ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Poherdy 420 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 14 ml vial of concentrate contains 420 mg of pertuzumab at a concentration of 30 mg/ml.
After dilution, one ml of solution contains approximately 3.02 mg of pertuzumab for the initial dose and approximately 1.59 mg of pertuzumab for the maintenance dose (see section 6.6).

Pertuzumab is a humanised IgG1 monoclonal antibody produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology.

Excipients with known effect

Each mL of solution contains 30 mg sorbitol. Each vial contains 420 mg sorbitol.
Each mL of solution contains 0.20 mg polysorbate 20. Each vial contains 2.8 mg polysorbate 20.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).
Clear to slightly opalescent, colourless to pale yellow, liquid with pH of 5.7 – 6.3 and osmolality of 180 – 240 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Early breast cancer
Poherdy is indicated for use in combination with trastuzumab and 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
Poherdy is indicated for use in combination with trastuzumab and 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

Poherdy must only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. Poherdy must be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are immediately available.

Posology

Patients treated with Poherdy must have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of ≥ 2.0 by in situ hybridisation (ISH) assessed by a validated test.

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

The recommended initial loading dose of pertuzumab is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes. An observation period of 30 - 60 minutes is recommended after completion of each infusion. The observation period should be completed prior to any subsequent infusion of trastuzumab or chemotherapy (see section 4.4).

Poherdy and trastuzumab must be administered sequentially and not mixed in the same infusion bag. Poherdy and trastuzumab can be given in any order. When administered with Poherdy the recommendation is to follow a 3 weekly schedule for trastuzumab administered as either:

- an IV infusion with an initial loading dose of trastuzumab 8 mg/kg body weight followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight

or

- a fixed subcutaneous dose of trastuzumab by injection (600 mg) every 3 weeks irrespective of the patient's body weight.

In patients receiving a taxane, Poherdy and trastuzumab should be administered prior to the taxane.

When administered with Poherdy, docetaxel can be started at 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 Poherdy 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, Poherdy and trastuzumab should be administered following completion of the entire anthracycline regimen (see section 4.4).

Metastatic breast cancer

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

Early breast cancer

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

In the adjuvant setting, Poherdy should be administered in combination with trastuzumab 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. Poherdy and trastuzumab should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued.

Delayed or missed doses

For recommendations on delayed or missed doses, please refer to Table 1 below.

Table 1 Recommendations regarding delayed or missed doses

Time between two sequential infusions	**Poherdy**	**Trastuzumab**	
		Intravenous (IV)	**Subcutaneous (SC)**
< 6 weeks	The 420 mg dose of Poherdy should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule.	The 6 mg/kg dose of trastuzumab IV should be administered as soon as possible. Do not wait until the next planned dose. Thereafter, revert to the original planned schedule.	The fixed dose of 600mg trastuzumab SC should be administered as soon as possible. Do not wait until the next planned dose.
≥ 6 weeks	The 840 mg loading dose of Poherdy should be re-administered as a 60 minute infusion, followed by a maintenance dose of 420 mg IV administered every 3 weeks thereafter.	The loading dose of 8 mg/kg of trastuzumab IV should be re-administered over approximately 90 minutes, followed by a maintenance dose of 6 mg/kg IV administered every 3 weeks thereafter.	

Dose modification

Dose reductions are not recommended for Poherdy or trastuzumab. For details regarding trastuzumab, please refer to the summary of product characteristics (SmPC).

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 SmPC.

If trastuzumab treatment is discontinued, treatment with Poherdy should be discontinued.

Left ventricular dysfunction

Poherdy and trastuzumab should be withheld for at least 3 weeks for any signs and symptoms suggestive of congestive heart failure. Poherdy 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%. Poherdy and trastuzumab 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.

Poherdy and trastuzumab 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). Poherdy and trastuzumab 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.

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

Elderly patients
No overall differences in efficacy of pertuzumab were observed in patients ≥ 65 and < 65 years of age. No dose adjustment is necessary in the elderly population ≥ 65 years of age. Limited data are available in patients > 75 years of age. Please see section 4.8 for assessment of safety of pertuzumab in elderly patients.

Renal impairment
Dose adjustments of pertuzumab 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 data available (see section 5.2).

Hepatic impairment
The safety and efficacy of pertuzumab have not been studied in patients with hepatic impairment. No specific dose recommendations can be made.

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

Method of administration

Poherdy is administered intravenously by infusion. It must not be administered as an intravenous push or bolus. For instructions on dilution of Poherdy prior to administration, see sections 6.2 and 6.6.

For the initial dose, the recommended infusion period is 60 minutes. If the first infusion is well tolerated, subsequent infusions may be administered over a period of 30 minutes to 60 minutes (see section 4.4).

Infusion reactions

The infusion rate may be slowed or interrupted if the patient develops an infusion reaction (see section 4.8). The infusion may be resumed when symptoms abate. Treatment including oxygen, beta agonists, antihistamines, rapid i.v. fluids and antipyretics may also help alleviate symptoms.

Hypersensitivity reactions/anaphylaxis

The infusion must 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).

4.3 Contraindications

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

Poherdy is contraindicated in subjects with hereditary fructose intolerance (HFI). Prior to initiating treatment HFI should be excluded via medical history or on clinical grounds (see section 4.4).

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. 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 with trastuzumab and chemotherapy. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines. The majority of cases of symptomatic heart failure reported in the adjuvant setting were in patients who received anthracycline-based chemotherapy (see section 4.8).

Pertuzumab has not been studied in patients with: a pre-treatment LVEF value of < 50%; a prior history of congestive heart failure (CHF); LVEF declines to < 50% during prior trastuzumab adjuvant therapy; or 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.

Assess LVEF prior to initiation of pertuzumab and at regular intervals during treatment with pertuzumab (e.g. once during neoadjuvant treatment and every 12 weeks in the adjuvant or 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 pertuzumab and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

Cardiac risk must be carefully considered and balanced against the medical need of the individual patient before use of pertuzumab 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 pertuzumab and anthracyclines than with sequential use.

Sequential use of 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. However, only limited safety data are available on concurrent use of pertuzumab and an anthracycline. In the TRYPHAENA study, pertuzumab 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).

Infusion reactions

Pertuzumab has been associated with infusion reactions, including events with a fatal outcome (see section 4.8). Close observation of the patient during and for 60 minutes after the first infusion and during and for 30-60 minutes after subsequent infusions of pertuzumab is recommended. If a significant infusion reaction occurs, the infusion must be slowed down or interrupted and appropriate medical therapies should be administered. Patients must be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe infusion 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).

Hypersensitivity reactions/anaphylaxis

Patients must be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis and events with a fatal outcome, has been observed with pertuzumab (see section 4.8). Medicinal products to treat such reactions, as well as emergency equipment, must be available for immediate use. Pertuzumab must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome (see section 4.2).

Febrile neutropenia

Patients treated with pertuzumab, 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

Pertuzumab 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 pertuzumab should be considered if no improvement in the patient's condition is achieved. When the diarrhoea is under control treatment with pertuzumab may be reinstated.

Excipients with known effect

Sorbitol

Each mL of this medicinal product contains 30 mg of sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not take this medicine. In HFI patients, a spontaneous aversion for fructose-containing foods develops and may be combined with the onset of symptoms (vomiting, gastro-intestinal disorders, apathy, height and weight retardation). Therefore, a detailed history with regards to HFI symptoms has to be taken of each patient prior to receiving Poherdy. In case of inadvertent administration and suspicion of fructose intolerance the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care (see section 4.3).

Polysorbate 20

This medicine contains 2.8 mg of polysorbate 20 in each vial and 0.2 mg/mL.Polysorbates may cause allergic reactions.

Sodium content

Poherdy contains less than 1 mmol of sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'. Poherdy is however, diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic (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 pharmacokinetic 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.

4.6 Fertility, pregnancy and lactation

Contraception

Women of childbearing potential should use effective contraception while receiving Poherdy and for 6 months following the last dose of Poherdy.

Pregnancy

There is limited amount of data from the use of pertuzumab in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Poherdy is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Because human IgG is secreted in human milk and the potential for absorption and harm to the infant is unknown, a decision should be made to discontinue breast-feeding or to discontinue treatment, taking into account the benefit of breast-feeding for the child and the benefit of Poherdy therapy for the woman (see section 5.2).

Fertility

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. In repeated dose toxicity studies in cynomolgus monkeys, no definitive conclusions could be drawn on the adverse effect on male reproductive organs. No adverse reactions were observed in sexually mature female cynomolgus monkeys exposed to pertuzumab (see section 5.3).

4.7 Effects on ability to drive and use machines

On the basis of reported adverse reactions, pertuzumab has a minor influence on the ability to drive or use machines. Dizziness may occur during treatment with pertuzumab (see section 4.8). Patients experiencing infusion reactions should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The safety of pertuzumab has been evaluated in more than 6,000 patients in Phase I, II, and III trials in patients with various malignancies and predominantly treated with pertuzumab in combination with other antineoplastic agents. Those studies included the pivotal trials CLEOPATRA (n=808), NEOSPHERE (n=417), TRYPHAENA (n=225), and APHINITY (n=4804) [pooled in Table 2]. The

safety of pertuzumab was generally consistent across studies, although the incidence and most common adverse drug reactions (ADRs) varied depending on whether pertuzumab was administered as monotherapy or with concomitant anti-neoplastic agents.

Tabulated list of adverse reactions

Table 2 summarizes the ADRs from the pertuzumab-treated groups of the following pivotal clinical trials:

- CLEOPATRA, in which pertuzumab was given in combination with docetaxel and trastuzumab 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=2364)

In addition, ADRs reported in the post-marketing setting are included in Table 2. As pertuzumab was used with trastuzumab and chemotherapy in these trials, it is difficult to ascertain the causal relationship of an adverse event to a particular medicinal product.

The 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.

The most common ADRs (≥30%) from this pooled data were diarrhoea, alopecia, nausea, fatigue, neutropenia, and vomiting. The most common NCI-CTCAE Grade 3-4 ADRs (≥10%) were neutropenia and febrile neutropenia.

Table 2 Summary of ADRs in patients treated with Pertuzumab in clinical trials^, and in the Post-marketing setting†

System organ class	***Very Common***	***Common***	***Uncommon***	***Rare***
Infections and infestations	Nasopharyngitis	Paronychia Upper respiratory tract infection		
Blood and lymphatic system disorders	Febrile neutropenia* Neutropenia Leucopenia Anaemia			
Immune system disorders	Infusion reaction°°, *	Hypersensitivity°, * Drug hypersensitivity°, *	Anaphylactic reaction°, *	Cytokine release syndrome°°
Metabolism and nutrition disorders	Decreased appetite			Tumour lysis syndrome†
Psychiatric disorders	Insomnia			

System organ class	***Very Common***	***Common***	***Uncommon***	***Rare***
Nervous system disorders	Neuropathy peripheral Headache Dysgeusia Peripheral sensory neuropathy Dizziness Paraesthesia			
Eye disorders	Lacrimation increased			
Cardiac disorders		Left ventricular dysfunction**	Cardiac failure congestive**	
Vascular disorders	Hot flush			
Respiratory, thoracic and mediastinal disorders	Cough Epistaxis Dyspnoea		Interstitial lung disease Pleural effusion	
Gastrointestinal disorders	Diarrhoea Vomiting Stomatitis Nausea Constipation Dyspepsia Abdominal pain			
Skin and subcutaneous tissue disorders	Alopecia Rash Nail disorder Pruritus Dry skin			
Musculoskeletal and connective tissue disorders	Myalgia Arthralgia Pain in extremity			
General disorders and administration site conditions	Mucosal inflammation Oedema peripheral Pyrexia Fatigue Asthenia	Chills Pain Oedema		

^ Table 2 shows pooled data from the overall treatment period in CLEOPATRA (data cutoff 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) and from the treatment period of APHINITY (median number of cycles of pertuzumab was 18).
* ADRs with a fatal outcome have been reported.
** For the overall treatment period across the 4 studies. The incidence of left ventricular dysfunction and cardiac failure congestive reflect the MedDRA Preferred Terms reported in the individual studies.
° Hypersensitivity/anaphylactic reaction is based on a group of terms.
°° Infusion reaction includes a range of different terms within a time window, see "Description of selected adverse reactions" below.
† ADRs reported in the post marketing setting.

Description of selected adverse reactions

Left ventricular dysfunction (LVD)
In the pivotal trial CLEOPATRA in metastatic breast cancer, the incidence of LVD during study treatment was higher in the placebo-treated group than in 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 4 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% (0.8% of pertuzumab-treated patients vs 0.4% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 62.5% of pertuzumab-treated patients and 66.7% 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 2.9% of placebo-treated patients, of whom 84.4% of pertuzumab-treated patients and 87.0% of placebo-treated patients had recovered at the data cutoff.

Infusion reactions
An infusion 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 reactions was 9.8% in the placebo-treated group and 13.2% in the pertuzumab-treated group, with the majority of infusion reactions being mild or moderate. The most common infusion reactions (≥ 1.0%) 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 reactions in the pertuzumab-treated group (≥ 1.0%) were fatigue, dysgeusia, drug hypersensitivity, myalgia and vomiting (see section 4.4).

In neoadjuvant and adjuvant trials, pertuzumab was administered on the same day as other study treatments in all cycles. Infusion reactions occurred in 18.6% - 25.0% 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 at the cycles when

pertuzumab was given on the same day as trastuzumab and docetaxel, with the majority of reactions being mild or moderate in severity.

Hypersensitivity reactions/anaphylaxis
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 2.0% 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
In the pivotal trial CLEOPATRA, the majority of patients in both treatment groups experienced at least one leucopenic event (63.0% of patients in the pertuzumab-treated group and 58.3% of patients in the placebo-treated group), of which the majority were neutropenic events (see section 4.4). Febrile neutropenia occurred in 13.7% of Pertuzumab-treated patients and 7.6% of placebo-treated patients. In both treatment groups, the proportion of patients experiencing febrile neutropenia was highest in the first cycle of therapy and declined steadily thereafter. An increased incidence of febrile neutropenia was observed among Asian patients in both treatment groups compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the Pertuzumab-treated group (25.8%) compared with the placebo-treated group (11.3%).

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

In the APHINITY trial, febrile neutropenia occurred in 12.1% of Pertuzumab-treated patients and 11.1% of placebo-treated patients. As in the CLEOPATRA, TRYPHAENA, and NEOSPHERE trials, a higher incidence of febrile neutropenia was observed among Pertuzumab-treated Asian patients compared with other races in the APHINITY trial (15.9% of Pertuzumab-treated patients and 9.9% of placebo-treated patients).

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

In the NEOSPHERE trial, rash occurred in 40.2% of patients treated with neoadjuvant Pertuzumab, trastuzumab and docetaxel compared with 29.0% of patients treated with trastuzumab and docetaxel.

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

In the APHINITY trial, the adverse event 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
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 77.0% 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.

Elderly Patients

The incidence of the following all grade adverse events was at least 5% higher in patients ≥ 65 years of age, compared to patients < 65 years of age: decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, peripheral neuropathy, hypomagnesemia and diarrhoea. Limited data are available in patients > 75 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 maximum tolerated dose of pertuzumab has not been determined. In clinical trials, single doses higher than 25 mg/kg (1727 mg) have not been tested.

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: L01FD02.

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

Mechanism of action

Pertuzumab is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby, blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signalling through two major signal 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. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

While pertuzumab alone inhibited the proliferation of human tumour cells, the combination of pertuzumab and trastuzumab significantly augmented antitumour activity in HER2-overexpressing xenograft models.

Clinical efficacy and safety

The efficacy of Pertuzumab in HER2-positive breast cancer is supported by a randomised phase III trial and a single-arm phase II trial in metastatic breast cancer, two randomised neoadjuvant phase II trials in early breast cancer (one controlled), a non-randomised neoadjuvant phase II trial, and a randomised phase III trial in the adjuvant setting.

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

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

Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as oestrogen receptor (ER) positive and/or progesterone receptor (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 65.0% (range 50% – 88%) in both groups.

The efficacy results from the CLEOPATRA study are summarised in Table 3. 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 3 Summary of efficacy from CLEOPATRA study

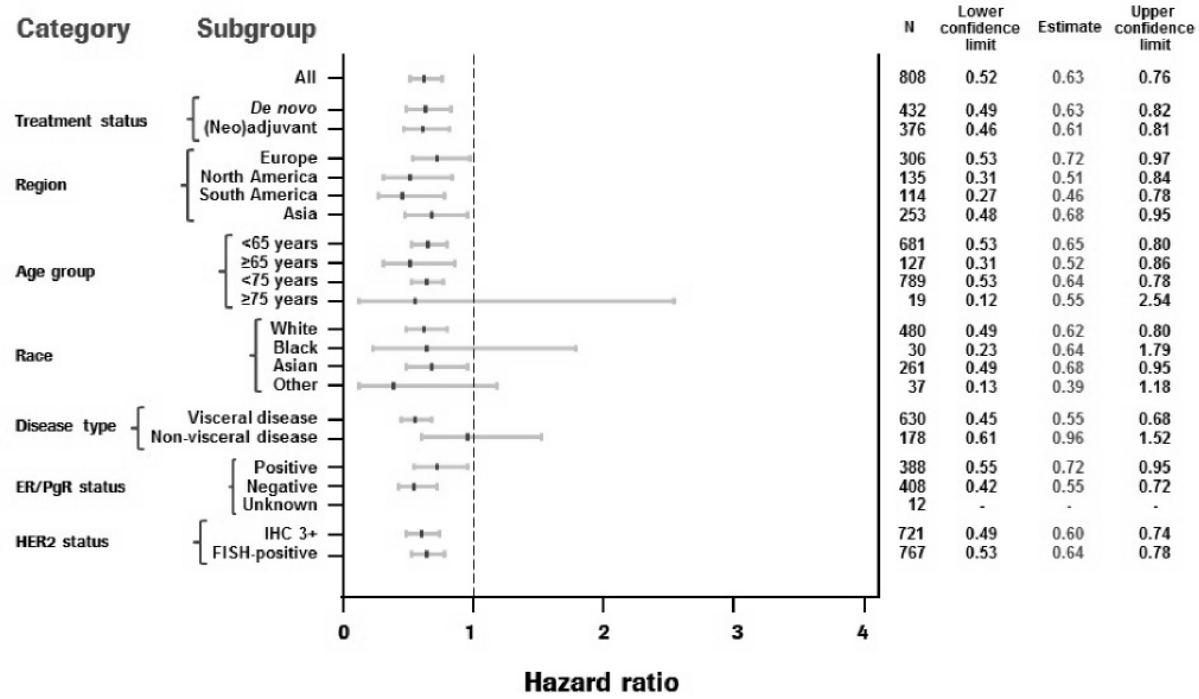
Parameter	**Placebo+ trastuzumab + docetaxel n=406**	**Pertuzumab+ trastuzumab + docetaxel n=402**	**HR (95% CI)**	**p-value**
Progression-Free Survival (independent review) – primary endpoint*				
no. of patients with an event	242 (59%)	191 (47.5%)	0.62	<0.0001
Median months	12.4	18.5	[0.51;0.75]	

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 analysis, 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 1). 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).

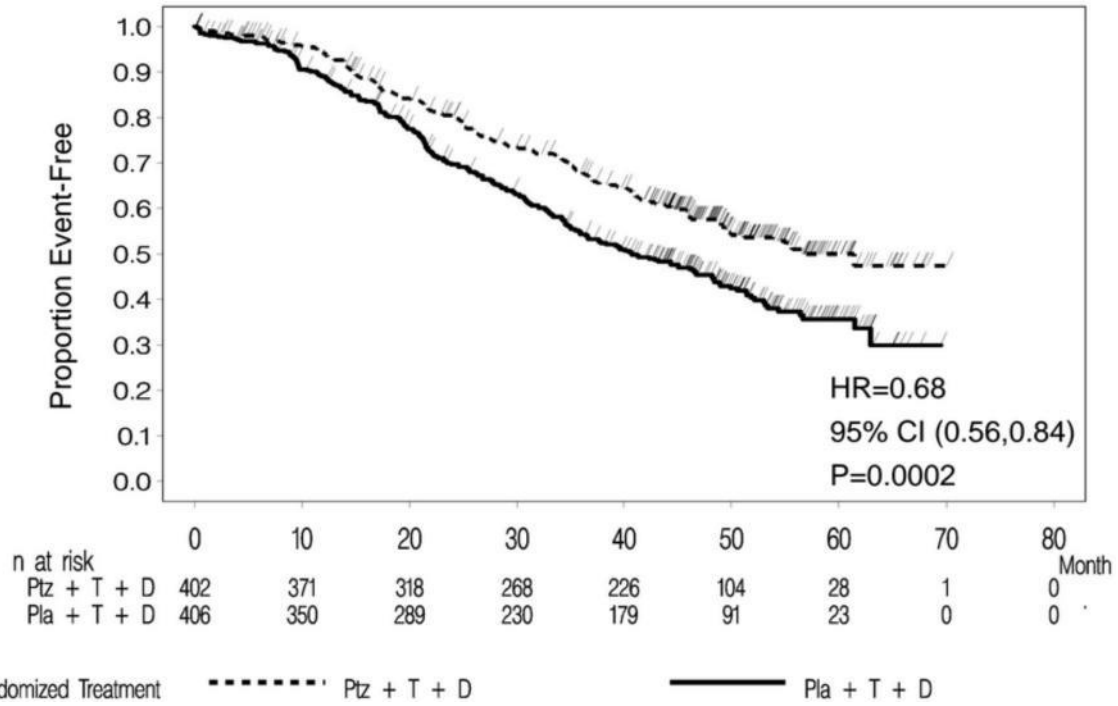
Figure 1 IRF-assessed PFS by patient subgroup



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 3, Figure 2).

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 2 Kaplan-Meier Curve of Event-Driven Overall Survival



HR= hazard ratio; CI= confidence interval; Pla= placebo; Ptz= pertuzumab; T= trastuzumab (Herceptin); 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.

Additional supportive clinical trial information

BO17929 - single-arm trial in metastatic breast cancer

BO17929 was a phase II, non-randomised study in patients with metastatic breast cancer whose tumours had progressed during treatment with trastuzumab. Treatment with Pertuzumab and trastuzumab resulted in a response rate of 24.2%, with a further 25.8% of patients experiencing stabilisation of disease lasting at least 6 months, indicating that Pertuzumab is active following progression on trastuzumab.

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, tumor 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 that nevertheless do not establish or precisely measure a benefit with regard to long-term outcomes, such as overall survival or disease-free survival.

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 > 2cm 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 ER 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. 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), disease-free survival (DFS), and PFS. Additional exploratory pCR rates included nodal status (ypT0/isN0 and ypT0N0).

Demographics were well balanced (median age was 49-50 years, 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 4. 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 29.0%, p value = 0.0141). A consistent pattern of results was observed regardless of pCR definition. The difference in pCR rate is considered likely to translate into a clinically meaningful difference in long term outcomes and is supported by positive trends in PFS (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 > 2cm 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 IV infusion every three weeks with the option to escalate to 100 mg/m^2 at the investigator's discretion if the initial dose was well tolerated. However, in the group treated with pertuzumab in combination with TCH, docetaxel was given intravenously at 75 mg/m^2 (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 4). 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 50.0%) than in patients with hormone receptor-negative tumours (range 65.0% 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 4 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 (29.0%) [20.6; 38.5]	49 (45.8%) [36.1; 55.7]	18 (16.8%) [10.3; 25.3]	23 (24.0%) [15.8; 33.7]	45 (61.6%) [49.5; 72.8]	43 (57.3%) [45.4; 68.7]	51 (66.2%) [54.6; 76.6]
Difference in pCR rates[2] [95% CI][3]		+16.8 % [3.5; 30.1]	-12.2 % [-23.8; -0.5]	-21.8 % [-35.1; -8.5]	NA	NA	NA
p-value (with Simes corr. for CMH test)[4]		0.0141 (vs. 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%) [24.0; 42.5]	6 (5.6%) [2.1; 11.8]	13 (13.2%) [7.4; 22.0]	37 (50.7%) [38.7; 62.6]	34 (45.3%) [33.8; 57.3]	40 (51.9%) [40.3; 63.5]
Clinical Response[5]	79 (79.8%)	89 (88.1%)	69 (67.6%)	65 (71.4%)	67 (91.8%)	71 (94.7%)	69 (89.6%)

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 > 2cm 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 section 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, overall survival (OS), disease-free survival (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% (hazard ratio [HR] = 0.81; 95% CI 0.66, 1.00 p-value 0.0446) reduction in risk of recurrence or death in patients randomised to receive pertuzumab compared with patients randomised to receive placebo.

After a median follow-up of 101.2 months (8.4 years), at the third OS interim analysis, the number of deaths in patients randomised to the pertuzumab arm was 168 deaths [7.0%] compared with 202 deaths [8.4%] in the placebo arm; HR=0.83, 95% CI [0.68, 1.02].

The efficacy results from the APHINITY trial are summarised in Table 5 and in Figure 3.

Table 5 Overall Efficacy: ITT Population

	Pertuzumab + trastuzumab + Chemotherapy N=2400	**Placebo + trastuzumab + Chemotherapy N=2404**
Primary Endpoint		
Invasive Disease Free Survival (IDFS)*		
Number (%) of patients with event	171 (7.1%)	210 (8.7%)
HR [95% CI]	0.81 [0.66, 1.00]	
p-value (Log-Rank test, stratified[1])	0.0446	
3 year event-free rate[2] [95% CI]	94.1 [93.1, 95.0]	93.2 [92.2, 94.3]
Secondary Endpoints[1]		
IDFS including second primary non-breast cancer		
Number (%) of patients with event	189 (7.9%)	230 (9.6%)
HR [95% CI]	0.82 [0.68, 0.99]	
p-value (Log-Rank test, stratified[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 (8.0%)	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)**		
Number (%) of patients with event	168 (7%)	202 (8.4%)
HR [95% CI]	0.83 [0.68, 1.02]	

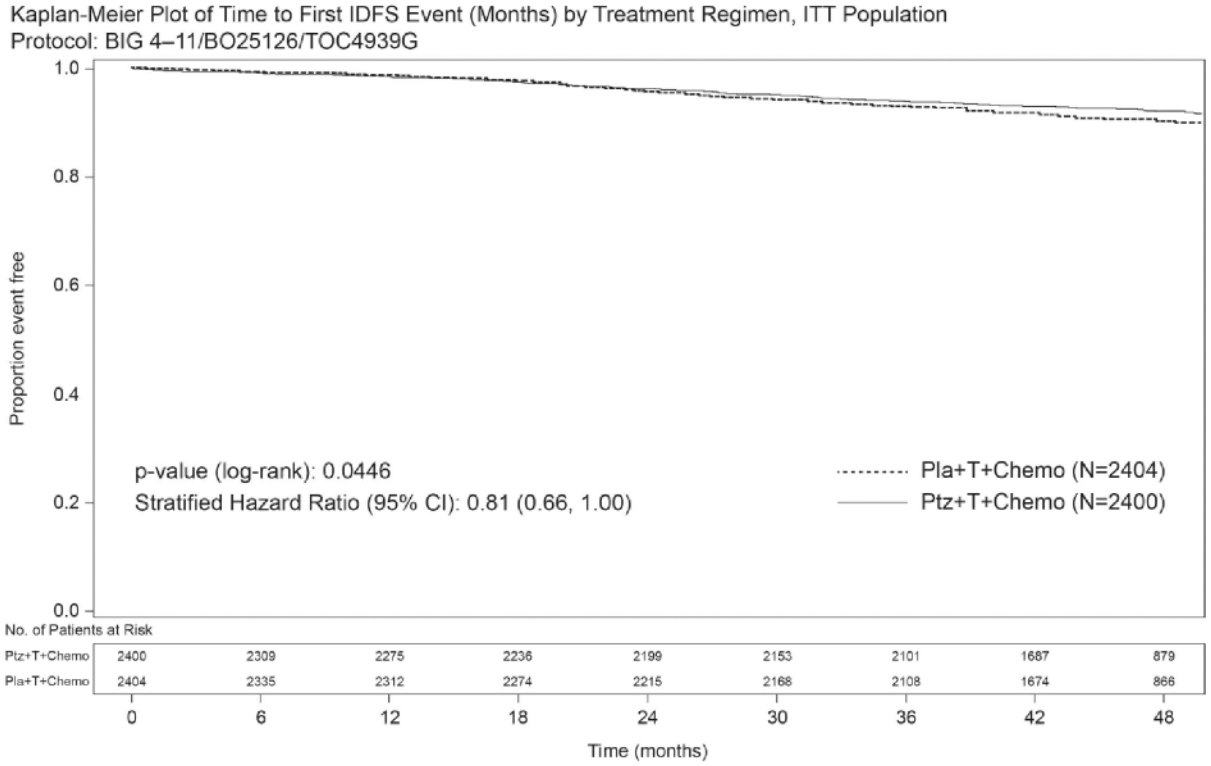
Key to abbreviations (Table 5): HR: Hazard Ratio; CI: Confidence Interval

* Primary Invasive Disease Free Survival analysis, cutoff date 19th December 2016

** Data from 3rd interim analysis for overall survival, cutoff date 10th January 2022.

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.

Figure 3 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 6).

Table 6 Efficacy results in subgroups by nodal status and hormone receptor status[1]

Population	Number of IDFS events/Total N (%)		Unstratified HR (95% CI)
	Pertuzumab + trastuzumab + chemotherapy	Placebo + trastuzumab + chemotherapy	
Nodal status			
Positive	139/1503 (9.2%)	181/1502 (12.1%)	0.77 (0.62, 0.96)
Negative	32/897 (3.6%)	29/902 (3.2%)	1.13 (0.68, 1.86)
Hormone receptor status			
Negative	71/864 (8.2%)	91/858 (10.6%)	0.76 (0.56, 1.04)
Positive	100/1536 (6.5%)	119/1546 (7.7%)	0.86 (0.66, 1.13)

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

Estimates of IDFS rates in the lymph node- positive subgroup were 92.0% versus 90.2% at 3 years and 89.9% vs. 86.7% at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively. In the lymph node- negative subgroup, estimates of IDFS rates were 97.5% versus 98.4% at 3 years and 96.2% versus 96.7% at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively. In the hormone receptor-negative subgroup, estimates of IDFS rates were 92.8% versus 91.2% at 3 years and 91.0% versus 88.7% at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively. In the hormone receptor-positive subgroup estimates of IDFS rates were 94.8% versus 94.4% at 3 years and 93.0% versus 91.6% at 4 years in pertuzumab-treated patients versus placebo-treated patients, respectively.

Patient Reported Outcomes (PRO)

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

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

Immunogenicity

Anti-pertuzumab antibodies may develop during treatment with pertuzumab. No apparent correlation of antibody development with clinical response or adverse events has been observed.

Paediatric population

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

5.2 Pharmacokinetic properties

A population pharmacokinetic analysis was performed with data from 481 patients across different clinical trials (phase I, II and III) with various types of advanced malignancies who had received pertuzumab as a single agent or in combination at pertuzumab doses ranging from 2 to 25 mg/kg administered every 3 weeks as a 30-60 minutes intravenous infusion.

Absorption

Pertuzumab is administered as an intravenous infusion.

Distribution

Across all clinical studies, the volume of distribution of the central (Vc) and the peripheral (Vp) compartment in the typical patient, was 3.11 litres and 2.46 litres, respectively.

Biotransformation

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

Elimination

The median clearance (CL) of pertuzumab was 0.235 litres/day and the median half-life was 18 days.

Linearity/non-linearity

Pertuzumab displayed linear pharmacokinetics within the recommended dose range.

Elderly patients

Based on the population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of pertuzumab between patients < 65 years (n=306) and patients ≥ 65 years (n=175).

Renal impairment

No dedicated renal impairment trial for pertuzumab has been conducted. Based on the results of the population pharmacokinetic analysis, pertuzumab exposure in patients with mild (creatinine clearance [CLcr] 60 to 90 ml/min, N=200) and moderate renal impairment (CLcr 30 to 60 ml/min, N=71) was similar to that in patients with normal renal function (CLcr greater than 90 ml/min, N=200). No relationship between CLcr and pertuzumab exposure was observed over the range of CLcr (27 to 244 ml/min).

Other special populations

The population PK analysis suggested no PK differences based on age, gender and ethnicity (Japanese versus non-Japanese). Baseline albumin and lean body weight were the most significant covariates influencing CL. CL decreased in patients with higher baseline albumin concentrations and increased in patients with greater lean body weight. However, sensitivity analyses performed at the recommended dose and schedule of pertuzumab showed that at the extreme values of these two covariates, there was no significant impact on the ability to achieve target steady-state concentrations identified in preclinical tumour xenograft models. Therefore, there is no need to adjust the dosage of pertuzumab based on these covariates.

The PK results of pertuzumab in the NEOSPHERE and APHINITY studies were consistent with the predictions from the previous population PK model. No differences in pertuzumab PK were observed in patients with early breast cancer compared to patients with metastatic breast cancer.

5.3 Preclinical safety data

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 study.

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 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 (2.5 to 20-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.

In cynomolgus monkeys, weekly intravenous administration of pertuzumab at doses up to 150 mg/kg/dose was generally well tolerated. With doses of 15 mg/kg and higher, intermittent mild treatment-associated diarrhoea was noted. In a subset of monkeys, chronic dosing (7 to 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine hydrochloride monohydrate
Sorbitol (E420)
Polysorbate 20 (E432)
Water for injections

6.2 Incompatibilities

Glucose (5%) solution must not be used to dilute pertuzumab since it is chemically and physically unstable in such solutions.

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

6.3 Shelf life

Unopened vial

3 years

Diluted solution

After dilution, the chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 8°C followed by 24 hours at 30°C protected from light. From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2℃ to 8℃, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2ºC – 8ºC).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial (Type I borosilicate glass) with a stopper (Chlorobutyl rubber) containing 14 ml of solution.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Pertuzumab does not contain any antimicrobial preservative. Therefore, care must be taken to ensure the sterility of the prepared solution for infusion and should be prepared by a healthcare professional.

Pertuzumab is for single use only.

The vial must not be shaken. 14 ml of pertuzumab concentrate should be withdrawn from the vial using a sterile needle and syringe and diluted into a 250 ml PVC or non-PVC polyolefin infusion bag of sodium chloride 9 mg/ml (0.9%) solution for infusion. After dilution, one ml of solution should contain approximately 3.02 mg of pertuzumab (840 mg/278 ml) for the initial dose where two vials are required and approximately 1.59 mg of pertuzumab (420 mg/264 ml) for the maintenance dose where one vial is required.
The bag must be gently inverted to mix the solution in order to avoid foaming.

Parenteral medicinal products must be inspected visually for particulates and discolouration prior to administration. If particulates or discoloration are observed, the solution must not be used. Once the infusion is prepared it must be administered immediately (see section 6.3).

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

Pertuzumab is compatible with polyvinylchloride (PVC) or non-PVC polyolefin bags including polyethylene.

7. MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2008/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 April 2026

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. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE 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. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Shanghai Henlius Biologics Co., Ltd.
Building 1, No. 182 Wenjun Road, Songjiang District, Shanghai, China

Name and address of the manufacturer responsible for batch release

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

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 PACKAGINGCARTON

1. NAME OF THE MEDICINAL PRODUCT

Poherdy 420 mg concentrate for solution for infusion
Pertuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 14 ml vial contains 420 mg of pertuzumab at a concentration of 30 mg/ml.

3. LIST OF EXCIPIENTS

L-Histidine
L-Histidine hydrochloride monohydrate
Sorbitol
Polysorbate 20
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
420 mg/14 ml
1 x 14 ml

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous use after dilution.
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

Patients with hereditary fructose intolerance (HFI) must not be given this medicine due to sorbitol content. See package leaflet for further information.

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

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2008/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

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

Poherdy 420 mg sterile concentrate
Pertuzumab
IV

2. METHOD OF ADMINISTRATION

For IV use after dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

420 mg/14 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Poherdy 420 mg concentrate for solution for infusion
Pertuzumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start being 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 or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Poherdy is and what it is used for

Poherdy contains the active substance pertuzumab and is used to treat adult patients with breast cancer when:
- The breast cancer has been identified to be of the "HER2-positive" form – your doctor will test you for this.
- The cancer has spread to other parts of the body such as the lungs or liver (metastasised) and has not previously been treated with anticancer medicines (chemotherapy) or other medicines designed to attach to HER2, or else the cancer has come back in the breast after previous treatment.
- The cancer has not spread to other parts of the body and treatment is going to be given before surgery takes place (treatment before surgery is called neoadjuvant therapy).
- The cancer has not spread to other parts of the body and treatment is going to be given after surgery (treatment after surgery is called adjuvant therapy).

As well as Poherdy you will also receive trastuzumab and medicines called chemotherapy. Information about these medicines is described in separate package leaflets. Ask your doctor or nurse to give you information about these other medicines.

How Poherdy works

Poherdy is a type of medicine called a "monoclonal antibody" which attaches itself to specific targets in your body and on the cancer cells.

Poherdy recognises and attaches to a target called "human epidermal growth factor receptor 2" (HER2). HER2 is found in large amounts on the surface of some cancer cells where it stimulates their

growth. When Poherdy attaches to the HER2 cancer cells, it may slow or stop the cancer cells from growing, or may kill them.

2. What you need to know before you are given Poherdy

You must not be given Poherdy

- If you are allergic to pertuzumab or to any of the other ingredients of this medicine (listed in section 6).
- If you have hereditary fructose intolerance (HFI), a quite rare genetic condition where the enzyme for breaking down fructose is not produced.

If you are not sure, talk to your doctor or nurse before you are given Poherdy.

Warnings and precautions

Treatment with Poherdy may affect the heart. Talk to your doctor or nurse before you are given Poherdy:

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

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

Infusion reactions
Infusion reactions, allergic or anaphylactic (more severe allergic) reactions can happen. Your doctor or nurse will check for side effects during your infusion and for 30 to 60 minutes afterwards. If you get any serious reaction, your doctor may stop treatment with pertuzumab. Very rarely, patients have died due to anaphylactic reactions during pertuzumab infusion. See section 4 “Serious side effects” for more details about infusion reactions to look out for during the infusion and thereafter.

Febrile neutropenia (Low white blood cells with fever)
When pertuzumab is given with other cancer treatments (trastuzumab and chemotherapy), the number of white blood cells may drop and fever (raised temperature) 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.

Diarrhoea
Treatment with pertuzumab 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. Diarrhoea is a condition where your body produces more watery stools than normal. If you experience severe diarrhoea while receiving your anti-cancer treatment, your doctor may start you on anti-diarrhoeal treatment and may stop your treatment with pertuzumab until the diarrhoea is under control.

Use in children and adolescents
Poherdy 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.

Use in the elderly
Patients over 65 years of age who are treated with pertuzumab are more likely to experience side effects such as reduced appetite, decrease in the number of red blood cells, weight loss, feeling tired, loss or altered taste, weak, numb, tingling or prickling sensations mainly affecting the feet and legs and diarrhoea, compared to patients younger than 65 years of age.

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

Pregnancy and breast-feeding
Before starting treatment, you must tell your doctor 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 advise you about the benefits and risks for you and your baby of taking pertuzumab while you are pregnant.

- Tell your doctor straight away, if you get pregnant during treatment with pertuzumab or during the 6 months after stopping treatment.
- Ask your doctor about whether you can breast-feed during or after treatment with pertuzumab.

Pertuzumab may harm the unborn baby. You should use effective contraception during treatment with pertuzumab and for 6 months after stopping treatment. Talk to your doctor about the best contraception for you.

Driving and using machines
Pertuzumab may have a minor effect on you being able to drive or use machines. However, if you get any dizziness, infusion reactions, allergic or anaphylactic reactions, wait until these have gone away before driving or using machines.

Poherdy contains sodium
Poherdy contains less than 1 mmol of sodium (23 mg) per dose, i.e. it is essentially sodium-free. However, before Poherdy is given to you, it is diluted with sodium chloride 9 mg/mL (0.9%) solution for infusion. Talk to your doctor if you are on a low salt diet.

Poherdy contains sorbitol
Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you have HFI.

Poherdy contains polysorbate
This medicine contains 0.2 mg of polysorbate 20 in each ml, which is equivalent to 2.8 mg in each vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How you are given Poherdy

Being given this medicine

Poherdy will be given to you by a doctor or nurse in a hospital or clinic.
- It is given by a drip into a vein (intravenous infusion) once every three weeks.
- The amount of medicine you are given and how long the infusion will last are different for the first dose and following doses.

- The number of infusions you will be given depends on how you respond to treatment and whether you are receiving treatment before or after surgery (neoadjuvant or adjuvant therapy) or for disease which has spread.
- Pertuzumab is given with other cancer treatments (trastuzumab andchemotherapy).

For the first infusion:
- You will be given 840 mg of pertuzumab over 60 minutes. Your doctor or nurse will check for side effects during your infusion and for 60 minutes afterwards.
- You will also be given trastuzumab and chemotherapyl.

For all following infusions, if the first infusion was well tolerated:
- You will be given 420 mg of pertuzumab over 30 to 60 minutes. Your doctor or nurse will check for side effects during your infusion and for 30 to 60 minutes afterwards.
- You will also be given trastuzumab and chemotherapy.

For further information on dosing of trastuzumab and chemotherapy (which can cause side effects as well), please refer to the package leaflet for these products. If you have questions about these medicines, please ask your doctor or nurse.

If you forget to have Poherdy
If you forget or miss your appointment to receive pertuzumab, make another appointment as soon as possible. If it has been 6 weeks or more since your last visit a higher pertuzumab dose of 840 mg will be given to you.

If you stop having Poherdy
Do not stop having this medicine without talking to your doctor first. It is important that you are given all the infusions that have been recommended.

If you have any further questions on the use of this medicine, ask your doctor 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:
- Very severe or persistent diarrhoea (7 or more stools per day).
- A decrease in the number or low amount of white blood cells (shown in a blood test), with or without fever, which may increase the risk of an infection.
- Infusion reactions with symptoms that can either be mild or more severe and may include feeling sick (nausea), fever, chills, feeling tired, headache, loss of appetite, joint and muscle pains, and hot flushes.
- Allergic and anaphylactic (more severe allergic) reactions with symptoms that may include swelling of your face and throat, with difficulty in breathing. Very rarely, patients have died due to anaphylactic reactions during pertuzumab infusion.
- Heart problems (heart failure) with symptoms that can include cough, shortness of breath, and swelling (fluid retention) in your legs or arms.
- Tumour lysis syndrome (a condition which may happen when cancer cells die quickly, causing changes in blood levels of minerals and metabolites shown in a blood test). Symptoms may include kidney problems (weakness, shortness of breath, fatigue and confusion), heart problems (fluttering of the heart at a faster or slower heartbeat), seizures, vomiting or diarrhoea and tingling in the mouth, hands or feet.

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

Other side effects include:

Very common (may affect more than 1 in 10 people):
- Diarrhoea
- Hair loss
- Feeling sick or being sick
- Feeling tired
- Rash
- Inflammation of your digestive tract (e.g. sore mouth)
- Decrease in the number of red blood cells – shown in a blood test
- Joint or muscle pain, muscle weakness
- Constipation
- Reduced appetite
- Loss of or altered taste
- Fever
- Swollen ankles or other body parts due to your body retaining too much water
- Not being able to sleep
- Hot flushes
- Weak, numb, tingling or prickling sensations mainly affecting the feet and legs
- Nose bleeds
- Cough
- Heartburn
- Dry, itchy or acne like skin
- Nail problems
- Sore throat, red, sore or runny nose, flu-like symptoms and fever
- Producing more tears
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Pain in the body, arms, legs, and belly
- Shortness of breath
- Feeling dizzy

Common (may affect up to 1 in 10 people):
- A feeling of numbness, prickling or tingling in feet or hands; sharp jabbing, throbbing, freezing or burning pain; feeling pain from something which should not be painful such as a light touch; less able to feel changes in heat or cold; loss of balance or coordination
- Inflammation of the nail bed where the nail and skin meet
- Infection of the ear, nose or throat
- Condition in which the left ventricle of the heart is functionally impaired with or without symptoms

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

If you experience any of the above symptoms after treatment with pertuzumab has been stopped, you should consult your doctor immediately and inform him or her that you have previously been treated with pertuzumab.

Some of the side effects which you get may be due to your breast cancer. If you are given pertuzumab with trastuzumab and 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 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 Poherdy

Poherdy 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 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.
- Do not use this medicine if you notice any particles in the liquid or it is the wrong colour (please 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 to protect the environment.

6. Contents of the pack and other information

What Poherdy contains
- The active substance is pertuzumab. Each vial contains a total of 420 mg pertuzumab at a concentration of 30 mg/ml.
- The other ingredients are L-histidine, L-histidine hydrochloride monohydrate, sorbitol (E420, see section 2 “Poherdy contains sorbitol”), polysorbate 20 (E432, see section 2 “Poherdy contains polysorbate”) and water for injections.

What Poherdy looks like and contents of the pack
Poherdy is a concentrate for solution for infusion. It is a clear to slightly opalescent, colourless to pale yellow liquid. It is supplied in a glass vial containing 14 ml concentrate.
Each pack contains one vial.

Marketing Authorisation Holder
N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

Manufacturer
N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

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

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