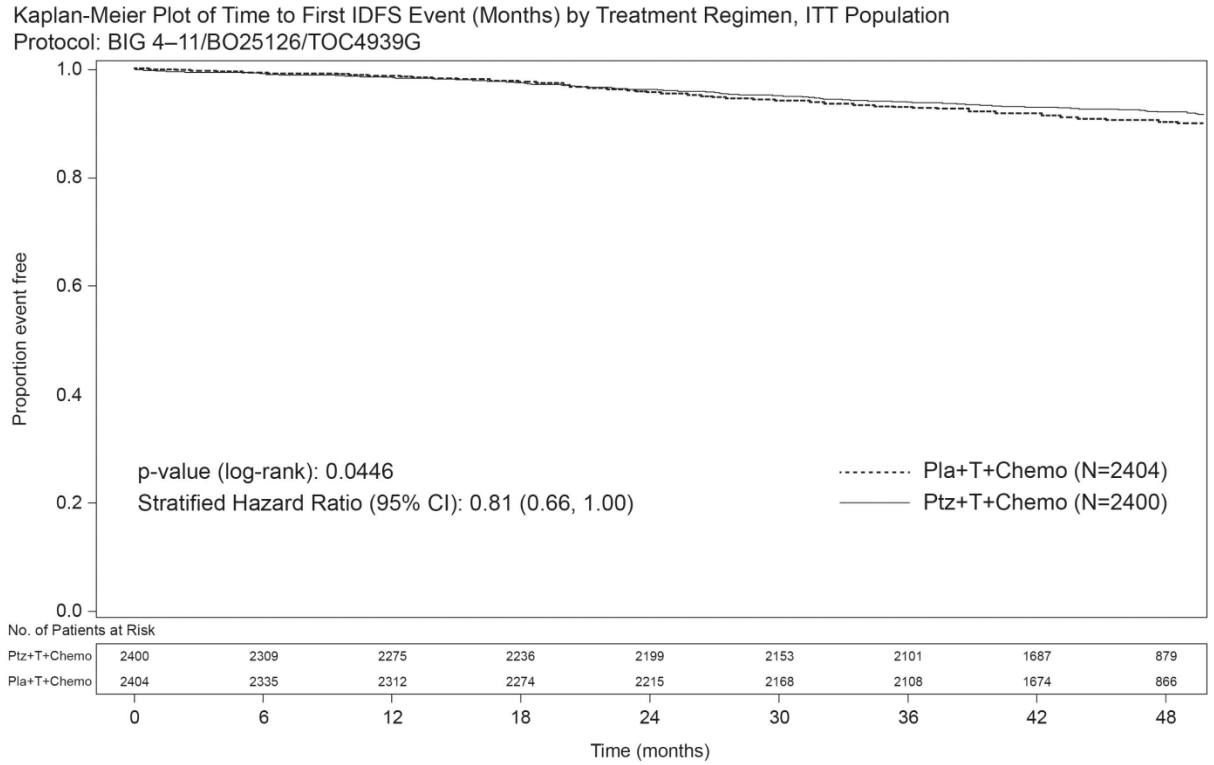
**Table 6 Overall efficacy: Intent to treat population**

| | **Pertuzumab + trastuzumab + chemotherapy N= 2 400** | **Placebo + trastuzumab + chemotherapy N= 2 404** |
|---|---|---|
| ***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[1]) | 0.0446 | |
| 3 year event-free rate[2] [95 % CI] | 94.1 [93.1; 95] | 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[1]) | 0.0430 | |
| 3 year event-free rate[2] [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 %) | 236 (9.8 %) |
| HR [95 % CI] | 0.81 [0.67; 0.98] | |
| p-value (Log-Rank test, stratified[1]) | 0.0327 | |
| 3 year event-free rate[2] [95 % CI] | 93.4 [92.4; 94.4] | 92.3 [91.2; 93.4] |
| **Overall survival (OS)[3]** | | |
| Number (%) of patients with event | 80 (3.3 %) | 89 (3.7 %) |
| HR [95 % CI] | 0.89 [0.66; 1.21] | |
| p-value (Log-Rank test, stratified[1]) | 0.4673 | |
| 3 year event-free rate[2] [95 % CI] | 97.7 [97; 98.3] | 97.7 [97.1; 98.3] |

**Key to abbreviations (Table 6):** HR: Hazard Ratio; CI: Confidence Interval

1. All analyses stratified by nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen.
2. 3-year event-free rate derived from Kaplan-Meier estimates.
3. Data from first interim analysis.

**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 7).

**Table 7 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 | 139/1 503 (9.2 %) | 181/1 502 (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 | 100/1 536 (6.5 %) | 119/1 546 (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 % versus 90.2 % at 3 years and 89.9 % vs. 86.7 % at 4 years in pertuzumab-treated patients versus 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 % versus 88.7 % at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively. In the hormone receptor-positive subgroup estimates of IDFS rates were 94.8 % versus 94.4 % at 3 years and 93 % 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) 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; 23.6) in the pertuzumab arm versus + 9.2 (95 % 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) 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 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 OS, PFS (investigator-assessed), objective response rate (ORR), duration of response, and time to symptom progression according to the FACT B Quality of Life questionnaire.

Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as ER-positive and/or PgR-positive) and approximately half of the patients in each treatment group had received prior adjuvant or neoadjuvant 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 % (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.

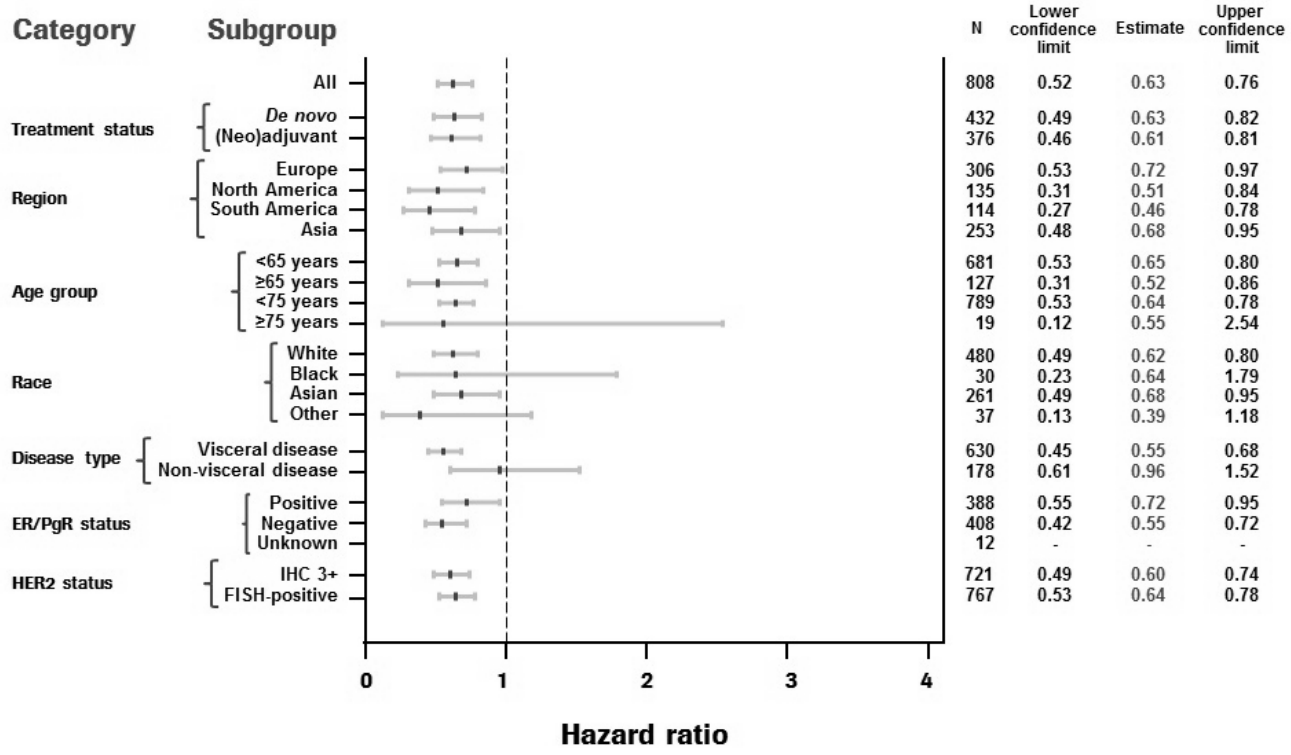
**Table 8 Summary of efficacy from CLEOPATRA study**

| **Parameter** | **Placebo+ trastuzumab + docetaxel n= 406** | **Pertuzumab + trastuzumab + docetaxel n= 402** | **HR (95 % CI)** | **p-value** |
|---|---|---|---|---|
| **Progression-free furvival (independent review) - primary endpoint*** | | | | |
| no. of patients with an event | 242 (59 %) | 191 (47.5 %) | 0.62 | < 0.0001 |
| Median months | 12.4 | 18.5 | [0.51; 0.75] | |
| **Overall survival - secondary endpoint**** | | | | |
| 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] | |
| **Objective response rate (ORR)^ - secondary endpoint** | | | | |
| no. of patients with measurable disease | 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] | | |

* Primary progression-free survival analysis, cutoff date 13th May 2011.
** Event-driven final overall survival, cutoff date 11th February 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).

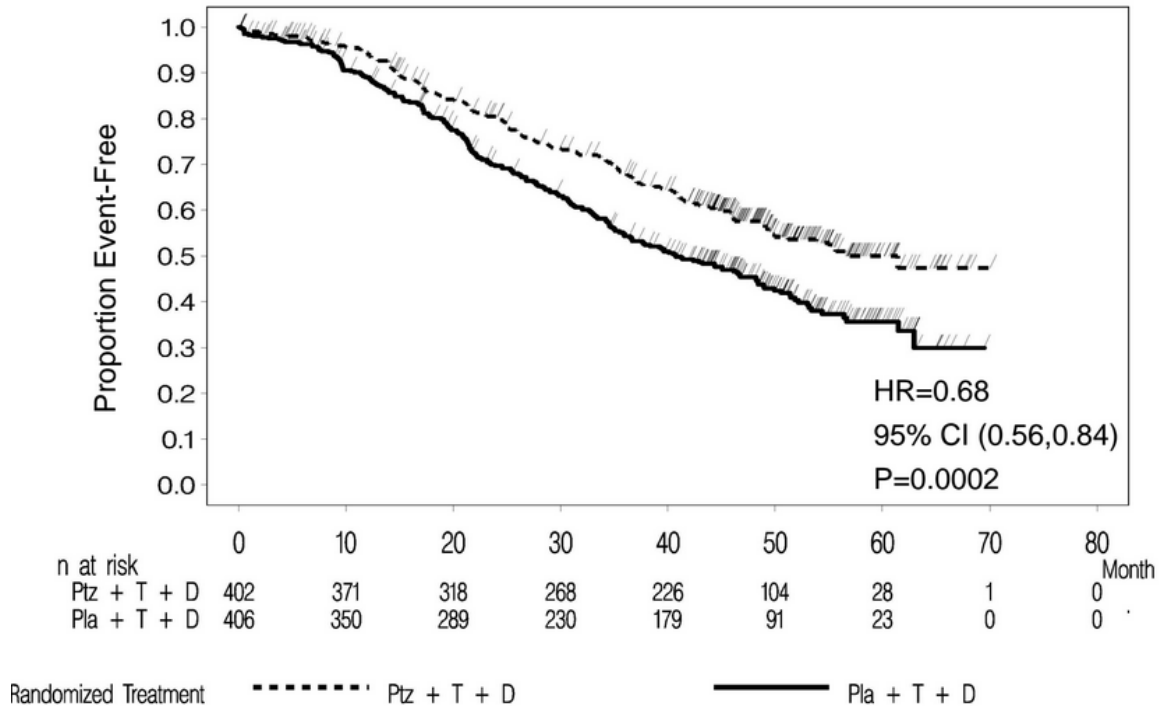
**Figure 2 IRF-assessed PFS by patient subgroup**




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 event-driven overall survival**




HR= hazard ratio; CI= confidence interval; Pla= placebo; Ptz= pertuzumab ; T= trastuzumab; D= docetaxel.

No statistically significant differences were found between the two treatment groups in Health Related Quality of Life as assessed by FACT-B TOI-PFB scores.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Phesgo in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

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 mcg/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 mcg/mL) compared to intravenous trastuzumab (geometric mean 43.2 mcg/mL) with a geometric mean ratio of 1.33 (90 % CI: 1.24-1.43).

Absorption

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

The median $C_{max}$ of trastuzumab within Phesgo and $T_{max}$ were 114 mcg/mL and 3.84 days, respectively. Based on population PK analysis, the absolute bioavailability was 0.771 and the Ka is 0.404 (1/day).

Distribution

Based on population PK analysis, the volume of distribution of the central ($V_c$) compartment of pertuzumab within Phesgo in the typical patient, was 2.77 litres.

Based on population PK analysis, the $V_c$ compartment of subcutaneous trastuzumab in the typical patient was 2.91 litres.

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 clearance of trastuzumab within Phesgo was 0.111 L/day. Trastuzumab is estimated to reach concentrations that are < 1 mcg/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.

Elderly

No studies have been conducted to investigate the pharmacokinetics of Phesgo in elderly 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 studies have been conducted to investigate the pharmacokinetics of Phesgo 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 pharmacokinetic analyses.

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

Hepatic impairment

No formal PK study 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.

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.

A study conducted in lactating Cynomolgus monkeys administered intravenous trastuzumab doses up to 16 times that of the human maintenance dose of 600 mg trastuzumab in the Phesgo formulation demonstrated that trastuzumab is secreted in the milk post-partum. The exposure to trastuzumab in

utero and the presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age.

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 embryofetal 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Vorhyaluronidase alfa
L-histidine
L-histidine hydrochloride monohydrate
α,α-trehalose dihydrate
Sucrose
L-methionine
Polysorbate 20 (E432)
Water for injections

### 6.2 Incompatibilities

Phesgo is a ready to use solution which should not be mixed or diluted with other products.

### 6.3 Shelf life

18 months.

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 and for 24 hours (cumulative time in the vial and the syringe) at ambient temperature (maximum 30 °C) in diffused daylight.

As Phesgo does not contain any antimicrobial-preservative, from a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless preparation of the syringe has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the opened medicinal product, see sections 6.3 and 6.6.

## 6.5 Nature and contents of container

Phesgo 600 mg/600 mg solution for injection

Pack of one 15 mL type I borosilicate glass vial tapered with fluororesin-laminated rubber stopper, containing 10 mL solution of 600 mg of pertuzumab and 600 mg of trastuzumab.
The stopper is sealed with aluminium and covered by an orange plastic flip-off cap.

Phesgo 1 200 mg/600 mg solution for injection

Pack of one 20 mL type I borosilicate glass vial tapered with fluororesin-laminated rubber stopper, containing 15 mL solution of 1 200 mg of pertuzumab and 600 mg of trastuzumab.
The stopper is sealed with aluminum and covered by a cool green plastic flip-off cap.

## 6.6 Special precautions for disposal and other handling

Phesgo should be inspected visually to ensure there is no particulate matter or discolouration prior to the administration. If particulate matter or discoloration is observed the vial should be discarded per local disposal guidelines.

Do not shake the vial.

A syringe, a transfer needle and an injection needle are needed to withdraw Phesgo solution from the vial and inject it subcutaneously. Phesgo may be injected using hypodermic injection needles with gauges between 25G-27G and lengths between 3/8"(10 mm)-5/8"(16 mm). Phesgo is compatible with stainless steel, polypropylene, polycarbonate, polyethylene, polyurethane, polyvinyl chloride and fluorinated ethylene polypropylene.

As Phesgo does not contain any antimicrobial-preservative, from a microbiological point of view, the medicinal product should be used immediately. If not used immediately, preparation should take place in a controlled and validated aseptic conditions. 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 syringe 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 15 mL if Phesgo 1 200 mg/600 mg is used or 10 mL if Phesgo 600 mg/600 mg is used.

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

# 7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

# 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1497/001 (1 200 mg/600 mg)
EU/1/20/1497/002 (600 mg/600 mg)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 2020
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

# ANNEX II

**A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances

*Pertuzumab*

Genentech, Inc.
1 Antibody Way
Oceanside, CA 92056-5701
USA

*Trastuzumab*

Roche Diagnostics GmbH
Nonnenwald 2
82377 Penzberg
Germany

Roche Singapore Technical Operations Pte. Ltd.
10 Tuas Bay Link
637394 Singapore
Singapore

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Phesgo 600 mg/600 mg solution for injection
pertuzumab/trastuzumab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 600 mg of pertuzumab and 600 mg of trastuzumab in 10 mL solution.

## 3. LIST OF EXCIPIENTS

Vorhyaluronidase alfa
L-histidine
L-histidine hydrochloride monohydrate
α,α-trehalose dihydrate
sucrose
polysorbate 20
L-Methionine
water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
600 mg/600 mg in 10 mL
1 vial

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use only
Do not shake
Read the package leaflet before use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1497/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Phesgo 600 mg/600 mg solution for injection

pertuzumab/trastuzumab

For subcutaneous use only

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

600 mg/600 mg in 10 mL

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Phesgo 1 200 mg/600 mg solution for injection

pertuzumab/trastuzumab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 1 200 mg of pertuzumab and 600 mg of trastuzumab in 15 mL solution.

## 3. LIST OF EXCIPIENTS

Vorhyaluronidase alfa
L-histidine
L-histidine hydrochloride monohydrate
α,α-trehalose dihydrate
sucrose
polysorbate 20
L-Methionine
water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 200 mg/600 mg in 15 mL
1 vial

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use only
Do not shake
Read the package leaflet before use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Keep the vial in the outer carton in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1497/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**
**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Phesgo 1 200 mg/600 mg solution for injection
pertuzumab/trastuzumab
For subcutaneous use only

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 200 mg/600 mg in 15 mL

## 6. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Phesgo 600 mg/600 mg solution for injection**
**Phesgo 1 200 mg/600 mg solution for injection**
pertuzumab/trastuzumab

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Phesgo is and what it is used for

Phesgo is a cancer medicine that contains two active substances: pertuzumab and trastuzumab.
- Pertuzumab and trastuzumab are 'monoclonal antibodies'. They are designed to attach to a specific target on cells called "human epidermal growth factor receptor 2" (HER2).
- HER2 is found in large amounts on the surface of some cancer cells and stimulates their growth.
- By attaching to HER2 on cancer cells, pertuzumab and trastuzumab slow down their growth, or kill them.

Phesgo is available in two different strengths. See section 6 for more information.

Phesgo is used to treat adult patients with breast cancer that is of the "HER2-positive" type – your doctor will test you for this. It can be used when:
- the cancer has spread to other parts of the body such as the lungs or liver (metastasised), or the cancer has come back in the breast and the area around breast, but cannot be operated, and no treatment with cancer medicines (chemotherapy) or other medicines designed to attach to HER2 has been given.
- the cancer has not spread to other parts of the body, and treatment is going to be given either before surgery (neoadjuvant therapy) or after surgery (adjuvant therapy).

As part of your treatment with Phesgo you will also receive other medicines called chemotherapy. Information about these medicines is described in separate package leaflets. Ask your doctor, pharmacist or nurse to give you information about these other medicines.

## 2. What you need to know before you are given Phesgo

**You must not be given Phesgo**

- if you are allergic to pertuzumab, trastuzumab, or to any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor, pharmacist or nurse before you are given Phesgo

**Warnings and precautions**

Heart problems

Treatment with Phesgo may affect the heart. Talk to your doctor, pharmacist or nurse before you are given Phesgo if:

- you have ever had heart problems (such as heart failure, treatment for serious irregular heart beats, uncontrolled high blood pressure, recent heart attack).Your doctor will run tests to check if your heart is working properly before and during treatment with Phesgo.
- you have ever had heart problems during previous treatment with a medicine containing trastuzumab.
- you have ever had a chemotherapy medicine from the class of cancer medicines called anthracyclines, e.g. doxorubicin or epirubicin – these medicines can damage heart muscle and increase the risk of heart problems with Phesgo.
- you have ever had a radiotherapy to the chest area, as it can increase the risk of heart problems.

If any of the above applies to you (or you are not sure), talk to your doctor or nurse before you are given Phesgo. See section 4 “Serious side effects” for more details about signs of heart problems to look out for.

Injection reactions

A reaction to the injection can happen. These are allergic reactions and can be severe.

If you get any serious reaction, your doctor may stop treatment with Phesgo. See section 4 ‘‘Serious side effects’’ for more details about injection related reactions to look out for during the injection and thereafter.

Your doctor or nurse will check for side effects during your injection and for:

- 30 minutes after the first injection of Phesgo.
- 15 minutes after subsequent injection of Phesgo.

If you get any serious reaction, your doctor may stop treatment with Phesgo.

Low levels of white blood cells and fever (Febrile neutropenia)

When Phesgo is given with chemotherapy medicines, the number of white blood cells may drop and fever may develop. If you have inflammation of the digestive tract (e.g. sore mouth or diarrhoea) you may be more likely to develop this side effect. If the fever persists for several days, this may be a sign of worsening of your condition and you should contact your physician.

Diarrhoea

Treatment with Phesgo may cause severe diarrhoea. Patients over 65 years of age have a higher risk of diarrhoea compared with patients younger than 65 years of age. If you get severe diarrhoea during your cancer treatment, your doctor may give you medicines to control diarrhoea. Your doctor may also stop your treatment with Phesgo until the diarrhoea is under control.

**Children and adolescents**

Phesgo should not be given to patients under the age of 18 years because there is no information on how it works in this age group.

**Elderly patients over 65**

Patients over 65 years of age are more likely to get side effects such as reduced appetite, decrease in the number of red blood cells, weight loss, tiredness, loss or altered taste, weakness, numbness, tingling or prickling sensations mainly affecting the feet and legs and diarrhoea, compared to patients younger than 65 years of age.

**Other medicines and Phesgo**

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

**Pregnancy, breast-feeding and contraception**

Before starting treatment, you must tell your doctor, pharmacist or nurse if you are pregnant or breast-feeding, or if you think you may be pregnant or are planning to have a baby. They will discuss with you the benefits and risks for you and your baby of taking Phesgo while you are pregnant.

- Tell your doctor straight away, if you get pregnant during treatment with Phesgo or during the 7 months after stopping treatment. Phesgo may harm the unborn baby. You should use effective contraception during treatment with Phesgo and for 7 months after stopping treatment.
- Ask your doctor about whether you can breast-feed during or after treatment with Phesgo.

**Driving and using machines**

Phesgo may affect your ability to drive or operate machines. If during treatment you experience symptoms, such as feeling dizzy, chills, fever or any injection or allergic reactions as described in section 4, you should not drive or use machines until these symptoms disappear.

**Phesgo contains sodium**

Phesgo contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium-free.

**Phesgo contains polysorbate 20 (E 432)**

Phesgo contains polysorbate 20. Each vial of 15 mL solution contains 6 mg of polysorbate 20. Each vial of 10mL solution contains 4 mg of polysorbate 20. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

## 3. How you are given Phesgo

Phesgo will be given to you by a doctor or nurse as an injection under your skin (subcutaneous injection). The treatment will begin in a hospital or clinic. If you tolerate the treatment, your doctor may decide whether you receive Phesgo outside of the hospital or clinic, for example at your home.

- Injections will be given every three weeks.
- You will get the injection first in one thigh and then in the other. You will keep getting the injection in one thigh then the other.
- Your doctor or nurse will make sure that each injection is given in a new place (at least 2.5 cm away from any previous place of injection), and where the skin is not red, bruised, tender or hard.
- Different places for injection should be used for other medicines.

**Start of the treatment (loading dose)**

- Phesgo 1 200 mg/600 mg will be given under your skin over 8 minutes. Your doctor or nurse will check for side effects during your injection and for 30 minutes afterwards.
- You will also be given chemotherapy

**Subsequent injections (maintenance doses),** which will be given if the first injection have not caused severe side effects:

- Phesgo 600 mg/600 mg will be given under your skin over 5 minutes. Your doctor or nurse will check for side effects during your injection and for 15 minutes afterwards.
- You will also be given chemotherapy, depending on the doctor's prescription.
- The number of injections you will be given depends on:
  - how you respond to treatment
  - whether you are having treatment before surgery or after surgery or for disease which has spread.

For further information on loading and maintenance dose see section 6.
For further information on dosing of chemotherapy (which can cause side effects as well), please read the package leaflet for these medicines. If you have questions about them, please ask your doctor, pharmacist or nurse.

**Administration outside the clinical setting**

Information for healthcare professionals on how to prepare and administer Phesgo is provided at the end of this leaflet.

**If you forget to have Phesgo**

If you miss your appointment to have Phesgo, make another appointment as soon as possible. Depending on how much time passed between the two visits, your doctor will decide which strength of Phesgo to give you.

**If you stop having Phesgo**

Do not stop your treatment with this medicine without talking to your doctor first. It is important that you are given the full course of injections at the right time every three weeks. This helps your medicine work as well as it can.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**

**Tell a doctor or nurse straight away, if you notice any of the following side effects:**

- **Heart problems:** a slower or faster heart beat than usual or fluttering of the heart and symptoms that can include cough, shortness of breath, and swelling (fluid retention) in your legs or arms.
- **Injection related reactions:** these may be mild or more severe and may include feeling sick, fever, chills, feeling tired, headache, loss of appetite, joint and muscle pains, and hot flushes.
- **Diarrhoea:** these may be mild or moderate but can be very severe or long-lasting diarrhoea, passing 7 or more watery stools in a day.
- **Low number of white blood cells** as shown in a blood test. This may or may not be with a fever.
- **Allergic reactions:** swelling of your face and throat, with difficulty in breathing, this may be a sign of a serious allergic reaction.

Tell a doctor or nurse straight away, if you notice any of the side effects above.

**Other side effects**

**Very common (may affect more than 1 in 10 people):**

- Hair loss
- Rash
- Inflammation of your digestive tract (e.g. sore mouth)
- Decrease in the number of red and white blood cells as shown in a blood test
- Muscle weakness
- Constipation
- Loss of taste, or a change in the way things taste
- Not being able to sleep
- Weak, numb, tingling or prickling sensations mainly affecting the feet, legs and hands
- Nose bleeds
- Heartburn
- Dry, itchy or acne like skin
- Pain at the injection site, reddened skin (erythema) and bruising at the injection site
- Nail problems, such as discoloration like white or dark streaks or change in nail color
- Sore throat, red, sore or runny nose, flu-like symptoms and fever which may lead to infection of the ear, nose or throat
- Producing more tears
- Pain in the body, arms, legs, and belly
- Sharp jabbing, throbbing, freezing or burning pain
- Feeling pain from something which should not be painful, such as a light touch
- Loss of balance or coordination

**Common (may affect up to 1 in 10 people):**

- Difficulty in breathing
- Reduced ability to feel changes in temperature
- Inflammation of the nail bed where the nail and skin meet
- Condition in which the left part of the heart is not working properly with or without symptoms
- Condition in which the heart muscle becomes weak which may translate to difficulty in breathing
- Allergic reaction causing range of symptoms from mild to severe such as fever, chills, headache, and difficulties in breathing.

**Uncommon (may affect up to 1 in 100 people):**

- Chest symptoms such as a dry cough or breathlessness (possible signs of ‘interstitial lung disease’, a condition of damage to the tissues around the air sacs in the lungs)
- Fluid around the lungs causing difficulty in breathing

Rare side effects such as Tumour Lysis Syndrome (where cancer cells die quickly have been seen with intravenous pertuzumab but not with Phesgo. Symptoms of Tumour Lysis Syndrome may include: kidney problems - (signs include weakness, shortness of breath, fatigue and confusion), heart problems (signs include fluttering of the heart or a faster or slower heart beat, seizures (fits), vomiting or diarrhoea and tingling in the mouth, hands or feet).

If you get any of the side effects above, talk to your doctor, nurse or pharmacist.

If you get any of the above after treatment with Phesgo has been stopped, you should get in touch with your doctor immediately and say that you have previously been treated with Phesgo.

Some of the side effects which you get may be due to your breast cancer. If you are given Phesgo with chemotherapy at the same time, some side effects may also be due to these other medicines.

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Phesgo

Phesgo will be stored by the health professionals at the hospital or clinic. The storage details are as follows:

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton and the vial after 'EXP'. The expiry date refers to the last day of that month.
- Store in a refrigerator (2 °C-8 °C).
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Once the vial is open, use the solution immediately. Do not use this medicine if you notice any particles in the liquid or it is the wrong colour (see section 6).
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Phesgo contains**

The active substances are pertuzumab and trastuzumab.

- One vial of 10 mL solution contains 600 mg of pertuzumab and 600 mg of trastuzumab. Each mL contains 60 mg of pertuzumab and 60 mg of trastuzumab.
- One vial of 15 mL solution contains 1 200 mg of pertuzumab and 600 mg of trastuzumab. Each mL contains 80 mg of pertuzumab and 40 mg of trastuzumab**.**

The other ingredients are vorhyaluronidase alfa, L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, sucrose, L-methionine, polysorbate 20 and water for injections (see section 2 "Phesgo contains sodium", "Phesgo contains polysorbate").

**What Phesgo looks like and contents of the pack**

Phesgo is a solution for injection. It is a clear to opalescent solution, colourless to slightly brown supplied in a glass vial. Each pack contains one vial with either 10 mL or 15 mL solution.

**Marketing Authorisation Holder**

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

**Manufacturer**

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien,**
**Luxembourg/Luxemburg**
N.V. Roche S.A.
België/Belgique/Belgien
Tél/Tel: +32 (0) 2 525 82 11

**България**
Рош България ЕООД
Тел: +359 2 474 5444

**Česká republika**
Roche s. r. o.
Tel: +420 – 2 20382111

**Danmark**
Roche Pharmaceuticals A/S
Tlf: +45 - 36 39 99 99

**Deutschland**
Roche Pharma AG
Tel: +49 (0) 7624 140

**Eesti**
Roche Eesti OÜ
Tel: + 372 - 6 177 380

**Ελλάδα, Κύπρος**
Roche (Hellas) A.E.
Ελλάδα
Τηλ: +30 210 61 66 100

**España**
Roche Farma S.A.
Tel: +34 - 91 324 81 00

**France**
Roche
Tél: +33 (0) 1 47 61 40 00

**Hrvatska**
Roche d.o.o.
Tel: +385 1 4722 333

**Ireland, Malta**
Roche Products (Ireland) Ltd.
Ireland/L-Irlanda
Tel: +353 (0) 1 469 0700

**Lietuva**
UAB “Roche Lietuva”
Tel: +370 5 2546799

**Magyarország**
Roche (Magyarország) Kft.
Tel: +36 - 1 279 4500

**Nederland**
Roche Nederland B.V.
Tel: +31 (0) 348 438050

**Norge**
Roche Norge AS
Tlf: +47 - 22 78 90 00

**Österreich**
Roche Austria GmbH
Tel: +43 (0) 1 27739

**Polska**
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

**Portugal**
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

**România**
Roche România S.R.L.
Tel: +40 21 206 47 01

**Slovenija**
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

**Ísland**
Roche Pharmaceuticals A/S
c/o Icepharma hf
Sími: +354 540 8000

**Italia**
Roche S.p.A.
Tel: +39 - 039 2471

**Latvija**
Roche Latvija SIA
Tel: +371 - 6 7039831

**Slovenská republika**
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

**Suomi/Finland**
Roche Oy
Puh/Tel: +358 (0) 10 554 500

**Sverige**
Roche AB
Tel: +46 (0) 8 726 1200

**This leaflet was last revised in** <{**month YYYY**}>.

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

.

---

The following information is intended for healthcare professionals only:

**Administration of Phesgo 600/600mg solution for injection outside of the clinical setting.**

Any healthcare professional treating patients outside of the clinical setting should be well informed on both the administration method, and the potential risks associated with Phesgo.

Healthcare professional should ensure that appropriate medications for the management of hypersensitivity reactions in line with local standard clinical practice (depending on severity and type of reaction e.g. epinephrine, beta-agonists, antihistamines and corticosteroids) are available with them for immediate use.
Phesgo should be stored at 2 °C-8 °C in the original carton until time of use.

**Instructions for use**

Phesgo should be administered as a subcutaneous injection only. Phesgo is not intended for intravenous administration.

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 600/600 mg (15mL vial, containing 10mL solution).

Phesgo should be inspected visually to ensure there is no particulate matter or discolouration prior to the administration. If particulate matter or discoloration is observed, the vial should be discarded per local disposal guidelines. Do not shake the vial.
Before use, leave the Phesgo vial at room temperature for about 15 minutes before preparing an injection.

A syringe, a transfer needle and an injection needle are needed to withdraw Phesgo solution from the vial and inject it subcutaneously. Phesgo may be injected using hypodermic injection needles with gauges between 25G-27G and lengths between 3/8"(10 mm)-5/8"(16 mm). Phesgo is compatible with stainless steel, polypropylene, polycarbonate, polyethylene, polyurethane, polyvinyl chloride and fluorinated ethylene polypropylene.

As Phesgo does not contain any antimicrobial-preservative, the medicinal product should be used immediately. The hypodermic injection needle must be attached to the syringe immediately prior to administration followed by volume adjustment to 10 mL.
The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. The dose should not be split between two syringes or between two sites of administration.

The dose should be administered over a period of 5 minutes. The injection may be slowed or paused if the patient experiences injection-related symptoms.

An observation period of 15 minutes after completion of the injection is recommended, where patients should be observed for injection-related reactions and hypersensitivity reactions.

The patient should be given guidance on recognizing symptoms of hypersensitivity reactions or other possible serious side effects (as described in Section 4 of the patient leaflet), and recommendation given to contact a healthcare professional if symptoms occur after the healthcare professional has left the patient.

Phesgo is for single use only. Any unused medicine or waste material should be disposed of in accordance with local requirements. The name and the batch number of the administered product should be clearly recorded.