

INJ-PHE-2021 05-0

# Pesgo<sup>®</sup>

## pertuzumab and trastuzumab



### 1. DESCRIPTION

#### 1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Antineoplastic agents, recombinant humanized IgG1 monoclonal antibodies  
ATC code: L01XY02

#### 1.2 TYPE OF DOSAGE FORM

Solution for subcutaneous injection

#### 1.3 ROUTE OF ADMINISTRATION

Subcutaneous injection

#### 1.4 STERILE / RADIOACTIVE STATEMENT

Sterile Product

#### 1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient(s): pertuzumab (Perjeta), trastuzumab (Herceptin)

Pesgo is a clear to opalescent solution, colourless to slightly brownish solution supplied in sterile, preservative-free, non-pyrogenic single-dose vials.

Single dose vials contain:

1200 mg Perjeta/600 mg Herceptin/15 mL solution in a vial  
600 mg Perjeta/600 mg Herceptin/10 mL solution in a vial

Excipients: rHuPH20, L-Histidine, L-Histidine Hydrochloride Monohydrate,  $\alpha$ -Trehalose Dihydrate, Sucrose, Polysorbate 20, L-Methionine, Water for Injection

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

## 2. CLINICAL PARTICULARS

### 2.1 THERAPEUTIC INDICATION(S)

#### Early Breast Cancer (EBC)

Pesgo is indicated for use in combination with chemotherapy for the:

- neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer (see 3.1.2 Clinical studies). This indication is based on demonstration of an improvement in pathological complete response rate. No data are available demonstrating improvement in event-free survival or overall survival.
- adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence (see 3.1.2 Clinical Studies)

#### Metastatic Breast Cancer (MBC)

Pesgo is indicated for use in combination with docetaxel for the treatment of 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.

### 2.2 DOSAGE AND ADMINISTRATION

#### Patient Selection

Patients treated with Pesgo should have HER2-positive tumor status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of  $\geq 2.0$  by in situ hybridization (ISH), assessed by a validated test.

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

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

#### Administration of Pesgo

Pesgo therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients.

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

Patients currently receiving intravenous Perjeta and Herceptin can switch to Pesgo. Switching treatment from intravenous Perjeta and Herceptin to Pesgo (or vice versa) was investigated in study MO40628 (see section 2.6.1 Undesirable Effects and section 3.1.2 Clinical / Efficacy Studies).

In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Pesgo.

Pesgo is for subcutaneous (SC) use in the thigh only. Do not administer intravenously.

#### Metastatic and Early Breast Cancer

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

**Table 1 Pesgo recommended dosing and administration**

	Dose (irrespective of body weight)	Approximate duration of SC injection	Observation time <sup>a,b</sup>
<b>Loading dose</b>	1200 mg Perjeta/ 600 mg Herceptin	8 minutes	30 minutes
<b>Maintenance dose (every 3 weeks)</b>	600 mg Perjeta/ 600 mg Herceptin	5 minutes	15 minutes

<sup>a</sup>Patients should be observed for injection-related and hypersensitivity reactions

<sup>b</sup>Observation period should start following administration of Pesgo and be completed prior to any subsequent administration of chemotherapy

In patients receiving intravenous Perjeta and Herceptin with < 6 weeks since their last dose, Pesgo should be administered as a maintenance dose of 600 mg Perjeta/600 mg Herceptin and every 3 weeks for subsequent administrations. In patients receiving intravenous Perjeta and Herceptin with  $\geq 6$  weeks since their last dose, Pesgo should be administered as a loading dose of 1200 mg Perjeta/600 mg Herceptin, followed by a maintenance dose of 600 mg Perjeta/600 mg Herceptin every 3 weeks for subsequent administrations.

The injection site should be alternated between the left and right thigh only. New injections should be given at least 1 inch/2.5 cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. Do not split the dose between two syringes or between two sites of administration. During the treatment course with Pesgo, other medications for SC administration should preferably be injected at different sites.

In patients receiving a taxane, Pesgo should be administered prior to the taxane. When administered with Pesgo, the recommended initial dose of docetaxel is 75 mg/m<sup>2</sup>, and the dose of docetaxel may be escalated to 100 mg/m<sup>2</sup> on subsequent cycles if the initial dose is well tolerated.

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

#### Early Breast Cancer (EBC)

In the neoadjuvant setting (before surgery), it is recommended that patients are treated with Pesgo for three to six cycles depending on the regimen chosen in combination with chemotherapy (see 3.1.2 Clinical / Efficacy Studies).

In the adjuvant setting (after surgery), Pesgo should be administered for a total of one year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever

occurs first), as part of a complete regimen for early breast cancer and regardless of the timing of surgery. Treatment should include standard anthracycline and/or taxane-based chemotherapy. Pesgo treatment should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued (see 3.1.2 Clinical/Efficacy Studies).

#### Metastatic Breast Cancer (MBC)

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

#### Delayed or Missed Doses

If the time between two sequential doses is less than 6 weeks, the 600 mg Perjeta/ 600 mg Herceptin maintenance dose of Pesgo should be administered as soon as possible. Do not wait until the next planned dose.

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

#### Dose Modifications

No dose reductions of Pesgo are recommended.

For chemotherapy dose modifications, see relevant prescribing information.

#### Injection-related reactions

The injection should be slowed or paused if the patient experiences injection-related symptoms (see 2.4 Warnings and Precautions).

#### Hypersensitivity/anaphylaxis

The injection should be discontinued immediately and permanently if the patient experiences a serious hypersensitivity reaction (e.g. anaphylaxis) (see 2.4 Warnings and Precautions).

#### Left ventricular dysfunction

Assess LVEF prior to initiation of Pesgo and at regular intervals during treatment to ensure that LVEF is within normal limits (see Table 2 below). If the LVEF declines as indicated in Table 2 and has not improved, or has declined further at the subsequent assessment, discontinuation of Pesgo should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. See 2.4 Warnings and Precautions for more information.

**Table 2 Dose recommendations for left ventricular dysfunction**

	Pre-treatment LVEF:	Monitor LVEF every:	Withhold Pesgo for at least 3 weeks for an LVEF decrease to:	Resume Pesgo after 3 weeks if LVEF has recovered to:
<b>Metastatic Breast Cancer<sup>a</sup></b>	$\geq 50\%$	~12 weeks	Either	Either
			< 40% with a fall of $\geq 10\%$ -points below pre-treatment value	> 45% with a fall of < 10%-points below pre-treatment value
<b>Early Breast Cancer</b>	$\geq 55\%$ <sup>b</sup>	~12 weeks (once during neoadjuvant therapy)	< 50% with a fall of $\geq 10\%$ -points below pre-treatment value	Either
				$\geq 50\%$ with a fall of < 10%-points below pre-treatment value

<sup>a</sup>based on intravenous Perjeta data (CLEOPATRA study)

<sup>b</sup>for patients receiving anthracycline-based chemotherapy, a LVEF of  $\geq 50\%$  is required after completion of anthracyclines, before starting Pesgo

### 2.2.1 Special Dosage Instructions

#### Pediatric use

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

#### Geriatric use

No dose adjustment of Pesgo is required in patients  $\geq 65$  years of age (see 2.5.5 Geriatric Use and 3.2.5 Pharmacokinetics in Special populations).

#### Renal Impairment

Dose adjustments of Pesgo 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 3.2.5 Pharmacokinetics in special populations).

#### Hepatic Impairment

The safety and efficacy of Pesgo have not been studied in patients with hepatic impairment. No dose recommendation can be made for Pesgo (see 3.2.5 Pharmacokinetics in Special populations).

## 2.3 CONTRAINDICATIONS

Pesgo is contraindicated in patients with a known hypersensitivity to Perjeta, Herceptin, or any of the excipients.

## 2.4 WARNINGS AND PRECAUTIONS

#### General

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

#### Left ventricular dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including Perjeta and Herceptin. The incidence of symptomatic left ventricular systolic dysfunction (LVSD [congestive heart failure]) was higher in patients treated with Perjeta in combination with Herceptin and chemotherapy compared to Herceptin and chemotherapy. In the adjuvant setting, the majority of cases of symptomatic heart failure reported were in patients who received anthracycline-based chemotherapy (see 2.6 Undesirable effects). Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF decreases based on studies with intravenous Perjeta in combination with Herceptin and chemotherapy.

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

Candidates for treatment with Pesgo, especially those with prior exposure to an anthracycline, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG) and echocardiogram or multigated acquisition scanning (MUGA) scan. In EBC, the following patients were excluded from the HERA trial (conducted with trastuzumab), there are no data about the benefit-risk balance, and therefore treatment cannot be recommended in such patients:

- History of documented congestive heart failure
- High-risk uncontrolled arrhythmias
- Angina pectoris requiring a medicinal product
- Clinically significant valvular disease
- Evidence of transmural infarction on ECG
- Poorly controlled hypertension

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. Cardiac function should be further monitored during treatment (e.g. every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction, including signs and symptoms of CHF. Cardiac assessments, as performed at baseline, should be repeated every 3 months

during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Pesgo.

#### Injection/infusion-related reactions (IRRs)

Pesgo has been associated with injection-related reactions. Injection-related reactions were defined as any systemic reaction with symptoms such as fever, chills, headache, likely due to a release of cytokines occurring within 24 hours of administration of Pesgo. Close observation of the patient during and for 30 minutes after administration of the loading dose and during and for 15 minutes following the administration of the maintenance dose of Pesgo is recommended. If a significant injection-related reaction occurs, the injection should be slowed down or paused and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe injection-related reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction (see 2.2 Dosage and Administration). Although fatal outcomes resulting from injection-related reactions have not been observed with Pesgo, caution should be exercised as fatal infusion related-reactions have been associated with intravenous Perjeta in combination with intravenous Herceptin and chemotherapy.

#### Hypersensitivity reactions/anaphylaxis

Patients should be observed closely for hypersensitivity reactions. Although severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have not been observed in patients treated with Pesgo, caution should be exercised as these have been associated with intravenous Perjeta in combination with Herceptin and chemotherapy (see 2.6 Undesirable effects). Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Pesgo is contraindicated in patients with known hypersensitivity to Perjeta, Herceptin, or to any of its excipients (see 2.3 Contraindications).

#### Pulmonary events

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

#### Exacerbation of chemotherapy-induced neutropenia

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

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

### 2.4.1 Drug Abuse and Dependence

There is no evidence that Pesgo has the potential for drug abuse and dependence.

### 2.4.2 Ability to Drive and Use Machines

Pesgo has a minor influence on the ability to drive and use machines. Injection-related reactions and dizziness may occur during treatment with Pesgo (see 2.4 Warnings and Precautions and 2.6 Undesirable effects). Patients experiencing administration-related reactions should be advised not to drive and use machines until symptoms abate.

## 2.5 USE IN SPECIAL POPULATIONS

### 2.5.1 Females and Males of Reproductive Potential

#### Fertility

No specific fertility studies in animals have been performed to evaluate the effects of Pesgo.

No specific fertility studies in animals have been performed to evaluate the effect of Perjeta. No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies of Perjeta for up to six month duration in cynomolgus monkeys (see 3.3.3 Impairment of Fertility).

Reproduction studies conducted in cynomolgus monkeys with Herceptin revealed no evidence of impaired fertility in female cynomolgus monkeys (see 3.3.3 Impairment of Fertility).

#### Contraception

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

### 2.5.2 Pregnancy

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

No clinical studies of Pesgo in pregnant women have been performed. Perjeta administered intravenously to cynomolgus monkeys during organogenesis led to oligohydramnios, delayed renal development and embryo fetal death (see 3.3.4 Reproductive Toxicity). In the post-marketing setting for Herceptin, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women.

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

#### Labor and Delivery

The safe use of Pesgo during labor and delivery has not been established.

### 2.5.3 Lactation

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

### 2.5.4 Pediatric Use

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

### 2.5.5 Geriatric Use

No overall differences in efficacy and safety of Pesgo was observed in patients  $\geq 65$  (n=26) and < 65 years of age (n=222).

However, with intravenous Perjeta in combination with Herceptin, the incidence of the following all grade adverse events were at least 5% higher in patients patients  $\geq 65$  years of age (n=418) compared to patients < 65 years of age (n=2926): decreased appetite, anemia, weight decreased, asthenia, dysgeusia, neuropathy peripheral, hypomagnesemia and diarrhea.

### 2.5.6 Renal Impairment

See 2.2.1 Special dosing instructions and 3.2.5 Pharmacokinetics in special populations.

### 2.5.7 Hepatic Impairment

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

## 2.6 UNDESIRABLE EFFECTS

### 2.6.1 Clinical Trials

#### Summary of the safety profile

The safety profile of Phesgo is based on data from the Phase III FEDERICA study in which HER2-positive early breast cancer patients were treated with either Phesgo (n=248) or intravenous Perjeta and Herceptin (n=252), in combination with chemotherapy.

The most common (≥ 5%) adverse drug reactions (ADRs) reported in patients treated with Phesgo or intravenous Perjeta in combination with Herceptin were diarrhea, injection site reaction, infusion-related reactions, asthenia, fatigue, rash, ejection fraction decreased, and anemia.

The most common (≥ 1%) serious adverse events (SAEs) reported in patients treated with Phesgo or intravenous Perjeta in combination with Herceptin were febrile neutropenia, pyrexia, neutropenia, neutropenic sepsis, infusion-related reaction and neutrophil count decreased. SAEs were equally distributed between the Phesgo treatment arm and the intravenous Perjeta in combination with Herceptin treatment arm. The following adverse drug reactions were reported with a higher frequency (≥ 5%) with Phesgo compared to intravenous Perjeta in combination with Herceptin: Alopecia 77% vs 70.2%, Dyspnea 10.1% vs 4.4%, and Fatigue 27.8% vs 22.6%.

#### Tabulated list of adverse drug reactions

The safety profile of Phesgo was overall consistent to the known safety profile of intravenous Perjeta in combination with Herceptin and chemotherapy as seen in the Perjeta and Herceptin-treated arms of the following pivotal studies (n=3344):

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

Table 3 presents ADRs that have been reported in association with the use of Perjeta, Herceptin and chemotherapy in the pivotal clinical trials and in the post-marketing setting.

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

In this section, the following categories of frequency have been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and unknown (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 3 Summary of adverse drug reactions reported from the Perjeta, Herceptin pivotal trials and in the post-marketing settings**

ADR (MedDRA Preferred Term) System Organ Class	Perjeta + Herceptin + chemotherapy <sup>b</sup> Frequency rate %		Frequency category
	All Grades %	Grades 3-4 %	
<b>Blood and lymphatic system disorders</b>			
Neutropenia	31.4	24.2	Very common
Anemia	24.8	5.7	Very common
Febrile neutropenia <sup>d</sup>	11.9	11.8	Very common
Leukopenia	10.8	6.1	Very common
<b>Cardiac disorders</b>			
Left ventricular dysfunction <sup>e</sup>	1.4	0.3	Common
Cardiac failure congestive <sup>e</sup>	0.1	<0.1	Uncommon
<b>Eye disorders</b>			
Lacrimation increased	12.1	-	Very common
<b>Gastrointestinal disorders</b>			
Diarrhea	67.9	8.9	Very common
Nausea	60.8	1.9	Very common
Vomiting	30.0	1.7	Very common
Stomatitis	24.9	1.6	Very common
Constipation	24.5	0.4	Very common
Dyspepsia	13.2	<0.1	Very common
Abdominal pain	11.7	0.4	Very common
<b>General disorders and administration site conditions</b>			
Fatigue	44.3	3.3	Very common
Mucosal inflammation	23.2	1.5	Very common
Asthenia	20.9	1.5	Very common
Pyrexia	18.9	0.6	Very common
Edema peripheral	16.2	<0.1	Very common
Injection site reactions <sup>f</sup>	12.9	0	Very common
<b>Immune system disorders</b>			
Hypersensitivity	3.3	0.4	Common
Drug hypersensitivity	2.5	0.4	Common
Anaphylactic reaction	0.2	0.1	Uncommon
<b>Infections and infestations</b>			
Nasopharyngitis	12.8	<0.1	Very common
Upper respiratory tract infection	9.5	0.3	Common
Paronychia	3.9	<0.1	Common
<b>Metabolism and nutrition disorders</b>			
Decreased appetite	23.1	0.8	Very common
Tumor lysis syndrome <sup>g</sup>		Unknown	
<b>Musculoskeletal and connective tissue disorders</b>			
Arthralgia	24.6	0.7	Very common
Myalgia	24.3	0.8	Very common
Pain in extremity	10.0	0.2	Very common
<b>Nervous system disorders</b>			
Dysgeusia	22.7	<0.1	Very common
Headache	21.8	0.4	Very common
Peripheral sensory neuropathy	15.7	0.5	Very common
Neuropathy peripheral	14.7	0.7	Very common
Dizziness	11.2	0.1	Very common
Paraesthesia	10.2	0.4	Very common
<b>Psychiatric disorders</b>			
Insomnia	15.9	0.2	Very common
<b>Respiratory, thoracic and mediastinal disorders</b>			
Epistaxis	15.6	<0.1	Very common
Cough	15.5	<0.1	Very common
Dyspnea	11.5	0.5	Very common
Pleural effusion	0.9	<0.1	Uncommon
Interstitial lung disease	0.1	<0.1	Uncommon
<b>Skin and subcutaneous tissue disorders</b>			
Alopecia	63.1	<0.1	Very common
Rash	26.4	0.5	Very common
Nail disorder	12.9	0.3	Very common
Pruritus	12.9	<0.1	Very common
Dry skin	11.7	<0.1	Very common
<b>Vascular disorders</b>			
Hot flush	15.7	0.1	Very common

<sup>a</sup> Table 3 shows pooled data from the overall treatment period in CLEOPATRA; from the neoadjuvant treatment period in NEOSPHERE and TRYPHAENA; and from the treatment period of APHINITY. Additionally, Table 3 shows an ADR specific to the Phesgo route of administration that has been reported in FEDERICA.

<sup>b</sup> In NEOSPHERE, 108 patients received Perjeta + Herceptin alone without docetaxel and 94 patients received Perjeta + docetaxel without Herceptin.

<sup>c</sup> In CLEOPATRA, 45 patients who were randomized to receive placebo and who had no prior exposure

to Perjeta, had crossed over to receive Perjeta and are included in the 3344 patients treated with Perjeta.

<sup>d</sup> In this table this denotes an adverse reaction that has been reported in association with a fatal outcome.

<sup>e</sup> The incidence of left ventricular dysfunction and cardiac failure congestive reflect the MedDRA preferred terms reported in the individual studies.

<sup>f</sup> observed with Phesgo only

<sup>g</sup> identified in the postmarketing setting

#### Description of selected adverse drug reactions from clinical trials

##### Phesgo

##### Left ventricular dysfunction

In FEDERICA, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10%-points from baseline and to < 50% was 0.4% of Phesgo treated patients vs 0% of intravenous Perjeta and Herceptin-treated patients. Of the patients who experienced symptomatic heart failure, all Phesgo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10%-points from baseline and to < 50% (confirmed by secondary LVEF) were reported in 0.4% of Phesgo-treated patients and 0.8% of intravenous Perjeta and Herceptin-treated patients, of whom none of the Phesgo-treated patients and one of the intravenous Perjeta and Herceptin-treated patients had recovered at the data cutoff.

##### Injection/infusion-related Reactions

In FEDERICA, an injection/infusion-related reaction was defined as any systemic reaction reported within 24hrs of Phesgo or intravenous Perjeta in combination with Herceptin administration. Injection-related reactions were reported in 1.2% of Phesgo-treated patients and infusion-related reactions were reported in 10.3% of intravenous Perjeta and Herceptin-treated patients.

Injection site reactions (defined as any local reaction reported within 24 hours of Phesgo) were reported in 12.9% of Phesgo treated patients and were all grade 1 or 2 events.

##### Hypersensitivity reactions/anaphylaxis

In FEDERICA, the overall frequency of hypersensitivity/anaphylaxis reported events related to HER2-targeted therapy was 1.6% in both the Phesgo-treated patients and intravenous Perjeta and Herceptin-treated patients, of which none were NCI-CTCAE (version 4) Grade 3-4 (see 2.4 Warnings & Precautions).

##### Febrile neutropenia

In the pivotal trial CLEOPATRA, the majority of patients in both treatment groups experienced at least one leucopenic event (62.4% of patients in the Perjeta-treated group and 58.2% of patients in the placebo-treated group), of which the majority were neutropenic events. Febrile neutropenia occurred in 13.8% of Perjeta-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 for 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 Perjeta-treated group (26%) compared with the placebo-treated group (12%).

In the NEOSPHERE trial, 8.4% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel experienced febrile neutropenia compared with 7.5% of patients treated with Herceptin and docetaxel. In the TRYPHAENA trial, febrile neutropenia occurred in 17.1% of patients treated with neoadjuvant Perjeta + TCH, and 9.3% of patients treated with neoadjuvant Perjeta, Herceptin and docetaxel following FEC. In TRYPHAENA, the incidence of febrile neutropenia was higher in patients who received six cycles of Perjeta compared with patients who received three cycles of Perjeta, 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 Perjeta, Herceptin and docetaxel experienced febrile neutropenia compared with 4.0% of Asian patients treated with neoadjuvant Herceptin and docetaxel.

In the APHINITY trial, febrile neutropenia occurred in 12.1% of Perjeta-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 Perjeta-treated Asian patients compared with other races in the APHINITY trial (15.9% of Perjeta-treated patients and 9.9% of placebo-treated patients).

##### Diarrhoea

In the pivotal clinical trial CLEOPATRA, diarrhoea occurred in 66.8% of Perjeta-treated patients and 46.3% of placebo-treated patients. Most events were mild-moderate in severity and occurred in the first few cycles of treatment. The incidence of NCI-CTCAE Grade 3-4 diarrhoea was 7.9% in Perjeta-treated patients vs 5.0% in placebo-treated patients. The median duration of the longest episode was 17 days in Perjeta-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 Perjeta, Herceptin and docetaxel compared with 33.6% of patients treated with Herceptin and docetaxel.

In the TRYPHAENA trial, diarrhoea occurred in 72.3% of patients treated with neoadjuvant Perjeta+TCH and 61.4% of patients treated with neoadjuvant Perjeta, Herceptin 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 Perjeta-treated arm (71.2%) compared to the placebo arm (45.2%). Grade ≥ 3 diarrhoea was reported in 9.8% of patients in the Perjeta 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 Perjeta 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 Perjeta arm vs. 9.2% of patients in the placebo arm in the post-chemotherapy targeted therapy period.

##### Rash

Rash occurred in 45.2% of Perjeta-treated patients, compared with 36.0% 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.

##### Laboratory Abnormalities

In FEDERICA, the incidence of NCI-CTCAE Grade 3-4 decreases in neutrophil counts were balanced in the Phesgo and intravenous Perjeta and Herceptin groups.

##### Intravenous Perjeta and Herceptin

##### Left ventricular dysfunction

In CLEOPATRA, the incidence of LVD during study treatment was higher in the placebo-treated group than the Perjeta-treated group (8.6% and 6.6%, respectively). The incidence of symptomatic LVD was also lower in the Perjeta-treated group (1.8% in the placebo-treated group vs. 1.5% in the Perjeta-treated group) (see 2.4 Warnings & Precautions).

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

In TRYPHAENA, the incidence of LVD (during the overall treatment period) was 8.3% in the group treated with Perjeta plus Herceptin and 5-fluorouracil, epirubicin and cyclophosphamide (FEC) followed by Perjeta plus Herceptin and docetaxel; 9.3% in the group treated with Perjeta plus Herceptin and docetaxel following FEC; and 6.6% in the group treated with Perjeta in combination with TCH. The incidence of symptomatic LVD (congestive heart failure) was 1.3% in the group treated with Perjeta plus Herceptin and docetaxel following FEC (this excludes a patient that experienced symptomatic LVD during FEC treatment prior to receiving Perjeta plus Herceptin and docetaxel) and also 1.3% in the group treated with Perjeta in combination with TCH. No patients in the group treated with Perjeta plus Herceptin and FEC followed by Perjeta plus Herceptin 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 AC followed by Perjeta plus Herceptin and paclitaxel and none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by Perjeta in combination with Herceptin and docetaxel. The incidence of asymptomatic LVD (PT ejection fraction decrease according to NCI-CTCAE v.4) was 7% in the group treated with dose dense AC followed by Perjeta plus

Herceptin and paclitaxel and 3.5% in the group treated with FEC followed by Perjeta plus Herceptin and docetaxel.

In APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10%-points from baseline and to < 50% was < 1% (0.6% of Perjeta-treated patients vs 0.2% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 46.7% of Perjeta-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 Perjeta-treated patients and 2.8% of placebo-treated patients, of whom 79.7% of Perjeta-treated patients and 80.6% of placebo-treated patients had recovered at the data cutoff.

##### Infusion-related reaction

An infusion-related reaction was defined in the pivotal trials as any event reported as hypersensitivity, anaphylactic reaction, acute infusion reaction or cytokine release syndrome occurring during an infusion or on the same day as the infusion. In CLEOPATRA, the initial dose of Perjeta was given the day before Herceptin and docetaxel to allow for the examination of Perjeta associated reactions. On the first day when only Perjeta was administered, the overall frequency of infusion-related reactions was 9.8% in the placebo-treated group and 13.2% in the Perjeta-treated group, with the majority of reactions being mild or moderate. The most common infusion-related reactions (≥ 1.0%) in the Perjeta-treated group were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting.

During the second cycle when all drugs were administered on the same day, the most common infusion related reactions (≥ 1.0%) in the Perjeta-treated group were fatigue, drug hypersensitivity, dysgeusia, hypersensitivity, myalgia, and vomiting (see 2.4 Warnings & Precautions).

In neoadjuvant and adjuvant trials, Perjeta was administered on the same day as the other study treatment drugs. Infusion-related reactions occurred in 18.6% - 25.0% of patients on the first day of Perjeta administration (in combination with Herceptin and chemotherapy). The type and severity of events were consistent with those observed in CLEOPATRA, with a majority of reactions being mild or moderate.

##### Hypersensitivity/anaphylaxis

In CLEOPATRA, the overall frequency of hypersensitivity/anaphylaxis reported events was 9.3% in the placebo-treated patients and 11.3% in the Perjeta-treated patients, of which 2.5% and 2.0% were NCI-CTCAE (version 3) grade 3-4, respectively. Overall, 2 patients in placebo-treated group and 4 patients in the Perjeta-treated group experienced anaphylaxis (see 2.4 Warnings & Precautions).

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

In neoadjuvant and adjuvant trials, hypersensitivity/anaphylaxis events were consistent with those observed in CLEOPATRA. In NEOSPHERE, two patients in the Perjeta and docetaxel-treated group experienced anaphylaxis. In both TRYPHAENA and APHINITY, the overall frequency of hypersensitivity/anaphylaxis was highest in the Perjeta 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.

##### Laboratory Abnormalities

In the pivotal trials CLEOPATRA, NEOSPHERE, and APHINITY the incidence of NCI-CTCAE Grade 3-4 decreases in neutrophil counts were balanced in the Perjeta-treated and control groups.

##### Switching treatment from intravenous Perjeta and Herceptin to Phesgo (or vice versa)

Switching from intravenous Perjeta and Herceptin to Phesgo (or vice versa) was well tolerated by patients and did not reveal any new or clinically relevant safety concerns and the adverse events experienced were in line with those reported in FEDERICA and in previous studies using intravenous Perjeta and Herceptin administration (see section 3.1.2 Clinical / Efficacy Studies).

#### 2.6.2 Postmarketing Experience

Not applicable

#### 2.7 OVERDOSE

There is no experience with overdose of Phesgo in human clinical trials. The highest Phesgo dose tested is 1200 mg Perjeta/600 mg Herceptin. In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

#### 2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No formal drug-drug interaction studies have been performed.

##### Intravenous Perjeta

A sub-study in 37 patients in the pivotal trial CLEOPATRA showed no evidence of drug-drug interaction between Perjeta and Herceptin and between Perjeta and docetaxel. In addition, no clinically relevant pharmacokinetic interaction of co-administered docetaxel or Herceptin on Perjeta was evident, based on the population pharmacokinetics analysis. This lack of drug-drug interaction was confirmed by pharmacokinetic data from the NEOSPHERE and APHINITY studies.

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

##### Intravenous Herceptin

There have been no formal drug interaction studies performed with Herceptin in humans. Clinically significant interactions between Herceptin and the concomitant medications used in clinical trials have not been observed.

In studies where Herceptin was administered in combination with docetaxel, carboplatin, or anastrozole, the pharmacokinetics of these medications was not altered nor was the pharmacokinetics of Herceptin altered.

Concentrations of paclitaxel and doxorubicin (and their major metabolites 6- $\alpha$  hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) were not altered in the presence of Herceptin. However, Herceptin may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite is unclear. No changes were observed in Herceptin concentrations in the presence of paclitaxel and doxorubicin.

The results of a drug interaction substudy evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without Herceptin suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus Herceptin. However, capecitabine itself showed higher concentrations and a longer half-life when combined with Herceptin. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus Herceptin.

### 3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

#### 3.1 PHARMACODYNAMIC PROPERTIES

##### 3.1.1 Mechanism of Action

Perjeta and Herceptin are recombinant humanized immunoglobulin (Ig)G1 $\kappa$  monoclonal antibodies, which target the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Perjeta and Herceptin bind to distinct HER2 epitopes, subdomains II and IV, respectively, without competing and have complementary mechanisms for disrupting HER2 signaling. This results in augmented anti-proliferative activity *in vitro* and *in vivo* when Perjeta and Herceptin are given in combination.

Additionally, the Fc portion of both their IgG1 framework provides for potent activation of antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, both Perjeta and

Herceptin ADCC are exerted preferentially on HER2-overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

### 3.1.2 Clinical / Efficacy Studies

This section presents the clinical experience from Phesgo and intravenous Perjeta in combination with Herceptin patients with HER2-positive early and metastatic breast cancer. HER2 overexpression in all trials outlined below was determined at a central laboratory and defined as a score of 3+ by IHC or an ISH amplification ratio  $\geq 2.0$ .

#### Early Breast Cancer

##### Fixed-dose combination of Perjeta and Herceptin [Phesgo]

##### FEDERICA WO40324

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

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

Following surgery, patients continued therapy with Phesgo or intravenous Perjeta and Herceptin as treated prior to surgery, for an additional 14 cycles, to complete 18 cycles of HER2-targeted therapy. Patients also received adjuvant radiotherapy and endocrine therapy as per local practice. In the adjuvant setting, substitution of intravenous Herceptin for subcutaneous Herceptin SC was permitted at investigator discretion. HER2-targeted therapy was administered every 3 weeks according to Table 4 as follows:

**Table 4 Dosing and administration of Phesgo, intravenous Perjeta, intravenous Herceptin, and subcutaneous Herceptin**

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

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

Non-inferiority of the Perjeta and Herceptin exposure from Phesgo was demonstrated (see 3.2 Pharmacokinetic properties). The analysis of secondary efficacy endpoint, tpCR, defined as an absence of invasive disease in the breast and axilla (ypT0/is, ypN0), is shown in Table 5.

**Table 5 Summary of total pathological Complete Response (tpCR)**

	Phesgo (n=248)	Intravenous Perjeta + Herceptin (n=252)
tpCR (ypT0/is, ypN0)	148 (59.7%)	150 (59.5%)
Exact 95% CI for tpCR Rate <sup>1</sup>	(53.28, 65.84)	(53.18, 65.64)
Difference in tpCR rate (SC minus IV arm)	0.15	
95% CI for the difference in tpCR <sup>2</sup> rate	-8.67 to 8.97	

<sup>1</sup> Confidence interval for one sample binomial using Pearson-Clopper method

<sup>2</sup> Hauck-Anderson continuity correction has been used in this calculation

#### Intravenous Perjeta and Herceptin

##### Neoadjuvant Treatment

##### NEOSPHERE (WO20697)

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

Perjeta and Herceptin were administered intravenously as outlined in Table 4 for 4 cycles. Following surgery all patients received three cycles of 5-Fluorouracil (600 mg/m<sup>2</sup>), epirubicin (90 mg/m<sup>2</sup>), cyclophosphamide (600 mg/m<sup>2</sup>) (FEC) given intravenously every three weeks and Herceptin administered intravenously every three weeks to complete one year of therapy. Patients in the Perjeta plus Herceptin and docetaxel arm received docetaxel every three weeks for four cycles prior to FEC after surgery so that all patients received equivalent cumulative doses of the chemotherapeutic agents and Herceptin.

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

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

The efficacy results are summarized in Table 6. A statistically significant and clinically meaningful improvement in pCR rate (ypT0/is) was observed in patients receiving Perjeta plus Herceptin and docetaxel compared to patients receiving Herceptin and docetaxel (45.8% vs 29.0%, p value = 0.0141). A consistent pattern of results was observed regardless of pCR definition.

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

##### TRYPHAENA (BO22280)

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

Perjeta and Herceptin were administered intravenously as outlined in Table 4. 5-Fluorouracil (500 mg/m<sup>2</sup>), epirubicin (100 mg/m<sup>2</sup>), cyclophosphamide (600 mg/m<sup>2</sup>) were given intravenously every three weeks for 3 cycles. Docetaxel was given as an initial dose of 75 mg/m<sup>2</sup> IV infusion every three weeks with the option to escalate to 100 mg/m<sup>2</sup> at the investigator's discretion if the initial dose was well tolerated. However, in the Perjeta in combination with TCH arm, docetaxel was given intravenously at 75 mg/m<sup>2</sup> and no escalation was permitted and carboplatin (AUC 6) was given intravenously every three weeks. Following surgery all patients received Herceptin to complete one year of therapy, which was administered intravenously every 3 weeks.

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study (see 2.6 Undesirable Effects). Secondary efficacy endpoints were pCR rate in the breast (ypT0/is), DFS, PFS and OS.

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

High pCR rates were observed in all 3 treatment arms (see Table 6). A consistent pattern of results was observed regardless of pCR definition. pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors (46.2% to 50.0% and 65.0% to 83.8% respectively).

**Table 6 NEOSPHERE (WO20697) and TRYPHAENA (BO22280): Summary of Efficacy (ITT population)**

Parameter	NEOSPHERE (WO20697)				TRYPHAENA (BO22280)		
	T+D N=107	Ptz+T+D N=107	Ptz+T N=107	Ptz+D N=96	Ptz+T+D N=73	FEC/ Ptz+T+D N=75	Ptz+TCH N=77
ypT0/is n (%) [95% CI] <sup>1</sup>	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 <sup>2</sup> [95% CI] <sup>3</sup>		+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) <sup>4</sup>		0.0141 (vs. T+D)	0.0198 (vs. T+D)	0.0030 (vs. Ptz+T+D)	NA	NA	NA
ypT0/is N0 n (%) [95% CI]	23 (21.5%) [14.1; 30.5]	42 (39.3%) [30.3; 49.2]	12 (11.2%) [5.9; 18.8]	17 (17.7%) [10.7; 26.8]	41 (56.2%) [44.1; 67.8]	41 (54.7%) [42.7; 66.2]	49 (63.6%) [51.9; 74.3]
ypT0 N0 n (%) [95% CI]	13 (12.1%) [6.6; 19.9]	35 (32.7%) [24.0; 42.5]	6 (5.6%) [2.1; 11.8]	13 (13.2%) [7.4; 22.0]	37 (50.7%) [38.7; 62.6]	34 (45.3%) [33.8; 57.3]	40 (51.9%) [40.3; 63.5]
Clinical Response <sup>5</sup>	79 (79.8%)	89 (88.1%)	69 (67.6%)	65 (71.4%)	67 (91.8%)	71 (94.7%)	69 (89.6%)

**Key to abbreviations (Table 6):** T: Herceptin; D: docetaxel; Ptz: Perjeta; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; TCH: docetaxel, carboplatin and Herceptin.

- 95% CI for one sample binomial using Pearson-Clopper method.
- Treatment Ptz+T+D and Ptz+T are compared with T+D, while Ptz+D is compared with Ptz+T+D.
- Approximate 95% CI for difference of two rates using Hauck-Anderson method.
- p-value from Cochran-Mantel-Haenszel test, with Simes multiplicity adjustment.
- 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, multicenter, multinational, Phase II trial conducted in 401 patients with HER2-positive locally advanced, inflammatory, or early-stage HER2-positive breast cancer.

The BERENICE study included two parallel groups of patients. Patients considered suitable for neoadjuvant treatment with Herceptin plus anthracycline/taxane-based chemotherapy were allocated to receive one of the two following regimens prior to surgery as follows:

Cohort A - 4 cycles of two-weekly doxorubicin and cyclophosphamide (dose dense AC) followed by 4 cycles of Perjeta in combination with Herceptin and paclitaxel

Cohort B - 4 cycles of FEC followed by 4 cycles of Perjeta in combination with Herceptin and docetaxel.

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

The primary endpoint of this study was cardiac safety during the neoadjuvant treatment period of the study (see 2.6 Undesirable Effects). Key secondary endpoints at the time of primary analysis were neoadjuvant safety and pCR rate in the breast and nodes (i.e. ypT0/is ypN0). Long-term clinical and safety outcomes will also be assessed (IDFS, EFS and OS, not yet available).

Demographics of the patients were well balanced between the groups. The median age of the patients was 49 years, the majority of patients were Caucasian (83%) and all but one patient was female. Approximately two-thirds of patients (64.3% [n = 128] in Cohort A and 61.7% [n = 124] in Cohort B) had hormone receptor-positive disease.

High pCR rates were observed in both treatment arms, with pCR (ypT0/is ypN0) rates of 61.8% in Cohort A and 60.7% in Cohort B. A consistent pattern of results was observed regardless of pCR definition. pCR rates were lower in the subgroup of patients with hormone receptor-positive tumors than in patients with hormone receptor-negative tumors in both Cohorts (51.6% to 81.5% and 57.3% to 68.0% respectively).

#### Adjuvant Treatment

##### APHINITY (BO25126)

APHINITY is a multicenter, randomized, double-blind, placebo-controlled Phase III trial conducted in 4804 patients with HER2-positive early breast cancer who had their primary tumor excised prior to randomization. Patients were then randomized to receive Perjeta or placebo, in combination with adjuvant Herceptin and chemotherapy. Investigators selected one of the following anthracycline-based or non-anthracycline-based chemotherapy regimens for individual patients:

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

Perjeta and Herceptin were administered intravenously as outlined in Table 4 starting on Day 1 of the first taxane-containing cycle, for a total of 52 weeks (maximum 18 cycles) or until recurrence, withdrawal of consent or unmanageable toxicity. Standard doses of 5-fluorouracil, epirubicin, doxorubicin, cyclophosphamide, docetaxel, paclitaxel and carboplatin were administered. After completion of chemotherapy, patients received radiotherapy and/or hormone therapy as per local clinical standard.

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

Demographics were 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 to 45.4 months, the APHINITY study demonstrated 19% (hazard ratio [HR] = 0.81) reduction in risk of recurrence or death in patients randomized to receive Perjeta compared with patients randomized to receive placebo.

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

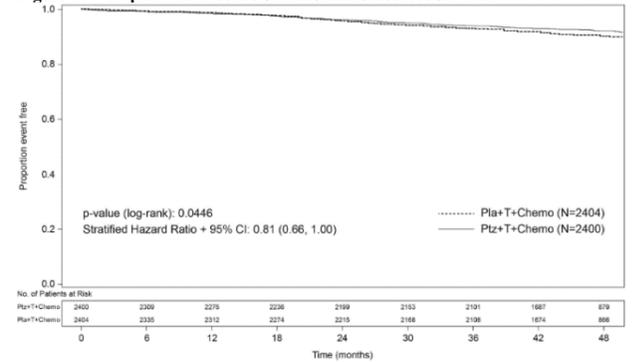
**Table 7 Overall Efficacy (ITT Population)**

	Perjeta + Herceptin + chemotherapy N=2400	Placebo + Herceptin + chemotherapy N=2404
<b>Primary Endpoint</b>		
<b>Invasive Disease Free Survival (IDFS)</b>		
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 <sup>2</sup> )	0.0446	
3 year event-free rate <sup>3</sup> [95% CI]	94.1 [93.1, 95.0]	93.2 [92.2, 94.3]
<b>Secondary Endpoints<sup>1</sup></b>		
<b>IDFS including second primary non-breast cancer</b>		
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 <sup>2</sup> )	0.0430	
3 year event-free rate <sup>3</sup> [95% CI]	93.5 [92.5, 94.5]	92.5 [91.4, 93.6]
<b>Disease Free Survival (DFS)</b>		
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 <sup>2</sup> )	0.0327	
3 year event-free rate <sup>3</sup> [95% CI]	93.4 [92.4, 94.4]	92.3 [91.2, 93.4]
<b>Overall Survival (OS)<sup>4</sup></b>		
Number (%) of patients with event	80 (3.3%)	89 (3.7%)
HR [95% CI]	0.89 [0.66, 1.21]	
p-value (Log-Rank test, stratified <sup>2</sup> )	0.4673	
3 year event-free rate <sup>3</sup> [95% CI]	97.7 [97.0, 98.3]	97.7 [97.1, 98.3]
<b>Recurrence Free Interval (RFI)</b>		
Number (%) of patients with event	138 (5.8%)	173 (7.2%)
HR [95% CI]	0.79 [0.63, 0.99]	
p-value (Log-Rank test, stratified <sup>2</sup> )	0.0430	
3 year event-free rate <sup>3</sup> [95% CI]	95.2 [94.3, 96.1]	94.3 [93.3, 95.2]
<b>Distant recurrence-free interval (DRFI)</b>		
Number (%) of patients with event	119 (5.0%)	145 (6.0%)
HR [95% CI]	0.82 [0.64, 1.04]	
p-value (Log-Rank test, stratified <sup>2</sup> )	0.1007	
3 year event-free rate <sup>3</sup> [95% CI]	95.7 [94.9, 96.5]	95.1 [94.3, 96.0]

**Key to abbreviations (Table 7):** ITT: Intent-to-treat; HR: Hazard Ratio; CI: Confidence Interval

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

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



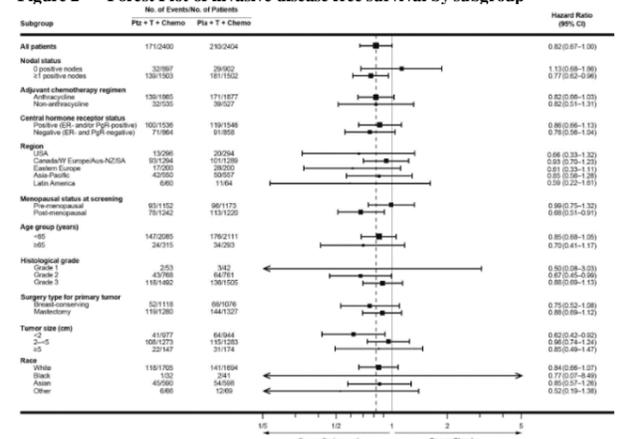
Pla = placebo; Ptz = Perjeta; T = Herceptin

The estimate of IDFS at 4-years was 92.3% in the Perjeta-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

Consistent results were observed across the majority of pre-specified patient subgroups. The benefits of Perjeta were more apparent for patients in certain high risk groups, notably patients with node-positive or hormone receptor-negative disease (see Figure 2 below).

**Figure 2 Forest Plot of invasive disease free survival by subgroup**



Pla = placebo; Ptz = Perjeta; T = Herceptin

Estimates of IDFS rates in the node positive subgroup were 92.0% versus 90.2% at 3 years and 89.9% versus 86.7% at 4 years in Perjeta-treated patients versus the placebo-treated patients, respectively. In the 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 Perjeta-treated patients versus placebo-treated patients, respectively.

In the hormone receptor-positive subgroup estimates of IDFS were 94.8% versus 94.4% at 3 years and 93.0% versus 91.6% at 4 years in Perjeta-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 Perjeta-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 diarrhea 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 Perjeta-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 Perjeta-arm and -10.2 (95% CI -11.1, -9.2) in the placebo arm. Change in diarrhea symptoms increased to +22.3 (95% CI 21.0, 23.6) in the Perjeta-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. Diarrhea symptoms returned to baseline after HER2 therapy in the Perjeta-arm. The addition of Perjeta to Herceptin plus chemotherapy did not affect patients' overall role function over the course of the study.

### Metastatic Breast Cancer

#### CLEOPATRA (WO20698)

CLEOPATRA is a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial conducted in 808 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. Patients were randomized 1:1 to receive placebo plus Herceptin and docetaxel (placebo-treated) or Perjeta plus Herceptin and docetaxel (Perjeta-treated). Randomization was stratified by prior treatment status (de novo or prior adjuvant / neoadjuvant therapy) and geographic region (Europe, North America, South America and Asia). Patients with prior adjuvant or neoadjuvant therapy were required to have a disease-free interval of at least 12 months before enrollment into the trial.

Perjeta and Herceptin were administered intravenously as outlined in Table 4. Patients were treated with Perjeta and Herceptin until disease progression, withdrawal of consent or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m<sup>2</sup> IV infusion every 3 weeks for at least 6 cycles. The dose of docetaxel could be escalated to 100 mg/m<sup>2</sup> at the investigator's discretion if the initial dose was well tolerated.

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

The primary endpoint of the study was progression-free survival (PFS) as assessed by an independent review facility (IRF) and defined as the time from the date of randomization to the date of disease progression or death (from any cause) if the death occurred within 18 weeks of the last tumor 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 QoL questionnaire.

Demographics were well balanced (median age was 54 years old, the majority were Caucasian (59%) and all were female with the exception of 2 patients). Approximately half the patients in each treatment group had hormone receptor-positive disease (defined as estrogen receptor [ER] positive and/or progesterone receptor [PgR] positive) and approximately half of the patients in each treatment group had received prior adjuvant or neo-adjuvant therapy (192 patients [47.3%] in the placebo-treated group vs 184 patients [45.8%] Perjeta-treated group). At the time of the primary progression-free survival analysis, a total of 242 patients (59%) in the placebo-treated group and 191 patients (47.5%) in the Perjeta-treated group had IRF-confirmed progressive disease or had died within 18 weeks of their last tumor assessment.

At the time of the primary analysis the CLEOPATRA study demonstrated a statistically significant improvement in IRF-assessed PFS (hazard ratio [HR] = 0.62, 95% CI = 0.51, 0.75, p<0.0001) in the Perjeta-treated group compared with the placebo-treated group, and an increase in median PFS of 6.1 months (median PFS of 12.4 months in the placebo-treated group vs 18.5 months in the Perjeta-treated group) (see Figure 3). The results for investigator-assessed PFS were comparable to those observed for IRF-assessed PFS (median PFS was 12.4 months for placebo vs 18.5 months for Perjeta) (see Table 8). 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 4).

The efficacy results from the CLEOPATRA trial are summarized in Table 8 below.

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

Parameter	Placebo + Herceptin + docetaxel n=406	Perjeta + Herceptin + docetaxel n=402	HR (95% CI)	p-value
<b>Primary Endpoint</b>				
<b>Progression-Free Survival (IRF review)</b>				
No. of patients with an event	242 (59%)	191 (47.5%)	0.62 [0.51;0.75]	<0.0001
Median months	12.4	18.5		
<b>Secondary Endpoints</b>				
<b>Overall Survival (Final analysis of OS)</b>				
No. of patients with an event*	221 (54.4%)	168 (41.8%)	0.68 [0.56;0.84]	0.0002
Median months	40.8	56.5		
<b>Progression-Free Survival (investigator assessment)</b>				
No. of patients with an event	250 (61.6%)	201 (50.0%)	0.65 [0.54;0.78]	<0.0001
Median months	12.4	18.5		
<b>Objective Response Rate (ORR)</b>				
No. of patients with an event	336	343	Difference in ORR: 10.8% [4.2;17.5%]	0.0011
Responders**	233 (69.3%) [64.1; 74.2]	275 (80.2%) [75.6; 84.3]		
95% CI for ORR	14 (4.2%)	19 (5.5%)		
Complete response (CR)	219 (65.2%)	256 (74.6%)		
Partial Response (PR)	70 (20.8%)	50 (14.6%)		
Stable disease (SD)	28 (8.3%)	13 (3.8%)		
Progressive disease (PD)				
<b>Duration of Response ^</b>				
n=	233	275		
Median weeks	54.1	87.6		
95% CI for Median	[46;64]	[71;106]		

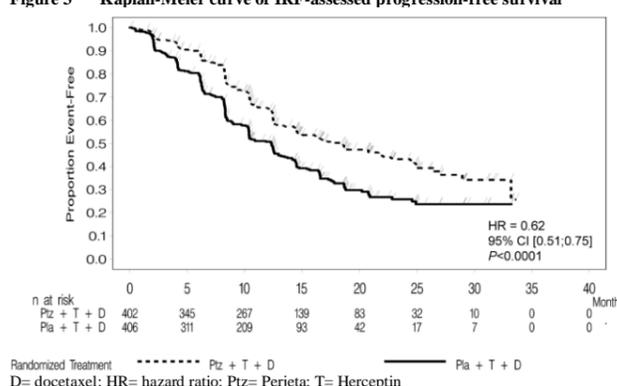
\*Final analysis of overall survival, cutoff date 11 Feb 2014

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

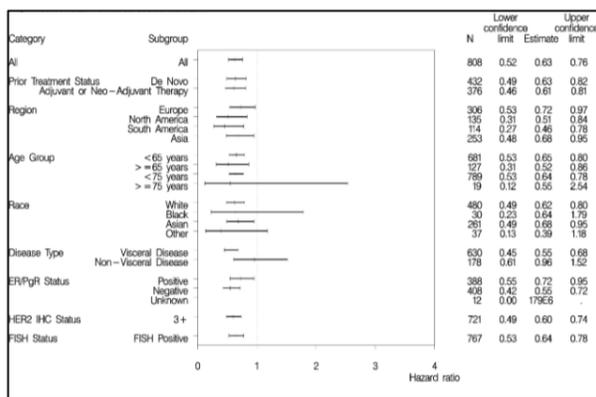
^ Evaluated in Patients with Best Overall Response of CR or PR

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

**Figure 3 Kaplan-Meier curve of IRF-assessed progression-free survival**



**Figure 4 IRF assessed PFS by patient subgroup**

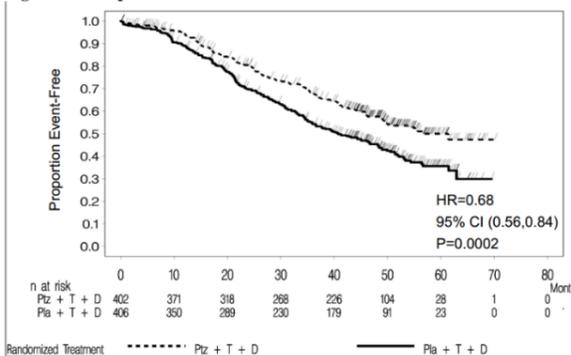


At the primary analysis of efficacy, an interim analysis of OS showed a strong trend suggestive of a survival benefit in favor of the Perjeta-treated group.

An interim analysis of OS performed one year after the primary analysis of efficacy, demonstrated a statistically significant OS benefit in favor of the Perjeta-treated group (HR 0.66, p = 0.0008 log-rank test). The median time to death was 37.6 months in the placebo-treated group but had not yet been reached in the Perjeta-treated group.

The final analysis of OS was performed when 389 patients had died (221 in the placebo-treated group and 168 in the Perjeta-treated group). The statistically significant OS benefit in favor of the Perjeta-treated group 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 Perjeta-treated group (see Table 8, Figure 5).

**Figure 5 Kaplan-Meier curve of overall survival**



D= docetaxel; HR= hazard ratio; Ptz= Perjeta; T= Herceptin

There was no statistically significant difference between treatment groups in Health Related Quality of Life as assessed by time to symptom progression on the FACTB TOI-PFB subscale, defined as a 5 point reduction in subscale score (HR =0.97, 95% CI =0.81; 1.16). In an exploratory analysis, patients treated with Perjeta in combination with Herceptin and docetaxel experienced a lower risk of symptom progression on the FACT-B breast cancer subscale (defined as a 2 point reduction in subscale score) compared to those treated with Herceptin and docetaxel alone (HR =0.78, 95% CI =0.65; 0.94).

#### PHranceSCa (MO40628)

Study MO40628 investigated the safety of switching from intravenous Perjeta and Herceptin to Phesgo (and vice versa) with a primary objective to evaluate patient preference for Phesgo. A total of 160 patients included in this 2-arm, cross-over study: 80 patients were randomized to Arm A (3 cycles of intravenous Perjeta and Herceptin followed by 3 cycles of Phesgo) and 80 patients were randomized to Arm B (3 cycles of Phesgo followed by 3 cycles intravenous Perjeta and Herceptin). After that, patients could choose to continue their treatment with intravenous Perjeta and Herceptin or with Phesgo to complete a total of 18 cycles of HER2 targeted therapy.

At primary analysis, 136 out of 160 patients (85%) reported preferring subcutaneous administration of Phesgo over intravenous Perjeta and Herceptin and the most common reason was that administration required less time in the clinic. 22 out of 160 patients (14%) reported preferring intravenous Perjeta and Herceptin over Phesgo and the most common reason was feels more comfortable during administration. Two out of 160 patients (1%) had no preference for the route of administration.

Among the patients in Arm A, the incidence of AEs was similar when switching from intravenous Perjeta and Herceptin to Phesgo. Within Arm A, the incidence of AEs during Cycles 1-3 (IV) was 77.5% compared to Cycles 4-6 (SC) which was 72.5%. Within Arm B, the incidence of AEs during Cycles 1-3 (SC) was 77.5% compared to Cycles 4-6 (IV) which was 63.8%. The total number of events was higher during Cycles 1-3 compared to Cycles 4-6, regardless of treatment administered.

#### 3.1.3 Immunogenicity

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

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

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

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

### 3.2 PHARMACOKINETIC PROPERTIES

Perjeta and Herceptin exposure following subcutaneous administration of Phesgo (1200 mg Perjeta/600 mg Herceptin loading dose followed by 600 mg Perjeta/600 mg Herceptin every 3 weeks) in the FEDERICA study is shown in Table 4. The pharmacokinetic (PK) results for the primary endpoint of Perjeta Cycle 7 C<sub>trough</sub> (i.e., pre-dose cycle 8), showed non-inferiority of Perjeta within Phesgo (geometric mean 88.7 mcg/mL) compared to intravenous Perjeta (geometric mean 72.4 mcg/mL) with a geometric mean ratio of 1.22 (90% CI: 1.14–1.31). The lower boundary of the two-sided 90% confidence interval for the geometric mean ratio of Perjeta within Phesgo and intravenous Perjeta was 1.14, i.e., greater than the predefined margin of 0.8.

The PK results for the secondary endpoint, Herceptin Cycle 7 C<sub>trough</sub> (i.e., predose Cycle 8), showed non-inferiority of Herceptin within Phesgo (geometric mean 57.5 mcg/mL) compared to intravenous Herceptin (geometric mean 43.2 mcg/mL) with a geometric mean ratio of 1.33 (90% CI: 1.24–1.43).

A population PK model of Perjeta with linear elimination from the central compartment was constructed using pooled Perjeta within Phesgo and intravenous Perjeta PK data from FEDERICA to describe the observed Perjeta PK concentrations following subcutaneous Phesgo administration and intravenous Perjeta administration.

A population PK model with parallel linear and nonlinear elimination from the central compartment was constructed using pooled Herceptin PK data from the phase III study BO22227 (Hannah) of subcutaneous Herceptin vs. intravenous Herceptin, to describe the observed PK concentrations following intravenous Herceptin or subcutaneous Herceptin administration in HER2 positive EBC patients. The PK analysis using the

HANNAH population PK model demonstrated that there was no impact on the PK of Herceptin within Phesgo from Perjeta within Phesgo as consistent PK were observed between Herceptin within Phesgo and subcutaneous Herceptin.

The population PK predicted Perjeta and Herceptin exposures are summarized in Table 9 below.

**Table 9 Perjeta and Herceptin exposure (median with 5th-95th Percentiles) following subcutaneous administration of Phesgo or intravenous Perjeta or Herceptin<sup>a</sup>**

Parameter	Perjeta within Phesgo	Intravenous Perjeta	Herceptin within Phesgo <sup>b</sup>	Intravenous Herceptin <sup>b</sup>
C <sub>trough</sub> (mcg/mL)	Cycle 5 (48.7 – 122.5)	74.9 (47.8 – 99.8)	27.7 (13.6 – 43.2)	31.4 (21.1 – 50.9)
	Cycle 7 (51.8 – 142.5)	78.5 (41.3 – 114.9)	57.5 (27.2 – 92.7)	44.9 (29.7 – 76.2)
C <sub>max</sub> (mcg/mL)	Cycle 5 (62.9 – 152.6)	304.8 (191.1 – 409.7)	44.6 (31.0 – 63.1)	172.9 (133.7 – 238.9)
	Cycle 7 (88.5 – 218.5)	225.9 (158.5 – 301.8)	117.3 (72.2 – 166.6)	169.1 (130.6 – 238.9)
AUC <sub>0-21 days</sub> (mcg/mL·day)	Cycle 5 (1388.4 – 3376.2)	2519.7 (1898.4 – 3138.9)	1023.8 (634.3 – 1442.6)	1341.0 (1033.1 – 2029.0)
	Cycle 7 (1487.4 – 3786.1)	2454.3 (1561.4 – 3346.1)	1838.7 (1024.3 – 2715.5)	1668.6 (1264.7 – 2576.9)

<sup>a</sup>first dose of Phesgo, intravenous Perjeta and Herceptin administered at Cycle 5;

<sup>b</sup>Study BO22227 Hannah population PK model used for Herceptin PK simulation

#### 3.2.1 Absorption

The median maximum serum concentration (C<sub>max</sub>) of Perjeta within Phesgo and time to maximal concentration (T<sub>max</sub>) were 157 ug/mL and 3.82 days, respectively. Based on population PK analysis, the absolute bioavailability was 0.712 and the first-order absorption rate (K<sub>a</sub>) is 0.348 (1/day).

The median maximum serum concentration (C<sub>max</sub>) of Herceptin within Phesgo and time to maximal concentration (T<sub>max</sub>) were 114 ug/mL and 3.84 days, respectively. Based on population PK analysis, the absolute bioavailability was 0.771 and the first-order absorption rate (K<sub>a</sub>) is 0.404 (1/day).

#### 3.2.2 Distribution

Based on population PK analysis, the volume of distribution of the central (V<sub>c</sub>) compartment of Perjeta within Phesgo in the typical patient, was 2.77 L.

Based on population PK analysis, the volume of distribution of the central (V<sub>c</sub>) compartment of subcutaneous Herceptin in the typical patient, was 2.91 L.

#### 3.2.3 Metabolism

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

#### 3.2.4 Elimination

Based on population pharmacokinetic (PK) analysis, the clearance of Perjeta within Phesgo was 0.163 L/day and the elimination half-life (t<sub>1/2</sub>) was approximately 24.3 days.

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

### Pharmacokinetics in Special Populations

#### Pediatric Population

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

#### Geriatric Population

No studies have been conducted to investigate the pharmacokinetics of Phesgo in geriatric patients.

In population PK analyses of Perjeta within Phesgo and intravenous Perjeta, age was not found to significantly affect PK of Perjeta.

In population PK analyses of subcutaneous or intravenous Herceptin, age has been shown to have no effect on the disposition of Herceptin.

#### Renal impairment

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

Based on population PK analyses of Perjeta within Phesgo and intravenous Perjeta, renal impairment was shown not to affect Perjeta exposure; however, only limited data from patients with severe renal impairment were included in population PK analyses.

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

#### Hepatic impairment

No formal pharmacokinetic study of Phesgo has been conducted in patients with hepatic impairment.

### 3.3 NONCLINICAL SAFETY

No dedicated studies were conducted with the combination of subcutaneous Perjeta, Herceptin, and vorhyaluronidase alfa.

#### Subcutaneous and Intravenous Perjeta and Herceptin

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

#### Intravenous Herceptin

##### Lactation

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

#### 3.3.1 Carcinogenicity

No carcinogenicity studies have been performed to establish the carcinogenic potential of Perjeta or Herceptin within Phesgo.

#### 3.3.2 Genotoxicity

No studies have not been performed to evaluate the mutagenic potential of Perjeta or Herceptin within Phesgo.

#### 3.3.3 Impairment of Fertility

##### Intravenous Perjeta

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

##### Intravenous Herceptin

Reproduction studies of female fertility have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg intravenous Herceptin and have revealed no evidence of impaired fertility.

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

### 3.3.4 Reproductive toxicity

#### Intravenous Perjeta

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..

#### Intravenous Herceptin

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg intravenous Herceptin and have revealed no evidence of harm to the fetus. Placental transfer of Herceptin during the early (days 20 - 50 of gestation) and late (days 120 - 150 of gestation) fetal development period was observed.

### 3.3.5 Other

#### Subcutaneous Herceptin

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

## 4. PHARMACEUTICAL PARTICULARS

### 4.1 STORAGE

#### Vials

Store at 2°C-8°C.

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

Do not freeze.

#### Shelf life

As registered locally

This medicine should not be used after the expiry date (EXP) shown on the pack.

### 4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

The 1200 mg Perjeta/600 mg Herceptin and 600 mg Perjeta/600 mg Herceptin solution are ready to use solutions for injection which does not need to be mixed with other drugs or diluted.

Phesgo should be inspected visually to ensure there is no particulate matter or discolouration prior to administration. Do not shake.

Phesgo solution for injection is for single use only and should be prepared by a healthcare professional using aseptic technique.

From a microbiological point of view, the medicine should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial-preservative. If not used immediately, preparation should take place in controlled and validated aseptic conditions. Once transferred from the vial to the syringe, the medicinal product is physically and chemically stable for 28 days at 2°C - 8°C or 24 hours at 9°C - 30°C.

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

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

#### Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

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

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

### 4.3 PACKS

Vial containing 1200 mg Perjeta/600 mg Herceptin/15 mL

1

Vial containing 600 mg Perjeta/600 mg Herceptin/10 mL

1

#### Medicine: keep out of reach of children

Current at May 2021



F. Hoffmann-La Roche Ltd, Basel, Switzerland