12 November 2020
EMA/CHMP/646782/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Phesgo

International non-proprietary name: pertuzumab / trastuzumab

Procedure No. EMEA/H/C/005386/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Phesgo
Applicant:	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen GERMANY
Active substance:	PERTUZUMAB / TRASTUZUMAB
International Non-proprietary Name/Common Name:	pertuzumab / trastuzumab
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agents, monoclonal antibodies (L01XY02)
Therapeutic indication(s):	Early breast cancer (EBC): Phesgo is indicated for use in combination with chemotherapy in: • the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence (see section 5.1) • the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence (see section 5.1) Metastatic breast cancer (MBC): Phesgo is indicated for use in combination with docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.
Pharmaceutical form(s):	Solution for injection
Strength(s):	600 mg / 600 mg and 1200 mg / 600 mg

Route(s) of administration:	Subcutaneous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

2-AB HILIC-UHPLC	2-aminobenzamide hydrophilic interaction liquid chromatography-ultra-high-performance liquid chromatography
AC	doxorubicin plus cyclophosphamide
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
ARR	administration related reaction
AUC	area under the concentration-time curve
bpCR	breast pathological complete response
CCOD	clinical cutoff date
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
CFU	Colony-forming unit
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CPA	corrected peak area
CQA	critical quality attribute
C_{trough}	concentration at the end of a dosing interval
ddAC	dose dense doxorubicin plus cyclophosphamide
DRFI	Distant recurrence-free interval
EBC	early breast cancer
ECD	extracellular domain
EFS	event free survival
EFS-SPNBC	event free survival including second primary non-breast cancer
EMA	European Medicines Agency
ER	estrogen receptor
E-R	exposure-response
EU	endotoxin unit
FDA	U.S. Food and Drug Administration
FFA	free fatty acid
G2	glyocosylation species with two terminal galactose residues
GBG pCR	German Breast Group pathological complete response
GMR	geometric mean ratio
HC	heavy chain
HER2	human epidermal growth factor receptor 2
HMV	healthy male volunteer

HMW	high molecular weight
HPLC-ELSD	high-performance liquid chromatography-evaporative light scattering detection
iDFS	invasive disease-free survival
iDFS-SPNBC	invasive disease-free survival including second primary non-breast cancer
IE-HPLC	ion-exchange high-performance liquid chromatography
IPC	in-process control
IRR	injection related reaction
ITT	intention-to-treat
IV	Intravenous
LAL	limulus amebocyte lysate
LC	light chain
LMW	low molecular weight
LVEF	left ventricular ejection fraction
MA	marketing authorisation
MAA	marketing authorisation application
MAb	monoclonal antibody
MBC	metastatic breast cancer
Man5	mannose 5
MoA	mode of action
NGHC	non-glycosylated heavy chain
OS	overall survival
pCR	pathological complete response
PgR	progesterone receptor
P+H IV	Perjeta + Herceptin IV
PH FDC SC	pertuzumab and trastuzumab fixed-dose combination for subcutaneous administration
PK	pharmacokinetic
popPK	population pharmacokinetics
PPP	per protocol pharmacokinetics
Q3W	every 3 weeks
QW	once weekly
RMP	Risk Management Plan
SAE	serious adverse event
SC	subcutaneous
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety

SE-HPLC	size-exclusion high-performance liquid chromatography
tpCR	total pathological complete response
TTE	time-to-event
UV	ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 9 January 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Phesgo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 May 2019.

The applicant applied for the following indication:

Early breast cancer (EBC)

Phesgo is indicated for use in combination with chemotherapy in:

• the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence

• the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence

Metastatic breast cancer (MBC)

Phesgo is indicated for use in combination with docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination products

The application submitted is a fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant received the following Scientific Advice on the development relevant for the indication subject

to the present application:

Date	Reference	SAWP co-ordinators
13 October 2016	EMEA/H/SA/3415/1/2016/III	Dr Helgi Helgason, Prof. Brigitte Blöchl-Daum
21 April 2017	EMEA/H/SA/3415/2/2017/I	Prof. Dieter Deforce, Dr Jens Reinhardt
14 December 2017	EMEA/H/SA/3415/1/FU/1/2017/II	Prof. Dieter Deforce, Dr Joao Manuel Lopes de Oliveira

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP, on 13 October 2016 (EMEA/H/SA/3415/1/2016/III), 21 April 2017 (EMEA/H/SA/3415/2/2017/I) and 14 December 2017 (EMEA/H/SA/3415/1/FU/1/2017/II). The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:

- the approach to control the high molecular weights (HMW) in the fixed dose combination (FDC) as sum of HMW forms of pertuzumab and trastuzumab for release and during stability;
- the approach to control the low molecular weights (LMW) species in the FDC as sum of LMW forms of pertuzumab and trastuzumab for release and during stability;
- Suitability of a proposed method to control the potential critical quality attributes.
- the proposal to control the bioactivity of the FDC using two HER2 binding cell-free assays;
- Adequacy of nonclinical pharmacology, pharmacokinetic, and toxicology studies conducted to support the proposed clinical studies for the FDC;
- Adequacy of the Phase I development programme to support the proposed Phase III study for the FDC;
- Adequacy of the design of the Phase III study to support the comparability of the benefit-risk profile of the FDC to the single components, Perjeta + Herceptin IV formulations in breast cancer, including the choice of the primary and secondary endpoints, the selected patient populations, choice of control arm and chemotherapy backbone, the safety monitoring plan of the Phase III study;
- The proposed statistical analysis of the proposed Phase III study to show the comparability between the FDC and Perjeta IV + Herceptin IV;
- The proposed size of the safety database for the Phase III study to support the comparability of benefit-risk profile for the FDC to Perjeta and Herceptin IV;
- Whether the clinical development plan is adequate to support the approval of a new MAA for the FDC for the treatment of patients in both early and metastatic breast cancer;
- Whether the available PK and safety results of the Phase I study (BO30185) can support the selected FDC doses (co-formulation of pertuzumab, trastuzumab and rHuPH20) for the Phase III clinical study;
- the choice of the proposed Patient-Reported Outcome (PRO) measures in the phase III trial [Patient Preference Questionnaire (PPQ) and validated Therapy Administration Satisfaction Questionnaire IV/SC (TASQ IV/SC)] to assess patient preference and satisfaction with the route of administration and whether the satisfaction data can be included in the label.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Outi Mäki-Ikola

The application was received by the EMA on	9 January 2020
The procedure started on	30 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 April 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 April 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 May 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 May 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 July 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 October 2020
The CHMP agreed on a list of outstanding issues in writing and to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	28 October 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Phesgo on	12 November 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indications for pertuzumab plus trastuzumab fixed-dose combination for subcutaneous use (PH FDC SC) are the same as those approved for pertuzumab (Perjeta) in the EU, in combination with trastuzumab (Herceptin) and chemotherapy for HER2+ breast cancer.

When these agents are administered via IV infusions, they can be given in any order. Both antibodies are administered sequentially as an IV infusion over 60-90 minutes, respectively, for the loading dose and 30 minutes for the maintenance dose. Following the infusion, there is an observation time of approximately 30–60 minutes for Perjeta and 2–6 hours for Herceptin. The usage of IV MAbs with the observation time required after infusion has placed a strain on medical centres with respect to time and resources required to prepare and administer the infusion (De Cock et al, PLOS ONE 2016).

Additionally, the required procedure to establish IV access in a patient is considered invasive. HER2-targeted therapy is usually given for long periods of time: pertuzumab and trastuzumab treatment is recommended for 1 year in the approved indication in the adjuvant early breast cancer (EBC) setting in patients with high risk of recurrence. In metastatic breast cancer (MBC), they are administered as first-line therapy until disease progression, which may be for several years for some patients. These patients often require installation of a port under the skin which can be associated with increased risk of infection, thrombosis, discomfort and high cost (Shivakumar et al. JCO 2009; Poorter et al. EJC 1996).

2.1.2. Epidemiology and risk factors, screening tools/prevention

Breast cancer is the most common cancer among women in the world. In 2018, according to the prediction of the European Cancer Information System (ECIS), breast cancer continues to be the most common female cancer, with incidence in the European Union (EU-28) accounting for 29.2% of all cancers in women. In the EU-28 countries, a total of 404,920 new female breast cancer cases was estimated to occur in 2018 (Dafni, BC 2019).

Breast cancer represents a major Public Health concern due to its high morbidity and mortality rates, with EUROSTAT reporting that it accounted for 1.8% of all deaths in the EU-28 in 2015 and 3.6% (i.e., double) of deaths in women. Breast cancer was the leading cause of death from cancer in women (138,000; 16.2% of 850,000 cancer deaths) among 40 European countries in 2018, but it was reported as the second cause after lung cancer in the EU-28 (Dafni, BC 2019).

The most important risk factors include: genetic predisposition, exposure to oestrogens [endogenous and exogenous, including long-term hormone replacement therapy (HRT)], ionizing radiation, low parity, high breast density and a history of atypical hyperplasia. The Western-style diet, obesity and the consumption of alcohol also contribute to the rising incidence of breast cancer (McTiernan, Oncologist 2003; Cardoso, Ann Oncol 2018).

Prevalence is increasing, due to increased incidence and improvements in treatment outcomes. In most Western countries, the mortality rate has decreased in recent years, especially in younger age groups, because of improved treatment and earlier detection (Allemani, Lancet 2015).

Breast cancer in males is rare, contributing to 1% of cases. The major risk factors include clinical disorders carrying hormonal imbalances (especially gynaecomastia and cirrhosis), radiation exposure, a positive family history and genetic predisposition (Ottini, Crit Rev Oncol Hematol, 2010).

Early Breast Cancer is a curable disease. Metastatic Breast Cancer remains virtually an incurable disease with a median overall survival (OS) of 3 years and a 5-year survival of only 25% (Cardoso, 2019).

2.1.3. Biologic features

Breast cancer is a heterogeneous, phenotypically diverse disease composed of several biologic subtypes that have distinct behaviour. Amplification or overexpression of the human epidermal growth factor receptor 2 (HER2) oncogene is present in approximately 15 percent of primary invasive breast cancers (King, SCIENCE 1985).

HER2 overexpression was initially associated with high rates of disease recurrence and death in the absence of adjuvant systemic therapy. However, the value of this prognostic information in current clinical practice is questionable, particularly with the earlier use of HER2-directed agents in the neoadjuvant and adjuvant setting.

HER2 status provides predictive information used for selecting optimal treatment. Several HER2-targeted therapies, such as trastuzumab (Herceptin), pertuzumab (Perjeta), trastuzumab emtansine (T-DM1; Kadcyla), lapatinib (Tyverb), and neratinib (Nerlynx) were developed and have transformed the treatment of HER2-positive breast cancer.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

In countries with established breast cancer screening programmes, most patients present due to an abnormal mammogram. However, up to 15 percent of women are diagnosed with breast cancer due to the presence of a breast mass that is not detected on mammogram, and another 30 percent present with a breast mass in the interval between mammograms. In addition, women without access to screening mammograms and younger women under 40 years who may not be undergoing routine screening mammograms may present with a breast or axillary mass with or without skin changes.

The diagnosis of breast cancer requires histologic evaluation. There are various histologic types of breast carcinoma that differ in microscopic appearance and biologic behaviour. Based on gene expression profiles, the following molecular subtypes have been identified: luminal A and B, HER2-enriched and basal (most of them under the category of triple negative).

Breast cancer is staged using the American Joint Committee on Cancer and the International Union for Cancer Control classification system for Tumour, Nodes, and Metastases (TNM). The eighth edition of the TNM staging system, which was effective as of January 1, 2018, includes anatomic stage groups as well as prognostic stage groups, which incorporate biomarker testing. Tumour stage is the most important prognostic indicator for breast cancer.

2.1.5. Management

In general, patients with early-stage breast cancer undergo primary surgery (lumpectomy or mastectomy) to the breast and regional nodes with or without radiation therapy (RT).

Following definitive local treatment, adjuvant systemic therapy may be offered based on primary tumour characteristics, such as tumour size, grade, number of involved lymph nodes, the status of oestrogen (ER) and progesterone (PR) receptors, and expression of the human epidermal growth factor 2 (HER2) receptor.

However, some patients with early-stage breast cancer (particularly those with HER2-positive or triple-negative disease) may be treated with neoadjuvant therapy first, followed by surgery.

The introduction of anti-HER2 therapies for the treatment of patients with HER2-positive breast cancer has led to outstanding improvements of survival in both early and advanced settings (Pernas and Tolaney, 2019).

The addition of trastuzumab (Herceptin®) to standard therapy dramatically improved prognosis for patients with metastatic HER2-positive breast cancer and became a landmark in the treatment of these patients (Slamon et al, 2001). The subsequent addition of pertuzumab (Perjeta) to a taxane and trastuzumab combination compared with taxane and trastuzumab therapy alone as a first-line treatment in advanced HER2-positive breast cancer resulted in an improvement not only in PFS but also in OS by almost 16 months, reaching a median survival of nearly 5 years (CLEOPATRA trial, Swain et al, 2015).

In the early breast cancer (EBC) setting, the addition of pertuzumab to trastuzumab and chemotherapy has also proved efficacious, both in the neoadjuvant and adjuvant phases of treatment. In the neoadjuvant EBC setting such combination showed a significant increase in pathological complete response (pCR) rates (NEOSPHERE and TRYPHAENA trials; Gianni et al 2016; Schneeweis et al 2013). In the adjuvant EBC setting it led to a marginal improvement of invasive disease-free survival (IDFS) in patients at high risk of recurrence (APHINITY trial, von Minckwitz et al, 2017).

Overall, the role of trastuzumab and pertuzumab in combination with chemotherapy in the neoadjuvant, adjuvant and metastatic settings of patients with HER2+ BC is clearly defined.

About the product

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

Mode of action: Pertuzumab and trastuzumab are recombinant humanised immunoglobulin (Ig)G1 monoclonal antibodies which target the human epidermal growth factor receptor 2 (HER2).

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies.

Approved indications:

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

Metastatic breast cancer (MBC): Phesgo is indicated for use in combination with docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Special pharmaceutical aspects: Phesgo is administered subcutaneously, as a fixed non-weight-based dose, which is similar to the approved pertuzumab IV and trastuzumab SC formulations. Phesgo was developed to offer patients a less invasive and faster administration of pertuzumab and trastuzumab as a single product compared to individual IV infusions.

Posology:

Dose recommendations in early and metastatic breast cancer are presented below.

Table 1: Phesgo recommended dosing and administration

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

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

Type of Application and aspects on development

Since the pertuzumab and trastuzumab active ingredients in the FDC for SC administration are identical to the active ingredients in the IV formulations, the underlying principle of the clinical development programme (CDP) of the FDC is a pharmacokinetic bridging approach. The CDP is based on the scientific consideration that pertuzumab and trastuzumab serum trough concentrations (C_{trough}) after SC administration are at least as high as those C_{trough} after IV infusion, resulting in a comparable degree of target-site saturation and thus comparable degree of efficacy, regardless of the route of administration. The CDP also builds on the development of the Herceptin SC formulation and the VELVET study (MO27782), in which Perjeta IV and Herceptin IV were administered in the same infusion bag.

2.2. Quality aspects

2.2.1. Introduction

The finished product, Phesgo, is presented as solution for injection containing either 600 mg (for the 10 mL maintenance dose) or 1200 mg (for the 15 mL loading dose) of pertuzumab together with 600 mg of trastuzumab as active substances.

Other ingredients are: vorhyaluronidase alfa, L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, sucrose, polysorbate 20, L-Methionine and water for injections.

The finished product is a fixed dose combination (FDC) of pertuzumab and trastuzumab for subcutaneous (SC) administration; it is developed by Genentech, Inc. (a member of the Roche group), to offer patients a less invasive and faster administration of pertuzumab and trastuzumab compared to the intra-venous (IV) infusion.

Pertuzumab concentrate for solution for infusion has been approved in the EU, under the trade name Perjeta, since March 2013; the MAH is the same as the proposed MAH for Phesgo. The changes introduced to the active substance (AS) manufacturing process to adapt to the SC formulation are described under the active substance section.

Trastuzumab for SC administration, co-formulated with recombinant human hyaluronidase (rHuPH20, vorhyaluronidase alfa), has been approved in the EU through the centralised procedure since August 2013, under the trade name Herceptin, (MA Number: EU/1/00/145/002); the MAH is the same as the proposed MAH for Phesgo.

2.2.2. Active substances

General information

Pertuzumab and trastuzumab active substances are produced in Chinese hamster ovary (CHO) cell cultures and then purified extensively using standard chromatographic and filtration methods. They are both recombinant, humanised monoclonal antibodies based on the human IgG1 (κ) framework sequences, containing an N-linked oligosaccharide. They are both directed against the extracellular domain of the human epidermal growth factor receptor 2 (HER2), however they bind to distinct HER2 epitopes (within the subdomain II for pertuzumab and within the subdomain IV for trastuzumab), without competing, and have complementary mechanisms for disrupting HER2 signalling. The result is augmented anti-proliferative activity. Trastuzumab also has ADCC as additional mode of action (MoA). Pertuzumab is based on an IgG1 framework, it also has the potential to engage immune effector functions, however this is only considered as secondary MoA.

2.2.2.1. Active substance - Trastuzumab

The trastuzumab active substance used in the FDC finished product is identical to the trastuzumab active substance in Herceptin SC, only section S.4.5 Batch Analysis has been updated with batch data and a description of batches used in clinical phase III studies and for finished product process performance qualification (PPQ). As all updated batch analysis results met the release specifications without trends observed, the trastuzumab active substance for the FDC finished product is not further discussed in this assessment report.

2.2.2.2. Active substance - Pertuzumab

General information

Pertuzumab is a humanised mAb based on a human IgG1(κ) framework. The recombinant antibody is produced in CHO cells and consists of two HCs (449 amino acid residues each) and two LCs (214 amino acid residues each). As is typical for IgG1 antibodies, pertuzumab contains an N-linked glycosylation site at Asn299 on each of the two HCs. The calculated molecular mass of the 448-residue HC form is 145,197 Da (without HC glycosylation or C-terminal lysine). The structure and the physicochemical and biological characteristics of pertuzumab SC active substance are the same as those of the pertuzumab IV active substance and hence they are only briefly discussed in this report.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The active substance manufacturing process for pertuzumab SC active substance is the same as the manufacturing process for pertuzumab IV active substance, with the exception that it has been optimised to obtain a more concentrated pertuzumab active substance and to implement the experience gained from the pertuzumab IV active substance manufacturing process.

Pertuzumab SC active substance is produced in a fed-batch process using a suspension-adapted CHO cell line. The manufacturing process has been adequately described. Main steps are cell culture, harvest, protein recovery and purification. The adaptations introduced for the cell culture harvest have been described. The purification process upstream of the ultrafiltration and diafiltration (UFDF) step (i.e. affinity chromatography, low pH virus inactivation, cation-exchange chromatography, virus filtration, anion-exchange chromatography steps) is the same as the approved pertuzumab IV active substance process. The UFDF step (concentration of the product and buffer exchange) has been modified to ensure an active substance concentration of pertuzumab. During purification, the samples are tested for bioburden, endotoxin, protein concentration and yield.

The primary container closure is equivalent to the primary container closure used for pertuzumab IV active substance.

Control of materials

The serum-free master cell bank (MCB) used for pertuzumab SC is the same as the one approved for pertuzumab IV. There are no changes in the development of the CHO DP-12 cell line. A working cell bank is not used for pertuzumab SC active substance due to the high frequency of growth issues with WCBs relative to the MCB.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. The raw materials of animal, human, or recombinant origin used in the production of the pertuzumab SC active substance are the same as those used for the pertuzumab IV active substance, thus the TSE risk is considered unchanged. Compliance with the current revision of the EMA/410/01 "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" is

confirmed for relevant raw materials and no TSE issue have been identified for the manufacture of the Pertuzumab-Trastuzumab Fixed Dose Combination.

Further information is provided under the Adventitious Agents part of the report.

Control of critical steps and intermediates

The in-process limits for pertuzumab SC active substance are the same as those for pertuzumab IV active substance with the exception of UFDF step. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process. Action limits and acceptance criteria are employed for bioburden sampling (either pre- or post-filtration through bioburden-reducing filters) and for in-process pools in the cell culture and purification processes. Actions taken if limits are exceeded are specified.

Process validation

The pertuzumab SC active substance manufacturing process is very similar to the validated pertuzumab IV active substance manufacturing process, hence, many of the validation studies previously performed for pertuzumab IV are directly applicable to pertuzumab SC.

Additionally, five full scale commercial scale batches, from three independent thaws of MCB, were manufactured during the PPQ campaign. Although all process parameters remained within the acceptance range for all batches, demonstrating a robust manufacturing process, one of the PPQ batches showed reduced cell growth and titre in the production culture; consequently, it did not meet all comparability and release acceptance criteria. The batch was not released. Such inherent variability is also seen in the pertuzumab IV process and it is thus not unexpected. The PPQ batches were also included in a process consistency study with four clinical pertuzumab SC batches and released pertuzumab IV batches. Both the pertuzumab IV and SC cell culture processes exhibit occasional reduced growth and titre, attributed to the pertuzumab cell line's sensitivity to low pH and potentially other cell environmental stressors. To address this issue, a new cell line (derived from a new transfection of a CHO host cell line) is being developed, in line with the recommendations obtained with a scientific advice given in parallel to this MAA.

Since the manufacturing process is a standard antibody manufacturing process, and in light of the extensive process knowledge already gained for the similar pertuzumab IV process, the results from the four remaining PPQ batches are considered sufficient to qualify the pertuzumab SC manufacturing process.

Pertuzumab SC-specific single-factor risk assessments and validation studies were performed to account for the introduced changes, and were used, along with prior knowledge, to identify CPPs and set acceptable ranges.

The frozen active substance is stored in tanks, which are either shipped via air and ground transportation. Sufficient shipping qualification/validation has been performed.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development programme. Several important changes have been introduced during the development of the manufacturing process. The pertuzumab SC active substance used for phase I clinical studies was manufactured with the pertuzumab IV active substance as starting material, which was reformulated and concentrated for SC administration. The active substance used for phase III studies was manufactured with a process highly similar to the IV process except for the introduction of a new working cell bank, changes to

the cell culture medium and modifications to the UFDF step. Between phase III and commercial the manufacturing site was transferred to the final proposed site, where PPQ was performed. A comparability study comparing PPQ/commercial pertuzumab SC versus phase III material confirmed comparability, including comparable degradation. One of the five batches failed the comparability acceptance criteria for some attributes and was not released. The four released PPQ batches manufactured at the proposed commercial site, which conform to all release specifications and comparability acceptance criteria, are considered comparable to phase III material in terms of quality, safety, and efficacy.

Characterisation

The Pertuzumab SC active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG1-type antibody; the same characterisation studies performed for pertuzumab IV active substance were repeated. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. The isolation and physicochemical characterisation of the product variants, which were described in the initial marketing application for Perjeta and have not been repeated, which is found acceptable as pertuzumab SC and pertuzumab IV active substances have similar chromatographic profiles in terms of overall peak shape and peak rank order. Heterogeneity of the active substance was adequately characterised; the levels of HMW forms was found to be slightly higher in the pertuzumab SC than in pertuzumab IV active substance, which is not unexpected considering the higher antibody concentration. The levels of deamidated forms was also slightly higher, however it does not raise concerns.

Only a subset of biological characterisation assays, namely anti-proliferation and ADCC potency assay, were performed using the pertuzumab SC secondary reference standard as more extensive bioactivity assessments of the primary reference standards were performed for Perjeta (i.e. anti-proliferation activity, ADCC activity, FcγR and FcRn binding, HER2 binding, C1q binding and CDC, and apoptosis-inducing activity). In summary, the characterisation is considered appropriate for this type of molecule. While the primary and the secondary reference standard displayed comparable inhibition of cell proliferation, the potency by ADCC for the secondary reference standard was below the comparability assessment criteria. The primary reference standard is therefore used as reference in the Potency by ADCC.

In summary, the characterisation is considered appropriate for this type of molecule.

The designated CQAs have been provided. The CQAs, for which changes are introduced compared to the CQAs listed for pertuzumab IV, are highlighted by the applicant. The risk ranking and filtering (RRF) tool addresses the recategorisation of some QAs and the risk assessment is considered appropriately conservative.

Specification

The test parameters and acceptance criteria for release and stability testing for pertuzumab SC active substance include parameters for: colour (Ph.Eur.), clarity and opalescence (Ph.Eur.), appearance (visual), pH, osmolality (Ph.Eur.), identity (peptide map, protein content by UV (Gravimetric)), purity (SE-HPLC), purity (non-reduced and reduced CE-SDS), purity (IE-HPLC), protein content by UV (Gravimetric), potency (anti-proliferation assay), potency (ADCC assay), bioburden (Ph.Eur.), bacterial endotoxins (Ph.Eur.), content of polysorbate 20 (HPLC-ELSD), relative glycan distribution (2-AB HILICUHPLC).

The parameters tested correspond to the approved test parameters for the active substance of Perjeta; however, the active substance specification has been extended with the potency by ADCC assay and purity by IE-HPLC.

Peptide mapping is used to confirm the identity of the drug substance. In order to distinguish pertuzumab SC active substance from pertuzumab IV active substance, which has an identical amino acid sequence, a secondary identity method, Protein Content by UV Spec Scan, is included as well.

The omission of tests for process-related impurities is acceptable based residual DNA, residual HCP, and leached Protein A measurements during process validation demonstrating consistent reduction to levels below or close to the assay QL.

The 2-AB HILIC-UHPLC method has replaced the CE-LIF method for the determination of relative glycan distribution. The test for determining the polysorbate content and the test for determining rodent parvovirus have also been replaced.

The proposed specification tests and parameters are considered adequate for this type of molecule. No changes were implemented in the specification during the procedure.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Potency is measured using two assays. The first one is an anti-proliferation assay, which measures pertuzumab SC active substance ability to inhibit the proliferation of the human HER2-expressing breast cancer cell line MDA-MB-175-VII, this is the same assay as used for pertuzumab IV active substance; the second is an ADCC assay.

Batch analysis

Batch analysis data on two phase I batches, 4 phase III clinical batches and 5 PPQ, full scale, batches of the active substance were provided. The results are within the specifications with the exception of the value for the Potency by ADCC assay for a PPQ Batch, which exceeded the upper limit of the acceptance criteria and was hence not released. The results provided confirm consistency of the manufacturing process.

Reference materials

The use of the same PRS as approved for pertuzumab IV commercial use is considered appropriate.

Stability

The proposed shelf life is 30 months at storage condition ≤-20 ºC protected from light. The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container (stainless steel or Hastelloy vessel).

Real time, real condition (-20ºC) stability data on three full scale batches of active substance from the commercial manufacturing process stored in the intended container for 9 months and for up to 6 months under accelerated conditions at 5 ºC according to the ICH guidelines were provided.

Additionally, real condition (-20ºC) stability data on four supportive batches of active substance used in the phase III clinical studies from manufacturing process representative of the commercial process, stored in a

container representative of the proposed container for 30 months and for up to 6 months under accelerated conditions at 5ºC according to the ICH guidelines were also provided.

The following parameters were tested during stability studies: colour (Ph.Eur.), clarity and opalescence (Ph.Eur.), purity (SE-HPLC), purity (non-reduced), purity (IE-HPLC) and potency (anti-proliferation assay); these stability indicating tests are in line with the stability tests for pertuzumab IV active substance.

The stability data provided is within the specifications and support the proposed 30 months shelf life.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is an FDC of pertuzumab and trastuzumab for SC administration; it is provided as a sterile, colourless-to-slightly brownish solution and it contains no preservatives. The product is available in two formulations:

The loading dose (LD) is formulated as 80 mg/mL pertuzumab and 40 mg/mL trastuzumab. Each single-dose vial contains 15 mL of the solution equivalent to 1200 mg pertuzumab, 600 mg trastuzumab and 2000 U/mL vorhyaluronidase alfa (also referred to as recombinant human hyaluronidase, rHuPH20) at target pH 5.5.

The maintenance dose (MD) is formulated as 60 mg/mL pertuzumab and 60 mg/mL trastuzumab. Each single-dose vial contains 10 mL of the solution equivalent to 600 mg pertuzumab, 600 mg trastuzumab and 2000 U/mL rHuPH20 at target pH 5.5

The intended commercial formulation is the same as that used during clinical studies.

The finished product contains vorhyaluronidase alfa (permeation enhancer), L-histidine and L-histidine hydrochloride monohydrate (buffer), α,α-trehalose dihydrate and sucrose (tonicity agents), polysorbate 20 (surfactant), L-Methionine (stabiliser) and water for injections (solvent). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of hyaluronidase (rHuPH20, vorhyaluronidase alfa), which has previously been assessed as (novel) excipient in the approved Herceptin SC (600 mg, solution for injection).

The finished product does not contain any overages. Extractable volume studies were used to establish the minimum fill volume of the vials for both LD and MD FDC finished products to permit withdrawal and administration of the dose when used as directed. The primary packaging is a 15ml or 20 mL type I borosilicate glass vial tapered with fluororesin-laminated rubber stopper. The stopper is sealed with aluminium and covered by a plastic flip-off cap. The flip off cap is cool green for the loading dose and orange color for the maintenance dose.

The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The suitability of the container closure system with the finished product was demonstrated in terms of protection, safety and compatibility.

The quality target product profile (QTPP), summarised in Table 2, is applied as guidance during pharmaceutical development.

Table 2: Quality Target Product Profile (QTPP) of the Finished Product

Product Attribute	Target
Molecule Type	Two humanized monovalent monoclonal antibodies (based on IgG1 framework)
Indication	HER-2-positive early breast cancer (neoadjuvant and adjuvant) and first-line metastatic breast cancer
Patient Population	Adults
Patient Weight	Average 70 kg
Mechanism of Action Pertuzumab	A recombinant humanized monoclonal antibody that binds to the dimerization domain of HER2 (sub-domain II of the ECD). Upon binding to HER2, it inhibits the ability of HER2 to dimerize with other HERs (HER1, HER3, and HER4), thereby inhibiting multiple HER signaling pathways that mediate cancer cell proliferation and survival. Pertuzumab may also work by activating ADCC.
Mechanism of Action Trastuzumab	A recombinant humanized monoclonal antibody that binds specifically and with high affinity to sub-domain IV of the ECD of HER2 and inhibits the proliferation of human tumor cells overexpressing HER2 both *in vitro* and *in vivo*. Trastuzumab-mediated ADCC is preferentially exerted on HER2-overexpressing cancer cells compared with cancer cells that do not overexpress HER2.
Dosage Form and Strength	Single-dose, sterile, preservative-free solution for subcutaneous injection containing: LD: 80 mg/mL pertuzumab + 40 mg/mL trastuzumab with 2000 U/mL rHuPH20 MD: 60 mg/mL pertuzumab + 60 mg/mL trastuzumab with 2000 U/mL rHuPH20
Protein Content per Vial	LD: net quantity 1200 mg pertuzumab/600mg trastuzumab (15 mL nominal fill volume, 20 mL vial size) MD: net quantity 600 mg pertuzumab/600 mg trastuzumab (10 mL nominal fill volume, 15 mL vial size)
Dose	LD: 1200 mg pertuzumab/600 mg trastuzumab MD: 600 mg pertuzumab/600 mg trastuzumab
Administration	Subcutaneous, undiluted
Co-Administered Drugs	Concomitantly with chemotherapy or as a single agent (without chemotherapy)
Drug Product Container Closure System	Type I borosilicate glass vials, fluororesin-laminated stopper, aluminum seal with plastic flip-off cap
Shelf Life	Minimal claim at submission drug product shelf life ≥ 18 months (target ≥ 21 months) at 2°C–8°C
Stability during Administration	Physicochemically stable for 28 days at 2°C–8°C and up to 24 hours at 9°C–30°C in disposable syringes.

For the finished product, the following quality attributes are considered as critical: subvisible particles, visible particles, sterility, container closure integrity, potency (by ELISA), protein content, primary packaging extractables/leachables, process-related impurities (including leachables). With the exception of the container closure integrity test, primary packaging extractables/leachables and process-related impurities (including leachables) all the CQAs are controlled by the finished product release specifications. Container closure

integrity is evaluated as part of stability testing, extractables/leachables and process-related impurities were also evaluated in respective studies.

The applicant's primary objective of the finished product development was to co-formulate pertuzumab, trastuzumab to enable a single subcutaneous injection.

The LD and MD formulation development was guided by prior knowledge from the development of commercially available trastuzumab SC drug product and pertuzumab IV drug product. The trastuzumab SC finished product formulation was chosen as basis for the finished product development to support the stability of trastuzumab. rHuPH20 is added to the formulation to facilitate large volume injection subcutaneously. The trastuzumab SC finished product formulation was modified to optimise the stability of the finished product; hence, sucrose was used instead of trehalose to support pertuzumab SC active substance frozen storage at -20C. The formulation development has been thoroughly described and the rationale for the selection of the formulation, including appropriate dosage form, protein concentration, buffer type, solution pH, stabiliser and surfactant, has been adequately addressed and justified.

Compatibility with the excipients is considered demonstrated based on long-term stability, formulation development studies, and extended characterisation studies, which included a subvisible particles study, charged variants and size variants studies, a study of potential interactions between the antibodies and rHuPH20 and a study of the antibody-dependent cellular cytotoxicity (ADCC). Additionally, the comprehensive data presented from the three formulation robustness studies support the acceptable ranges of the formulation factors, including the pH, antibody and excipient concentration and ratios, and the surfactant polysorbate 20 concentration range.

To reduce the risk of particle formation in Phesgo, the applicant has optimised the formulation. Based on previous experience, polysorbate 20 fatty acid degradants accumulate over time and form particles that eventually can be detected during stability testing. The root cause for polysorbate 20 degradation, will be addressed to mitigate the risk of FFA particle formation upon its degradation. A recommendation (REC 1) to evaluate and implement measures to mitigate the root cause for particle formation in the finished product has been given.

To confirm that the polysorbate 20 surfactant in the formulation provides suitable protection from agitation stress, an agitation formulation robustness stress study was performed. The data provided are satisfactory. However, to fully conclude on the suitability of polysorbate to protect from shipping stress, the applicant is recommended to perform a finished product agitation stress study, to simulate mechanical shipping stress (agitation) including stability 2°C-8°C until end of shelf life post stress (REC 2).

The manufacturing process development history has been described in sufficient details. The pivotal clinical batches were manufactured utilizing the same manufacturing process main steps as the commercial site. A comparability exercise between the finished products from the pivotal clinical process and commercial process has been performed and confirms the comparability between the manufacturing process used for the pivotal clinical batches and commercial process. The comparability study includes quantitative comparison with predefined comparability acceptance criteria, qualitative comparison and extended characterisation as well as a stress stability comparability study.

The measurements to control microbiological quality and sterility of the finished product is considered acceptable and include process validation (media fills, bacterial retention test of filters, microbial hold times), manufacturing controls, IPC testing and release testing. The integrity of the container closure system to prevent microbial contamination has been adequately described and continues to be controlled during stability.

A compatibility study was performed to address potential hold times subsequent to the preparation of the syringe and prior to administration. The results demonstrate that finished product in simulated SC administration is physically and chemically stable under the tested conditions (4 weeks at 2°C-8°C protected from light followed by 24 hours at 30°C exposed to ambient room lighting conditions) when stored in polypropylene (PP) or polycarbonate (PC syringes). The in-use physico-chemical stability has been addressed properly by the applicant. A minor issue concerning the microbiological stability has been resolved. The proposed in use shelf-life, as described in section 6.3 of the SmPC, is supported.

Manufacture of the product and process controls

The Phesgo finished product manufacturing process consist of simple physical unit operations involving no chemical modifications or reactions and include the following steps: active substance and excipient thawing (pertuzumab SC AS, trastuzumab SC AS and rHuPH20), compounding of the finished product, bioburden reduction filtration, in-line sterile filtration, aseptic filling and stoppering, capping and crimping, final vial inspection, storage, transportation, and labelling and secondary packaging.

Validation of the finished product manufacturing process included the manufacture of three consecutive PPQ batches for both the LD and MD of the finished product (total of six), representing the full range of batch sizes for commercial manufacturing. A bracketing approach was used during the finished product PPQ campaign to cover the full manufacturing batch size ranges. Four different pertuzumab SC active substance batches, six different trastuzumab SC active substance batches and two rHuPH20 batches were used for the FDC finished product PPQ batch manufacturing campaign. The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

One Post Approval Change Management Protocol (PACMP) concerning scale-up of the MD manufacturing process has been submitted with the application and found acceptable.

Product specification

The proposed finished product release and shelf-life specifications for both the loading dose (LD) and the maintenance dose (MD) include general tests (appearance, colour, clarity/opalescence, extractable volume, visible particles subvisible particles, pH and osmolality, all Ph.Eur.), test for identity (Identity by Content of Proteins by RP-UHPLC Lys-C peptide mapping), test for quantity (protein concentration, RP-UHPLC, extractable volume), potency test (two specific ELISAs), purity and impurity tests (SE-HPLC, non-reduced CE-SDS, IE-HPLC) as well as test for safety (sterility, endotoxin). In addition, tests for excipients; Polysorbate 20 and hyaluronidase (rHuPH20) are included. Tests for osmolality, identity tests, bacterial endotoxin test and test for sterility are excluded from the shelf-life specifications, while container closure integrity is included in the shelf-life specifications. Overall, the parameters included in the finished release and shelf-life specifications are found adequate to control the quality of the finished product. The overall approach for setting the specification is found satisfactory and in line with ICH Q6B.

Adequate justification for not testing specific CQAs for pertuzumab SC is provided based on the control of the active substance. The anti-proliferative and Fc-mediated (ADCC) activities are controlled at the active substance level. At the finished product level the potency of each antibody is controlled by two specific ELISA methods. The ELISAs are based on the binding of the antibodies to the respective epitopes on HER2 and are designed to eliminate cross-reactivity between the co-formulated antibody. The specificity of each ELISA has further been

demonstrated during method validation. The anti-proliferation assay is not a suitable assay to be used at the finished product level due to the masking effect of the second antibody on the response of the first antibody. Based on this, it is agreed, that the ELISAs are considered the best possible assays to control the potency of the finished product.

The collective potency control strategy with control of the anti-proliferation and ADCC activity at the active substance level and the control by ELISA at the finished product level is considered sufficient to control the potency of the final finished product and ensure manufacturing consistency.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A quality risk assessment on the possible presence of nitrosamine components in Phesgo has been submitted during the procedure. The biological components pertuzumab, trastuzumab and rHuPH20, the excipients, WFI and the primary packaging have been evaluated to determine the risk of nitrosating conditions or the presence of nitrosamine in the drug product. No risk was identified.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data of 3 commercial scale PPQ batches for the LD and 3 for the MD of the finished product, 3 phase III clinical batches for the LD and 3 for the MD finished product and 2 phase I clinical studies were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

For the finished product two-tiered (primary and secondary) reference standard systems have been established for commercial use for LD and MD. The assay reference standard used for testing of rHuPH20 bulk enzyme activity has been described. Reference standards for pertuzumab SC and trastuzumab SC active substances are described in the respective Module 3 Sections.

Stability of the product

Based on available stability data, the 18 months proposed shelf-life and storage conditions “Store in a refrigerator (2°C 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light”, as stated in the SmPC, are acceptable.

Real time/real condition stability data of 14 primary stability batches (3 commercial scale PPQ batches for the LD and 3 for the MD; 3 phase III clinical batches for the LD and 3 for the MD; 2 phase I clinical studies batches) for up to 24 months under long term conditions at 5ºC and for up to 6 months under accelerated conditions at 25ºC / 60% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Shift of charge variants, LMW formation and HMW formation are the primary modes of degradation. Changes observed at recommended storage condition are within acceptance criteria and do not result in a potential failure to meet the acceptance criteria at the end of the proposed shelf life.

Data generated from temperature excursion at above and below the recommended storage condition temperature confirm the stability of the finished product under conditions that might occur during manufacturing, shipping, and handling.

In addition, 2 commercial scale batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results confirm that the finished product is light sensitive with changes observed in SE-HPLC main peak, SE-HPLC sum of HMW forms, and shift of charge variants in IE-HPLC. Data from the control samples, exposed to light but stored in the proposed secondary packaging confirm that the packaging configuration adequately protects the finished product from light.

Adventitious agents

For the production of one of the recombinant human insulins used for the culture process of the pertuzumab and trastuzumab active substances, several animal-derived raw materials were used. Sufficient information to confirm the acceptability of these animal-derived raw materials with respect to TSE and adventitious agents are provided including the relevant Certificates of Suitability. An appropriate raw material specification has been set for the recombinant human insulin.

The media used to establish the pertuzumab SC cell bank contained amino acids derived from human hair or chicken feathers. As no ruminant tissues were used, there is no significant TSE risk from this material; additionally, the process used to manufacture the two amino acids effectively inactivates all viruses.

Viral and non-viral adventitious agents are controlled by heat treatment, irradiation, and/or filtration of materials used in the process. The procedure for cell culture media sterilisation and viral barriers is the same as that used for the approved pertuzumab IV process.

The cell culturing and harvest includes sufficient IPCs for bioburden, endotoxin, mycoplasma, leptospira, rodent parvoviruses, and other adventitious viruses, and the purification process includes in-process tests for bioburden and endotoxin.

Viral removal capacity studies performed for pertuzumab IV remain applicable to the pertuzumab SC process.

GMO

Not applicable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The finished product, Phesgo, is presented as solution for injection containing pertuzumab and trastuzumab as active substances. Its development is based on the already approved pertuzumab solution for injection (Perjeta) and trastuzumab for SC administration, co-formulated with recombinant human hyaluronidase (Herceptin). Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. No major objections were raised during the procedure and the other concerns have been adequately addressed.

One PACMP concerning scale up of the MD manufacturing process has been submitted with the application and it is considered acceptable.

At the time of the CHMP opinion, there were two minor unresolved quality issues, linked to the observed presence of FFA particles upon storage, and having no impact on the Benefit/Risk ratio of the product, as described under 'Recommendations for future quality development'.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety and it is considered adequate.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Area	Number	Description	Classification*	Due date
Quality Finished product 3.2.P.2.	1	The applicant is recommended to evaluate and implement measures to mitigate the root cause for particle formation in the FDC finished product.	REC	N.A.
Quality Finished product 3.2.P.2.	2	The applicant commits to perform a simulated shipment study including stability at 2°C-8°C until end of shelf life post stress.	REC	N.A.

2.3. Non-clinical aspects

2.3.1. Introduction

The current MAA concerns a fixed-dose combination (FDC) of pertuzumab and trastuzumab for subcutaneous (SC) injection (referred to as "PH FDC SC"). PH FDC SC is a new ready-to-use solution co-formulated with recombinant human hyaluronidase PH20 (rHuPH20), a permeation enhancer which allows SC administrations of high drug volumes.

Pertuzumab and trastuzumab are recombinant humanised immunoglobulin (Ig)G1κ monoclonal antibodies (MAbs), which target the human epidermal growth factor receptor 2 (HER2, c-erbB2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. The MAbs bind to distinct HER2 epitopes, subdomains II and IV respectively, without competing, and they have complementary mechanisms for disrupting the HER2 signalling.

Both active substances are approved and marketed by Roche as individual products for IV injection under the names Perjeta (pertuzumab) and Herceptin (trastuzumab). Trastuzumab is additionally approved in a SC formulation in combination with rHuPH20 (Herceptin SC line extension). Pertuzumab IV and trastuzumab IV/SC in combination with chemotherapy is already used clinically in free combination in the "Perjeta treatment regimen" for HER2-posivtive breast cancer. The proposed indication for the fixed-dose combination is therefore in line with currently approved therapeutic indications for patients with HER2-positive Early or Metastatic Breast Cancer (EBC/MBC) described in the Perjeta product information.

The non-clinical strategy to support the application of PH FDC SC is therefore primarily based on a pharmacokinetic bridging approach. In addition to references to the initial marketing authorisation dossiers of Perjeta, Herceptin IV and the Herceptin SC line extension, one new non-clinical study was conducted, a single-dose PK bioavailability study in Göttingen minipigs (Study 1038750). This approach is generally acceptable according to the ICH M3 (R2) guideline (EMA/CPMP/ICH/286/1995) and the guideline on fixed combinations (EMEA/CHMP/SWP/ 258498/2005), provided that sufficient documentation of their individual and combined use exists.

Scientific advice on the nonclinical strategy was received from the EMA (EMEA/H/SA/3415/1/2016/III) for PH FDC SC. The submitted nonclinical data are in line with the recommendations in this scientific advice.

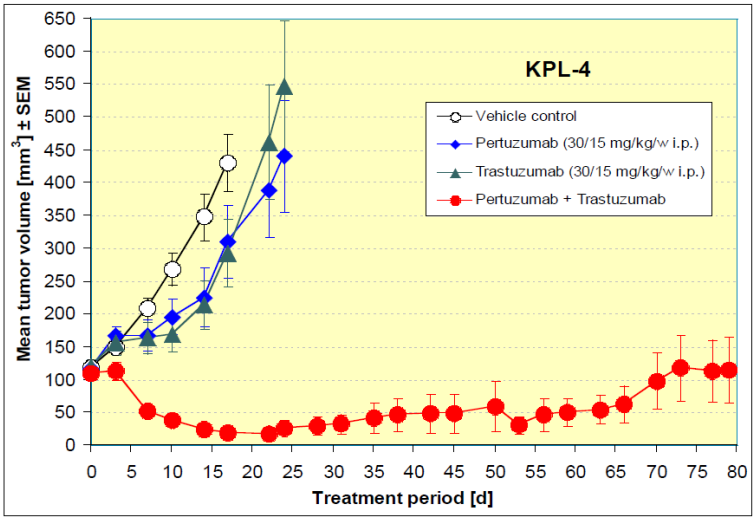
The previously performed studies for the already marketed Perjeta and Herceptin IV/SC supporting this application have already been assessed and are only summarised in brief where relevant. Additional information about the pharmacology, pharmacokinetic and toxicology of the individual approved substance can be found in the respective EPARs. Reference to relevant parts of the initial MAA's for the individual compounds were provided by the applicant in the submitted non-clinical overview. It should be noted, that the non-clinical overview only consisted of very brief summaries of the previous conducted studies.

2.3.2. Pharmacology

No new pharmacological data was presented by the applicant, which is acceptable, as no harmful pharmacodynamic effects was expected for the fixed-combination which has not been seen for the individual products applied in free combination. The synergistic effect of the two active substances has additionally been described in literature from 2009 by their complementary modes of action (Junttila et al. 2009; Scheuer et al. 2009). From the data presented in figure 1 below, it is apparent that combination treatment with

pertuzumab and trastuzumab has a beneficial effect in mice by reducing tumour growth and metastatic potential.

Figure 1 Pertuzumab+Trastuzumab Combination Therapy in a HER2-Positive Human Breat Cancer Xenograf Model



Source: Scheuer et al. 2009.
i.p. = intraperitoneally; SEM = standard error of mean.

The cynomolgus monkey was identified as the relevant toxicological species, as pertuzumab and trastuzumab bind to human HER2 and monkey ErbB2 with comparable affinity *in vitro* and neither of the antibodies bind to the rodent orthologue, neu.

No dedicated safety pharmacology studies were performed for PH FDC SC. Safety pharmacological endpoints were in accordance with ICH S6(R1) guideline incorporated into the initial pivotal repeat-dose toxicological studies for pertuzumab and trastuzumab, respectively. The repeat-dose studies in cynomolgus monkeys did not identify any concerns regarding cardiovascular, respiratory, neurologic, or ophthalmic abnormalities for either pertuzumab or trastuzumab (MAA's of Perjeta and Herceptin), and no safety concerns are therefore expected for the fixed combination PH FDC SC.

2.3.3. Pharmacokinetics

Beside a bioavailability study conducted in minipigs to support SC administration of Pertuzumab + rHuPH20 with and without co-administration of trastuzumab + rHUPH20, no new studies were conducted to support the pharmacokinetics (PK) of PH FDC SC. The PK of the current MAA is therefore to a large degree supported by the data from the marketed products Perjeta (IV) and Herceptin (IV/SC line extension). This is an acceptable approach according to the guidelines on fixed combination medicinal products (EMEA/CHMP/SWP/258498/2005).

The applicant has highlighted the most important observations from the PK and TK studies of Perjeta (IV) and Herceptin (IV/SC line extension). According to the applicant, IV studies in mice, rats and monkeys have shown that the pharmacokinetics of pertuzumab and trastuzumab follows that of other IgG1 monoclonal

antibodies with similar Fc region (distribution phase less than 1 day, $T_{1/2}$ of approximately 10 days, Vc of 30 to 50 mL/kg). However, clearance of pertuzumab is faster in tumour bearing mice compared to non-tumour bearing mice.

Studies of SC administration of trastuzumab co-administrated with rHuPH20 in mice and cynomolgus monkeys indicated rapid absorption with C_{max} values reached after 7 and 24 h and a bioavailability of 83.4% and 100% in mice and monkeys respectively.

Absorption of SC trastuzumab in minipigs was much faster when co-administrated with rHuPH20 than without (changes in T_{max} from 72h to 24h). No increases were seen in the absorption rate or absorbed fraction of trastuzumab when increasing the rHuPH20 dose above 2000 U/mL and the bioavailability of trastuzumab was independent of rHuPH20 co-administration. These findings corresponded to a large degree with the result from the pertuzumab SC minipig bioavailability study (report 1038750) addressed below.

The toxicokinetics of trastuzumab co-formulated with rHuPH20 in the repeat-dose toxicology study in cynomolgus monkeys confirms systemic exposure after SC administration (MAA of Herceptin SC line extension).

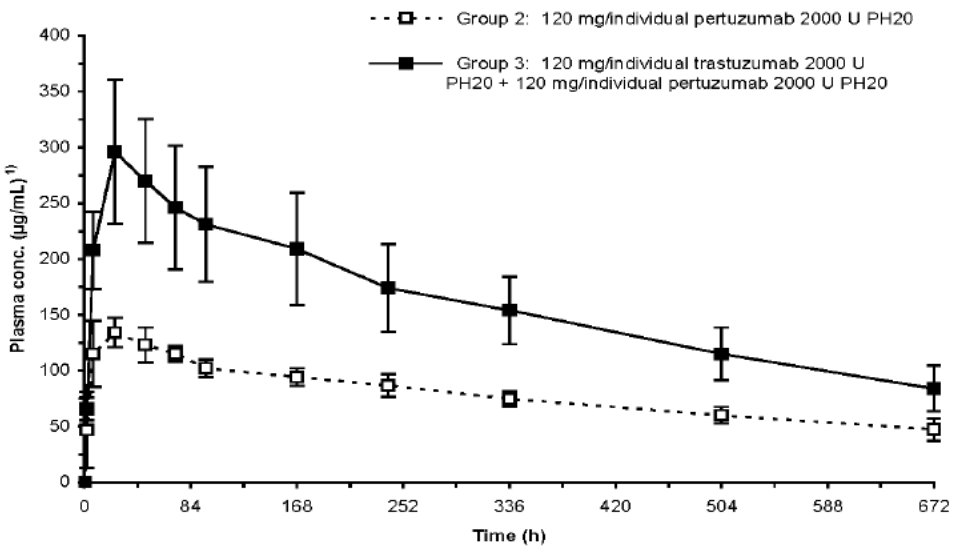
<u>The minipig bioavailability study (Report 1038750)</u>

The absorption study in minipigs ("RO5221651 (Pertuzumab) and RO0452317 (Trastuzumab): Bioavailability Study following a Single Intravenous or Subcutaneous Administration to the Minipig") is the only full study submitted in order to support this MAA for the fixed-combination product PH FDC SC. The study was conducted to support the use of Pertuzumab for subcutaneous administration, in addition to assessing the effect of concurrent administration of trastuzumab on SC absorption of both compounds. The study aims to fulfill the gaps not covered by the MAA for the already marked products Perjeta and Herceptin for IV and IV/SC use respectively. Conduction of the study to non-GLP is acceptable.

The ELISA assay for determination of pertuzumab and trastuzumab in minipigs is considered adequately validated. It should be noted, however, that the assay does not differentiate between trastuzumab or pertuzumab when combined, as it binds the Fc region of the antibody which is similar for the two compounds. Only the sum of the two antibodies is measured. A test system with the ability of separating the plasma concentrations of the two compounds would have been preferred.

Following subcutaneous administration of 120 mg/animal pertuzumab co-formulated with 2000 U rHuPH20 to minipigs, pertuzumab was relatively rapidly absorbed with maximum plasma levels observed at 7 - 48 hours post dose (see Figure 3.2.2.1 below, from report 1038750). The average C_{max} and $AUC_{(0\text{-}672h)}$ values were 138 µg/mL and 52800 ug. h/mL, respectively (see Table 3.2.2.1 below, from report 1038750). The half-life (524 hours) was similar to that following intravenous administration. The average subcutaneous bioavailability of pertuzumab was estimated at 73.8%.

Figure 2 Mean plasma concentration-time profiles of pertuzumab after single subcutaneous administration of pertuzumab, and sequential subcutaneous administration of trastuzumab and pertuzumab to male minipigs



Footnote 1): Plasma concentrations were expressed as total concentrations of pertuzumab and trastuzumab for Group 3. The assay could not differentiate pertuzumab and trastuzumab.

Table 3 K parameters of pertuzumab in plasma after single SC administration of pertuzumab (Group2), or sequential subcutaneous administrations of trastuzumab and pertuzumab to male minipigs (Group 3)

Parameter	Unit	N	Group 2 120 mg pertuzumab + 2000 U rHuPH20 SC	Group 3 120 mg trastuzumab* + 2000 U rHuPH20 120 mg pertuzumab + 2000 U rHuPH20 SC
AUC(0-inf)	[(µg·h)/mL]	5	90000	157000
AUC(rest, tlast-inf)	[%]	5	39.7	30.8
AUC(0-672h)	[(µg·h)/mL]	5	52800	108000
Cmax	[µg/mL]	5	138	296
tmax	[h]	5	25.4	24
t1/2	[h]	5	524	396
MRT(tot)	[h]	5	752	570
F**	[%]	5	73.8	ND

* Plasma concentrations were expressed as total concentrations of pertuzumab and trastuzumab. The assay could not differentiate pertuzumab and trastuzumab.

** 10.0 kg body weight was assumed for all minipigs for calculation of F.
ND: not detemined

Co-administration of trastuzumab had no obvious effect on the SC absorption of both compounds. The doubling of the exposure (both C_{max} and AUC) after administration of pertuzumab and trastuzumab as compared to the administration of pertuzumab alone indicated that the subcutaneous absorption of pertuzumab is not impaired by the co-administration of trastuzumab (see Figure 3.2.2.1 and Table 3.2.2.1 above). However, since the ELISA assay was not able to differentiate between pertuzumab and trastuzumab the specific contribution of each compound to the detected increase could not be estimated.

Subcutaneous sequential administration of pertuzumab and trastuzumab both co-formulated with 2000 U rHuPH20 seemed to have a beneficial effect on a more homogenous T_{max} of 24 h for all five animals compared to the T_{max} of 7-48 h of the individual animals in Group 2. A reason for this stabilisation of the T_{max}

has not been discussed by the applicant. The average C_{max} and $AUC_{(0\text{-}672h)}$ values of total concentration were 296 µg/mL and 108000 ug.h/mL, respectively. The half-life was 396 hours.

According to the protocol the injection site was inspected on clinical examinations after the SC injection and no specific mentioning of local reaction (adverse or none) was made in the report.

In conclusion, the study meets the requirements and successfully bridges the gap between the results from the already marketed individual products and the results needed to support this MAA of PH FDC SC. Data showed that pertuzumab was similarly rapidly absorbed in minipigs after SC administration compared to IV administration, and that co-administration of trastuzumab has no apparent effect on the SC absorption of pertuzumab. The population kinetic modelling provided concordant data in non-linear mixed effect model. The data indicate that in minipigs, the pharmacokinetics of pertuzumab is not adversely impacted in combination with trastuzumab and rHUPH20 after subcutaneous administration.

The lack of distribution, metabolism, excretion and pharmacokinetic drug interaction studies is in line with the ICH S6(R1) guideline, the guidelines on fixed combination medicinal products (EMEA/CHMP/SWP/258498/2005) and the justification presented by the applicant.

2.3.4. Toxicology

As no new single- or repeat-dose studies were conducted for PH FDC SC, the toxicity assessment relied on the data presented in the previous MAA of Perjeta and Herceptin (IV/SC). This in line with the ICH M3 (R2) guideline (EMA/CPMP/ICH/286/1995) and the guideline on fixed combinations (EMEA/CHMP/SWP/258498/2005), provided that sufficient experience of concomitant use exists.

As pertuzumab and trastuzumab have been used clinically in free combinations and as clinical data for the fixed combination product has been provided (see clinical part), the experience on concomitant use is considered sufficient and the approach taken by the applicant is supported. Additionally, SC administration of pertuzumab and trastuzumab in the minipig bioavailability study (Report 1038750) showed that the combination of the two compounds was well tolerated.

The nonclinical studies supporting Perjeta and Herceptin have previously been assessed in support of the respective MAA and relevant extensions. Therefore, a detailed discussion will not be provided here. However, a few points for consideration have been highlighted below.

Based on the toxicity results presented by the applicant from the MAAs of the individual products, pertuzumab and trastuzumab seem to be relatively well tolerated after both IV and SC administration and no safety pharmacology findings (with a particular focus on detection of cardiac toxicity) were detected. IV pertuzumab administration has, however, been associated with episodes of diarrhoea without histopathological findings in 7 and 26-week repeat-dose studies in cynomolgus monkeys (IV doses ≥ 15 mg/kg). Diarrhoea has according to the EPAR for Perjeta also been seen clinically, where it is assessed as manageable and the combination with trastuzumab and docetaxel in the clinic has according to the EPAR only added little toxicity to the adverse event profile (Perjeta EPAR).

According to the applicant, repeat-dose SC administration of trastuzumab + rHuPH20 (30 mg/kg once weekly for 13-weeks) revealed similar exposure as for IV administration in cynomolgus monkeys (25 mg/kg twice weekly).

The omission of genotoxicity and carcinogenicity studies is acceptable in accordance with the ICH S6 (R1) guideline and the fixed combination guideline (EMEA/CHMP/SWP/258498/2005).

Reproduction Toxicity

Pertuzumab related changes were seen in an embryo-foetal development study in cynomolgus monkeys leading to restrictions in section 4.6 of the SmPC (i.e. women of childbearing potential should use effective contraception and Perjeta was not recommended for pregnant women). The same restrictions are included in the SmPC for the PH FDC SC fixed-dose combination. In accordance with the fixed combination guideline (EMEA/CHMP/SWP/258498/2005), it is considered to be acceptable that no new embryo-foetal developmental (EFD) toxicity studies are conducted, especially since the before mentioned restriction is included in the SmPC of PH FDC SC.

No findings were observed in trastuzumab EFD toxicity studies in cynomolgus monkeys. However, clinical observations of trastuzumab related EFD changes were identified in post marketing settings questioning the cynomolgus monkey as an appropriate model for trastuzumab EFD studies. This is addressed in the SmPC of PH FDC SC.

Systemic maternal and foetal exposure at clinically relevant concentrations were confirmed for both pertuzumab and trastuzumab. Transfer of both pertuzumab and trastuzumab across the placenta was confirmed in the initial MAAs of the individual products.

Local Tolerance

No new dedicated non-clinical local tolerance studies were conducted for PH FDC SC. Generally stand-alone nonclinical studies assessing local tolerance are not needed, as local tolerance endpoints should be included in the pivotal toxicity studies, if relevant. Two clinical studies confirmed SC tolerability of the final formulation of the fixed dose combination. Only slight erythema and bruising (grade 1 in severity) was observed at the injection site in the clinical setting.

Local tolerance of pertuzumab and trastuzumab was assessed in their respective MAAs. For the approval of trastuzumab SC with rHuPH20, local tolerance was assessed in a dedicated rabbit study and as part of a 13-week SC toxicity study in cynomolgus monkeys. No test item related changes with regards to local tolerance, were observed in either study. In addition, local tolerance of rHuPH20 was sufficiently addressed in the MAA of the Herceptin SC line extension.

SC local tolerance of pertuzumab was assessed in a repeat-dose cynomolgus study and by clinical observations. Additionally, local tolerance parameters were, according to the study protocol, included in the minipig bioavailability study as observations of the injection site. However, no detailed records of these observations being performed are included in the study report, nor any summary of findings, or even absence of findings are presented. No histological examination was conducted. Nevertheless, it was stated in the local tolerance section in the non-clinical overview prepared by the applicant that SC administration of pertuzumab was well tolerated in the minipig study.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant has submitted a justification for not providing a full ERA. The fixed-dose combination of pertuzumab and trastuzumab do not provide an environmental risk, as monoclonal antibodies are readily biodegradable. In general, proteins and peptides are exempted from the need to provide an ERA, because they are unlikely to result in significant risk to the environment, in accordance with the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA, 2006). Additionally, as the

indication for the SC formulation is to substitute the IV administration, no increase in the exposure of pertuzumab and trastuzumab is foreseen.

2.3.6. Discussion on non-clinical aspects

There is a clear scientific rationale for combining pertuzumab and trastuzumab for the treatment of HER2 positive breast cancer. Both antibodies target HER2 with different but complementary mechanisms of actions. Inclusion of the permeation enhancer rHuPH20 in the formulation to increase absorption of pertuzumab and trastuzumab after subcutaneous dosing has been shown not to impair the anti-tumour activity of trastuzumab in tumour xenograft model (Herceptin SC line extension). Although not experimentally tested, similar effect can be assumed for pertuzumab. To increase the absorption of pertuzumab and trastuzumab after subcutaneous administration the permeation enhancer rHuPH20 has also been included in the fixed-dose formulation.

Overall, no non-clinical major concerns have been identified during the non-clinical assessment of the fixed-dose combination of pertuzumab and trastuzumab (PH FDC SC) for SC administration.

No new pharmacology or safety pharmacology studies were conducted with the PH FDC SC formulation. This is acceptable in accordance with the ICH M3 (R2) guideline (EMA/CPMP/ICH/286/1995) and the guideline on fixed-combinations (EMEA/CHMP/SWP/258498/2005), as the efficacy of the two monoclonal antibodies administered alone, as well as in free combination, has been established in the already approved individual MAAs, as well as by clinical use in free combination. Additionally, a summary of the synergistic effect of pertuzumab and trastuzmab on the HER-2 receptor was provided based on available public literature and studies submitted in the approved MAA's of Perjeta (IV) and Herceptin (IV/SC line extension). The cynomolgus monkey was identified as the relevant toxicological species based on comparable receptor binding affinity to the monkey ErbB2 receptor.

Beside a bridging bioavailability study in minipigs to support SC administration of Pertuzumab + rHuPH20 with and without co-administration of trastuzumab + rHUPH20 (Report 1038750), no additional pharmacokinetics (PK) studies were conducted with the fixed-dose combination PH FDC SC. As sufficient PK data from the individual MAAs exists, this is an acceptable approach according to the guidelines on fixed combination medicinal products (EMEA/CHMP/SWP/258498/2005).

The minipig bioavailability study (Report 1038750) showed a good absorption with a relatively high bioavailability of 73.8% for SC administration of pertuzumab co-formulated with rHuPH20. It was shown that after subcutaneous administration antibodies are rapidly absorbed yielding essentially the same Cmax and AUC values as after intravenous administration. Inclusion of rHuPH20 does not significantly impact the half-life. Subcutaneous co-administration of trastuzumab in combination with rHuPH20 had no obvious effect on the absorption or exposure of either compound. It is noteworthy that the concentration of rHUPH20 has been lower in the nonclinical studies than what is proposed for the fixed dose combination.

Toxicity of pertuzumab and trastuzumab has been comprehensively characterised in the context of the initial MAAs of Perjeta and Herceptin, and of rHuPH20 in the context of subcutaneous line extension of trastuzumab, and no new toxicology studies were conducted. This approach is acceptable in accordance with the ICH M3 (R2) guideline (EMA/CPMP/ICH/286/1995) and the guideline on fixed combinations (EMEA/CHMP/SWP/258498/2005), provided that sufficient experience of concomitant use exists. As pertuzumab and trastuzumab have been used clinically in free combinations and that clinical data for the

fixed combination product has been provided (see clinical part), the experience on concomitant use is considered sufficient and the approach taken by the applicant is supported.

Previously, toxicological and clinical findings of diarrhea have been identified for pertuzumab and clinical findings of cardiotoxicity identified for trastuzumab. Furthermore, pertuzumab related changes were also seen in an embryo-foetal development study in cynomolgus monkeys and evidence of reproduction toxicity was also seen for trastuzumab as well as for rHuPH20. This has been reflected in the SmPC section 4.6 and 5.3, where relevant restrictions to the use of PH FDC SC in women of child-bearing potential, pregnant and lactating women are included.

The applicant has presented available data regarding local tolerance of both pertuzumab and trastuzumab administered alone, as well as data from the bioavailability study of pertuzumab administered SC alone and in combination with trastuzumab. Although the reporting of clinical signs of local tolerance (adverse or none) appears to have been omitted in the bioavailability study report (report 1038750), the applicant stated in the non-clinical overview that the SC administration of pertuzumab was well tolerated and it is indicated in several places that the same is true for the sequential SC administration of the pertuzumab trastuzumab combination. However, as clinical information supersedes non-clinical information and only grade 1 injection site changes were seen in the clinical studies, the lack of traceability of non-clinical tolerability in study 1038750, is not pursued further.

It is agreed with the applicant, that the fixed-dose combination of pertuzumab and trastuzumab do not provide an environmental risk, as monoclonal antibodies are readily biodegradable.

2.3.7. Conclusion on the non-clinical aspects

Comprehensive PD, PK and toxicological characterisation of trastuzumab, pertuzumab, and rHuPH20 has been performed. There is a clear scientific rationale for combining trastuzumab and pertuzumab in the treatment of breast cancer and no findings leading to any non-clinical major objections have been identified during the non-clinical assessment of the MAA for the fixed-dose combination of pertuzumab and trastuzumab (PH FDC SC).

Overall, from the non-clinical perspective, the applicant has provided sufficient documentation and justification to support this MAA for the fixed-dose combination product PH FDC SC.

2.4. Clinical aspects

2.4.1. Introduction

The applicant has submitted two new clinical studies and a population pharmacokinetic (popPK) analysis (see Table 2.3.1.1).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 4. Overview of clinical studies providing data for PH FDC SC

Study Protocol No.	Study Title	PK-Evaluable Population	Key Objectives	Status
BO30185	A Phase I, open-label, two-part, multicentre Perjeta subcutaneous dose-finding study in combination with Herceptin in healthy male volunteers and female patients with early breast cancer	Healthy male volunteer (n=48) HER2-positive EBC patients (n=40)	**Dose-finding and dose-confirmation:** • Determine the optimal dose of pertuzumab for SC administration, injected alone or mixed with trastuzumab, which results in comparable exposure to Perjeta IV. • Confirm the dosing regimen in women with EBC	Completed
WO40324 (FeDeriCa)	A phase III, randomized, multicentre, open label, two-arm study to evaluate the pharmacokinetics, efficacy, and safety of subcutaneous administration of the fixed dose combination of pertuzumab and trastuzumab in combination with chemotherapy in patients with HER2-positive early breast cancer	HER2-positive EBC patients PH FDC SC (n=206) [a] P+H IV (n=203) [a]	**PK non-inferiority assessment:** • Non-inferiority of serum pertuzumab Cycle 7 C_{trough} (pre-dose Cycle 8) in PH FDC SC compared with P+H IV • Non-inferiority of serum trastuzumab Cycle 7 C_{trough} (pre-dose Cycle 8) in PH FDC SC compared with P+H IV • Evaluate the efficacy and safety of the PH FDC SC compared with P+H IV	Ongoing Primary analysis completed (cut-off date: 4 July 2019)
			•	

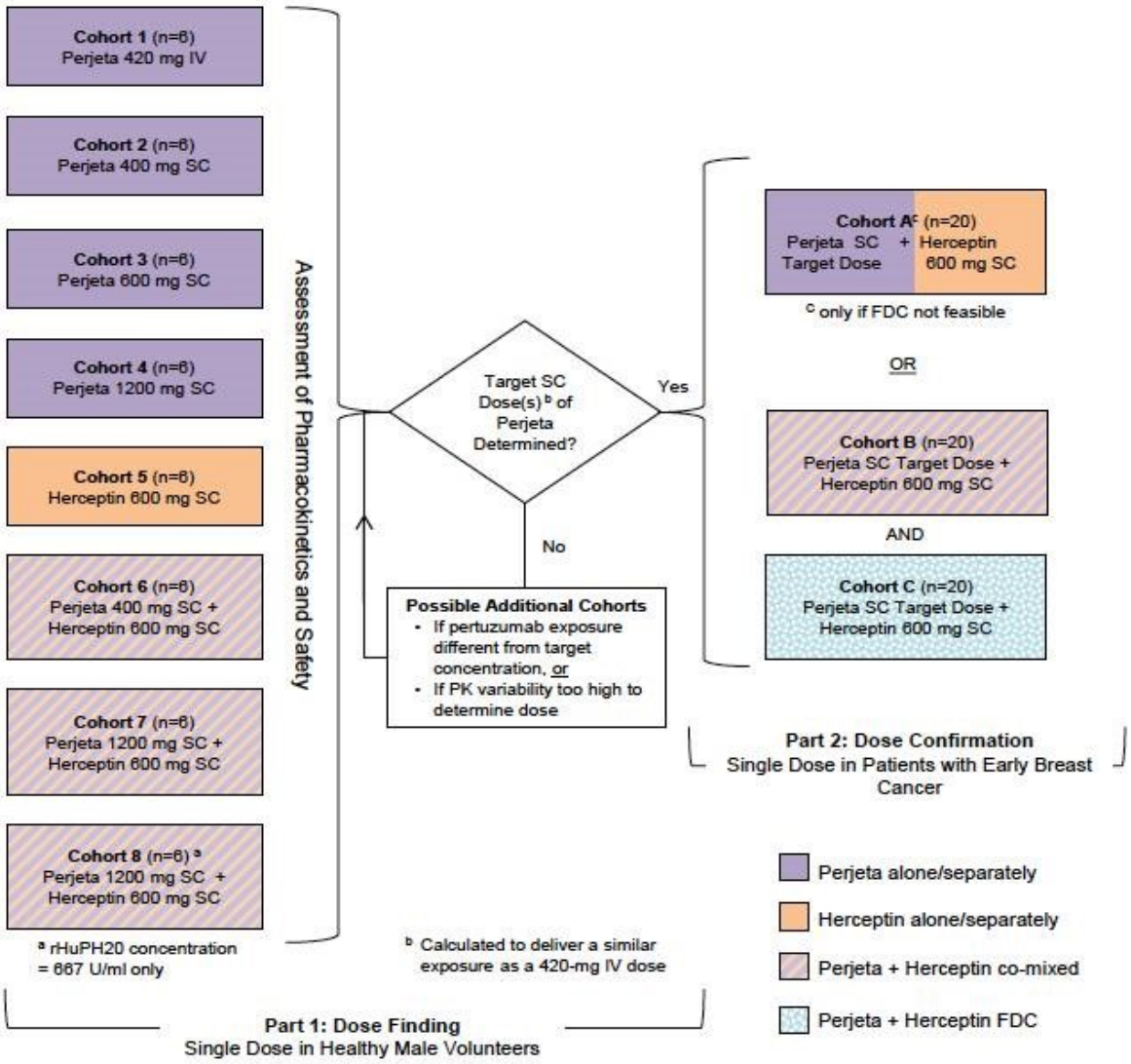
2.4.2. Pharmacokinetics

Study BO30185

Methods

Study BO30185 was a single dose, Phase I, open label, multi-centre, dose finding study, that consisted of two parts. Healthy male volunteers (HMV) were enrolled in the **Part 1** of the study, which was intended for determining loading and maintenance dose of pertuzumab SC, whereas in the **Part 2** of the study, which was intended for dose confirmation, females with EBC were enrolled who have completed their (neo)adjuvant breast cancer therapy. The overview of the BO30185 study design can be seen in Figure 3

Figure 3 Key features of the Study BO30185 design



FDC = fixed-dose combination; SC = subcutaneous.

Permeation enhancer rHuPH20 was used in Part 1 and Part 2 of the study. Following concentrations of rHuPH20 were used in different cohorts: 0 U/mL (Cohort 1), 2000 U/mL (Cohort 2-7), 667 U/mL (Cohort 8), 1000 U/mL (Cohort B), and 2000 U/mL (Cohort C). PK samples were collected in the following days for the SC administration route: Day 1 (Pre-dose, 6, 8, and 12 hrs post dose), Days 2, 3, 5, 8, 10, 15, 22, 43, 85, and the follow-up visit. PK samples were collected in the following days for the IV administration route: Day 1 (Pre-dose and end of infusion, and 3 hrs post dose), Days 2, 3, 5, 8, 15, 22, 35, 43, 85, and the follow-up visit. Samples for rHuPH20 plasma concentrations were collected at baseline (pre-dose) and 0.5 and 1.0 hours post-dose.

Results

Forty-eight HMVs were enrolled in **Part 1** of the study (six in each Cohorts 1-8). In **Part 2,** 40 female patients with EBC were enrolled (20 patients in each Cohort B and C). Cohort A was not required, since feasibility of the PH FDC SC had been demonstrated. The comparison of the approved dosage of IV pertuzumab 420 mg (Cohort 1) for EBC with SC pertuzumab 600mg (Cohort 3) showed similar exposure

results, both cohorts consisted of HMVs. Results for pertuzumab and trastuzumab from Part 1 and Part 2 of the study are presented below in Table 5 and Table 6, respectively. Based on the results obtained, the maintenance dosage of SC pertuzumab 600mg in the PH FDC SC formulation is deemed acceptable.

The approved IV loading dose of pertuzumab 840 mg was not included in the study as a control. According to applicant, an approximately dose-proportional increase of exposure was seen in the study. As a result, the loading dose for PH FDC SC formulation was estimated based on dose-proportionality, and it was determined to be 1200 mg. This was deemed acceptable in the scientific advice EMA/CHMP/SAWP/791149/2017.

Table 5. Serum pertuzumab PK parameter summary following a single dose of the study drug

Cohort	Mean (CV%)			
	C_{max} (µg/mL)	**C_{min}** (µg/mL)	**$T_{½}$** (day)	**AUC_{inf}** (µg/mL*day)
Part 1				
Cohort 1: IV pertuzumab 420 mg (n=6)	142 (6.66)	32.7 (11.5)	11.3 (17.7)	2180 (10.9)
Cohort 2: SC pertuzumab 400 mg (n=6)	36.1 (18.0)	21.9 (17.6)	9.73 (18.3)	1190 (19.9)
Cohort 3: SC pertuzumab 600 mg (n=6)	68.8 (19.4)	38.3 (26.7)	14.6 (40.1)	2390 (31.3)
Cohort 4: SC pertuzumab 1200 mg (n=6)	147 (13.9)	77.1 (20.3)	22.2 (17.7)	4930 (16.2)
Cohort 6: co-mixed pertuzumab 400 mg and trastuzumab 600 mg(n=6)	49.0 (15.6)	21.8 (10.1)	8.47 (9.80)	1230 (12.1)
Cohort 7: co-mixed pertuzumab 1200 mg and trastuzumab 600 mg (n=6)	151 (14.9)	74.7 (27.5)	20.7 (10.9)	4360 (25.5)
Cohort 8: co-mixed pertuzumab 1200 mg and trastuzumab 600 mg (n=6)	160 (19.2)	92.1 (20.7)	24.5 (14.5)	6160 (22.7)
Part 2				
Cohort B: co-mixed pertuzumab target dose (600 mg) and trastuzumab 600 mg (n=20)	62.9 (35.9)	33.0 (41.0)	15.9 (46.4)	2050 (40.6)
Cohort C: co-formulated FDC pertuzumab target dose (600 mg) and trastuzumab 600 mg (n=20)	62.3 (18.8)	35.4 (21.7)	15.0 (35.0)	2010 (25.5)

AUC_{inf}=area under the concentration-time curve extrapolated to infinity; C_{max}=maximum concentration; C_{min}=minimum concentration; CV=coefficient of variation; FDC=fixed-dose combination; IV=intravenous; SC=subcutaneous. Note: rHuPH20 concentration received by each cohort in Part 1 and Part 2 are as follows: 0 U/mL (Cohort 1), 2000 U/mL (Cohort 2-7), 667 U/mL (Cohort 8), 1000 U/mL (Cohort B), and 2000 U/mL (Cohort C).

During study BO30185 various concentrations of rHuPH20 were tested. Cohort 8 had higher pertuzumab and trastuzumab exposure (higher Cmin and AUCinf) than Cohort 7 despite using lower concentrations of rHuPH20 (667 U/mL vs. 2000 U/mL). Whereas Cohort B (rHuPH20 concentration of 1000 U/mL) had similar exposure of trastuzumab and pertuzumab to Cohort C (rHuPH20 concentration of 1000U/mL). The MAA chose the 2000U/ml concentration of rHuPH20 for the PH FDC SC formulation. The decision to choose this concentration was based on the available clinical experience with rHuPH20.

Administration of pertuzumab and trastuzumab as single agents resulted in similar exposure results compared to co-mixed and co-formulated administration. As a result, no significant PK interactions are expected between these two agents. (see Table 5 and Table 6)

Table 6. Serum trastuzumab PK parameter summary following a single dose of the study drug

Cohort	Mean (CV%)			
	C_{max} (µg/mL)	C_{min} (µg/mL)	$T_{½}$ (day)	AUC_{inf} (µg/mL*day)
Part 1				
Cohort 5: SC tratstuzumab 600 mg (n=6)	65.6 (15.7)	32.0 (20.2)	8.85 (21.6)	1690 (24.8)
Cohort 6: co-mixed pertuzumab 400 mg and trastuzumab 600 mg(n=6)	71.3 (15.6)	28.4 (11.6)	7.62 (9.30)	1580 (13.1)
Cohort 7: co-mixed pertuzumab 1200 mg and trastuzumab 600 mg (n=6)	68.5 (17.6)	27.8 (27.2)	7.24 (8.39)	1440 (26.5)
Cohort 8: co-mixed pertuzumab 1200 mg and trastuzumab 600 mg (n=6)	73.6 (20.1)	34.0 (23.2)	7.85 (15.3)	1860 (26.6)
Part 2				
Cohort B: co-mixed pertuzumab target dose (600 mg) and trastuzumab 600 mg (n=20)	56.1 (35.3)	25.4 (47.2)	8.68 (19.3)	1380 (44.2)
Cohort C: co-formulated FDC pertuzumab target dose (600 mg) and trastuzumab 600 mg (n=20)	57.7 (19.6)	28.9 (18.5)	8.06 (28.1)	1440 (20.8)

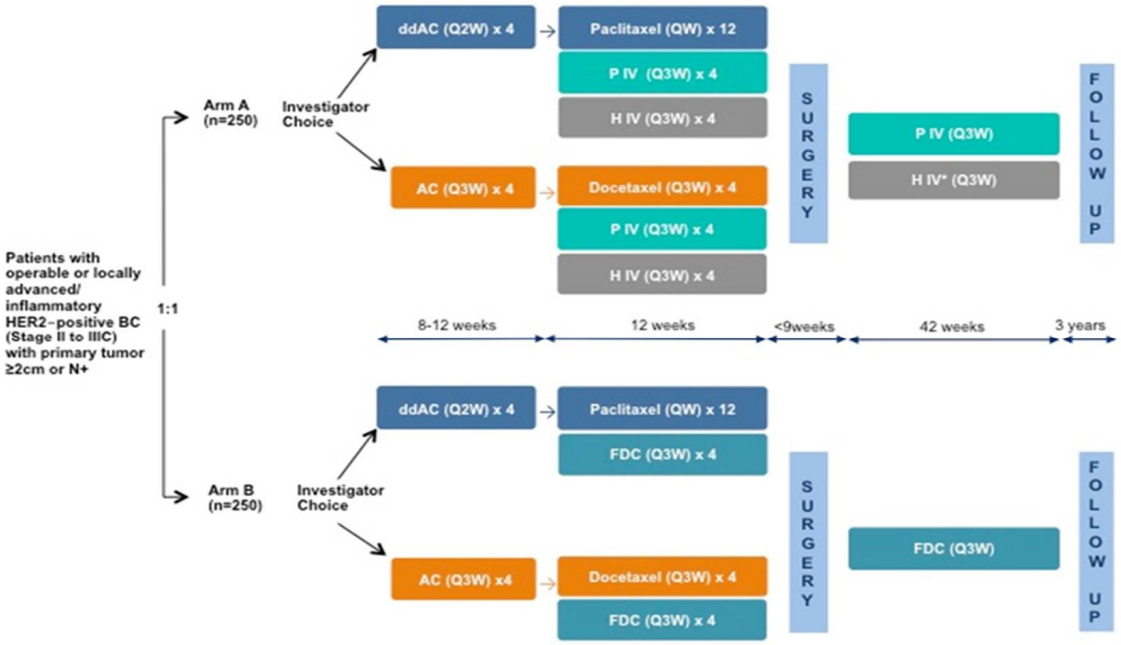
AUC_{inf}=area under the concentration-time curve extrapolated to infinity; C_{max}=maximum concentration; C_{min}=minimum concentration; CV=coefficient of variation; FDC=fixed dose combination; SC=subcutaneous. Note: rHuPH20 concentration received by each cohort in Part 1 and Part 2 are as follows: 0 U/mL (Cohort 1), 2000 U/mL (Cohort 2-7), 667 U/mL (Cohort 8), 1000 U/mL (Cohort B), and 2000 U/mL (Cohort C).

Study WO40324 FeDeriCa

Methods

This was a global Phase III, two-arm, open-label, multicentre, randomised study which aimed to investigate the PK, efficacy, and safety of PH FDC SC in combination with chemotherapy in patients with HER2-positive EBC in the neoadjuvant/ adjuvant setting. Study design overview is presented in Figure 4

Figure 4 Key features of the FeDeriCa study design



AC=doxorubicin plus cyclophosphamide; BC=breast cancer; ddAC=dose-dense doxorubicin plus cyclophosphamide; FDC=fixed-dose combination of pertuzumab and trastuzumab SC (PH FDC SC); H=Herceptin (trastuzumab); N+=node-positive; P=pertuzumab; QW=once a week; Q2W=every 2 weeks; Q3W=every 3 weeks.

The **primary objective** of this study was to demonstrate non-inferiority of the Cycle 7 (*i.e.*, pre-dose Cycle 8) pertuzumab serum C_{trough} (measured concentration at the end of dosing interval *at steady state*) of pertuzumab SC within the PH FDC SC compared with the Perjeta IV formulation in patients with HER2-positive EBC. The **secondary objective** of this study was to demonstrate non-inferiority of the Cycle 7 (*i.e.*, pre-dose Cycle 8) trastuzumab serum C_{trough} of trastuzumab SC within the PH FDC SC compared with the Herceptin IV formulation in patients with HER2-positive EBC. Schedule of pharmacokinetic sampling is presented in Table 7 The primary and secondary PK analysis were performed on the Per Protocol PK (PPP) analysis population, which included all patients enrolled who adhered to the protocol.

Table 7. Schedule of PK Assessment in the FeDeriCa Study

Arm	Planned PK Sample Times
PH FDC SC	Cycle 5: Day 1 pre-dose, Days 2 and 15 post-dose; Cycles 6, 8, 9, 10, 11, 13, 18 and 22: Day 1 Pre-dose; Cycles 7 and 12: Day 1 pre-dose, Days 2, 4, 8, and 15 post-dose.
P+H IV	Cycle 5: Day 1 (pre-dose, end of IV), Days 2 and 15 post-dose; Cycles 6, 8, 9, 10 and 11: Day 1 (Pre-dose and end of IV); cycles 13, 18, and 22: Day 1 Pre-dose; Cycles 7 and 12: Day 1 (pre-dose, end of IV) and Days, 2, 4, 8, and 15 post-dose.

Results

The PPP analysis population comprised 203 patients in the P+H IV arm and 206 patients in the PH FDC SC arm, of the 252 (P+H IV arm) and 248 (PH FDC SC arm) patients who were randomised.

Primary endpoint: The mean and geometric mean Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough} values were higher in the PH FDC SC arm than the P+H IV arm. The geometric mean for the PH FDC SC arm was 88.7 µg/mL compared with 72.4 µg/mL for the P+H IV arm (Table 8 below). The resulting GMR of Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough}, SC/C_{trough}, IV values were 1.22 (90% CI: 1.14, 1.31). The corresponding lower limit of the two-sided 90% CI of 1.14 was above the pre-specified non-inferiority margin of 0.8.

Table 8 FeDeriCa Study: Observed Cycle 7 (Pre-dose Cycle 8) Serum Pertuzumab C_{trough} (µg/mL) by Randomised Treatment (Per Protocol Pharmacokinetic Population)

	P+H IV N=203	PH FDC SC N=206
Mean	78.5	93.7
Geometric mean	72.4	88.7
Median	76.6	88.1
Range	0.5—180.0	30.2—201.0
SD	26.8	31.5
%CV	34.1	33.6
GMR[a]	1.22	–
90% CI of the GMR	1.14–1.31	–

C_{trough}=steady state trough concentration; CV=percent coefficient of variation; GMR=geometric mean ratio; P+H IV=Perjeta and Herceptin intravenous; PH FDC SC=pertuzumab and trastuzumab fixed dose combination subcutaneous.
[a]ratio of test treatment group (PH FDC SC arm) to reference treatment group (P+H IV arm).

The applicant has provided adequate justification that the selected C_{trough} is the actual steady state C_{trough}.

Secondary endpoint: The mean and geometric mean Cycle 7 (pre-dose Cycle 8) serum trastuzumab C_{trough} values were higher in the PH FDC SC arm than the P+H IV arm. The resulting GMR Cycle 7 (pre-dose Cycle 8) C_{trough}, SC/C_{trough}, IV value was 1.33 (90% CI: 1.24, 1.43). The corresponding lower limit of the two-sided 90% CI of 1.24 was greater than the pre-specified non-inferiority margin of 0.8 (Table 9 below). It is known that the target C_{trough} concentration for trastuzumab is 20 µg/mL.

Table 9 FeDeriCa Study: Observed Cycle 7 (Pre-dose Cycle 8) Serum Trastuzumab C_{trough} (µg/mL) by Randomised Treatment (Per Protocol Pharmacokinetic Population)

	P+H IV N=203	PH FDC SC N=206
Mean	47.1	61.6
Geometric mean	43.2	57.5
Median	45.8	57.9
Range	0.5 – 95.2	16.5 – 150.0
SD	16.3	22.8
%CV	34.7	37.0
GMR[a]	1.33	–
90% CI of the GMR	1.24–1.43	–

C_{trough}=concentration at the end of a dosing interval; CV=percent coefficient of variation; GMR=geometric mean ratio; P+H IV = Perjeta and Herceptin IV formulation; PH FDC SC=pertuzumab and trastuzumab fixed-dose combination for subcutaneous injection.
[a] ratio of test treatment group (PH FDC SC arm) to reference treatment group (P+H IV arm).

Analytical methods

The applicant submitted information on performance of the analytical methods used in Studies BO30185 and WO40324 to measure pertuzumab, trastuzumab, and rHuPH20, as well as ADAs to them. The methods were developed and validated prior to the analysis of clinical study samples and met predefined criteria. Details of the assays' performance are provided in the bioanalytical reports as well as in the method validation reports (included in Module 5).

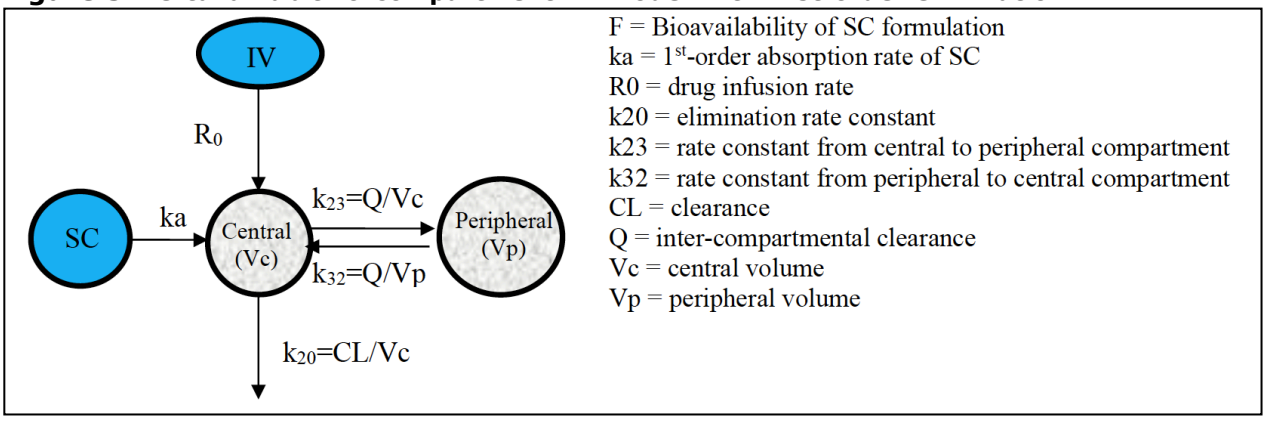
The applicant reported that the bioanalytical vendor confirmed a calibration error in the assay method for the trastuzumab pharmacokinetic (PK) sample analysis resulting in approximately 3% higher reported concentration of trastuzumab in clinical samples. Although the corrected PK calculations show only minor corrections for Cycle 7 C_{trough}, the observed error is much less than the normal trastuzumab PK variability. The study conclusions are not impacted by this issue.

Population PK exposure-response study BO40324

Population pharmacokinetic modelling and exposure-response analysis were performed. Plasma concentrations from the one phase III study FeDeriCa (WO40324) was included in the population PK analysis. A total of 5656 plasma samples were taken, out of which 5180 quantifiable samples from 489 patients were used in the current final pertuzumab PopPK analysis.

The PK model that best described the data was a two-compartment model with first-order elimination from the central compartment, refer to Figure 5. SC absorption was modelled as a first–order process (see Figure below). The PK model was parameterised in terms of clearance (CL), central volume (V_c), intercompartmental clearance (Q), peripheral volume (V_p), first-order absorption rate (k_a) and bioavailability (F). Inter-individual variability (IIV) was estimated for CL, V_c, V_p and F. Due to the limited samples collected during the distribution phase and absorption phase, no IIV was estimated for Q and k_a.

Figure 5 Pertuzumab two-compartment PK model with first-order elimination



Using step wise covariate model building, in the forward step, in addition to LBW on CL, V_c, and V_p and albumin on CL, Asian (region) was added as significant covariate (p-value <0.01) on CL. No covariate was excluded through the backward step and all remained in the final model.

Parameter estimates for final model

The equations for the final model are:

$$CL\ (L/d) = 0.163 \times (ALB/43.25)^{-0.629} \times (LBW/45.09)^{1.252} \times (1.123 \text{ if in Asian Region}) \times e^{\eta_{CL}}$$

$$Vc\ (L) = 2.77 \times (LBW/45.09)^{0.839} \times e^{\eta_{V2}}$$

$$Q\ (L/d) = 0.616$$

$$Vp\ (L) = 2.49 \times (LBW/45.09)^{0.716} \times e^{\eta_{V3}}$$

$$F = 0.712 \times e^{\eta_F}$$

The pertuzumab population PK model parameter estimates are presented in Table 10.

Table 10 Pertuzumab population PK model parameters' estimates

Parameter	Parameter description	Estimate	RSE for Estimate (%)	IIV (CV%)	RSE for IIV (%)	Shrinkage (%)
θ_1	Clearance (CL, L/d)	0.163	5.81	23.5	48.8	14.4
θ_2	Central Volume (Vc, L)	2.77	3.15	34.8	7.52	11.2
θ_3	Inter-compartmental clearance (Q, L/d)	0.616	5.23			
θ_4	Peripheral Volume (Vp, L)	2.49	7.69	25.6	7.93	49.7
θ_5	Apparent first-order absorption rate (ka, /d)	0.348	7.72			
θ_6	Bioavailability (F)	0.712	16.0	17.8	1.10	50.2
Residual Error						
θ_7	Proportional residual error - SC	0.155	4.32			10.1
θ_8	Proportional residual error – IV	0.175	4.41			10.1
Covariates						
θ_9	Albumin on CL	-0.629	33.1			
θ_{10}	Lean body weight on CL	1.25	13.4			
θ_{11}	Lean body weight on Vc	0.839	17.9			
θ_{12}	Lean body weight on Vp	0.716	33.1			
θ_{13}	Change of CL in Asian region	0.123	31.0			
Half-life (d)		24.3		28.2		

IIV = inter-individual variability, IV = intravenous, RSE = relative squared error, SC = subcutaneous. Half-life estimate is calculated from typical parameter values. The half-life IIV is calculated from post-hoc estimates.

The effects of LBW, albumin and Region (Asian vs. non-Asian) on pertuzumab PK were quantified in the final model. After inclusion of all significant covariates in the final model, IIV was reduced from 27.4% to 23.5% for CL, from 35.2% to 34.8% for V_c, from 27.4% to 25.6% for V_p and from 20.2% to 17.8% for F. The following **covariate parameter relationships were identified**: **1.** CL increased in patients with higher

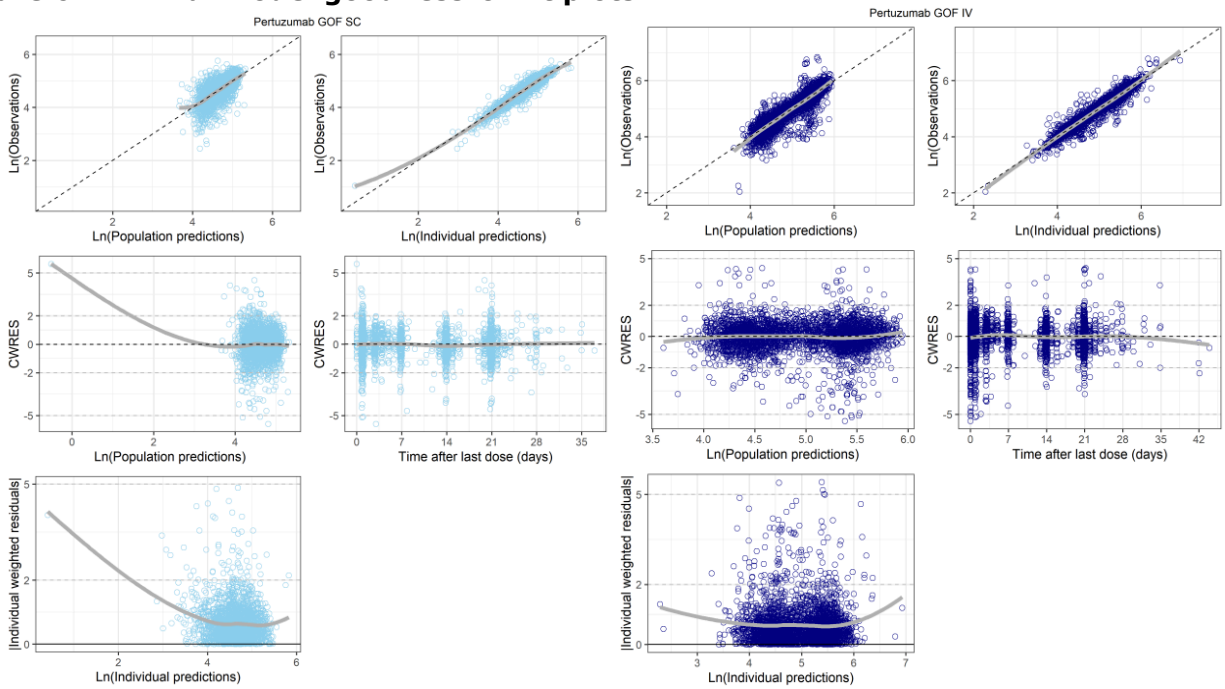
LBW: CL could increase by 22% when LBW is at the 95th percentile while other covariates are fixed to typical values. CL could decrease by 34% when LBW is at the 5th percentile; **2.** V_c increased in patients with higher LBW. Vc could increase by 14.5% when LBW is at the 95th percentile. V_c could decrease by 13.4% when LBW is at the 5th percentile; **3.** V_p increased in patients with higher LBW. Vp could increase by 12.3% when LBW is at the 95th percentile. V_p could decrease by 11.5% when LWT is at the 5th percentile; **4.** CL also decreases in patients with higher albumin by 6% when albumin is at the 95th percentile and increases by 16% when albumin is at the 5th percentile; **5.** CL was increased in Asians (12.3%).

The parameter values estimated in the current popPK model are similar to the ones estimated in previously used popPK model described in Garg et al. 2014[1]. However, **no bootstrapping was performed** for the current popPK model evaluation. The applicant argues that bootstrapping was not performed for the final model as the standard error of the final model were obtained after the estimation step from NONMEM. This issue is not further pursued.

According to the developed pertuzumab s/c PopPK patients of **Asian ethnicity have an increased CL of pertuzumab** (12.3%). However, the exposure, efficacy and safety results for subjects of Asian ethnicity are similar to non-Asians.

According to MAA, the standard goodness-of fit diagnostics, separated for SC and IV patients, in Figure 6 show good agreement between predicted and observed pertuzumab concentrations.

Figure 6 Final model goodness-of-fit plots



Left panel: SC observations, right panel: IV observations. Top panel: Observed versus population and individual predicted concentrations (ln-scale), Middle panel: CWRES versus population prediction (log-scale) and time, Bottom panel: absolute values of individual WRES versus individual predictions (log-scale) for the final PK model.

[1] Garg A *et al*. Population pharmacokinetic and covariate analysis of pertuzumab, a HER2-targeted monoclonal antibody, and evaluation of a fixed, non-weight-based dose in patients with a variety of solid tumours. Cancer Chemother Pharmacol 2014, DOI: 10.1007/s00280-014-2560-3.

One of the issues identified evaluating goodness-of-fit plots is that there was a single low observation, diverting the smooth line of the agreement between predicted and observed concentrations. The applicant explains, that the estimate did not match outlier criteria throughout the modelling process, and thus was retained. It is acceptable, as in general, the model predicts the concentration well, we can see in the top left most panel of Figure 2.3.14, that most of the observation lay on the quantile-quantile (QQ) line.

Absorption

The Tmax determined in the Phase I study BO30185 was between 4 to 7 days, in HMVs. In the phase 3 study in patients, the median time to reach C_{max} was 3.82 days. Pertuzumab exposure appeared to increase proportionally with SC dose. In both studies, PH FDC SC was administered subcutaneously in the thigh over 5 - 8 minutes.

Bioavailability

The FeDeriCa pertuzumab population PK model is a two-compartment model with first-order subcutaneous absorption with estimated bioavailability of 71%.

Distribution

The central compartment volume of distribution (Vc) was estimated to be 2.77 L. Vc increased in patients with higher lean body weight. Vc could increase by 14.5% when LBW is at the 95th percentile while other covariates are fixed to typical values. Similarly, Vc could decrease by 13.4% when LBW is at the 5th percentile.

The peripheral compartment volume of distribution (Vp) was estimated to be 2.49 L. Vp increased in patients with higher lean body weight. Vp could increase by 12.3% when LBW is at the 95th percentile while other covariates are fixed to typical values. Similarly, Vp could decrease by 11.5% when LBW is at the 5th percentile.

Elimination

The primary elimination pathways for pertuzumab and trastuzumab are degradation by the reticulo-endothelial system (like endogenous IgG) or by target-mediated elimination. Metabolites are amino acids and small peptides.

In the Pop PK analyses, pertuzumab clearance is 0.163 L/day with 23% inter-individual variability. The inter-compartmental clearance (Q) was estimated to be 0.616 L/day. Clearance was smaller than previous estimates for P+H IV pertuzumab (0.163 L/d for current model, 0.235 L/d for previous model). In the previous model, the median lean body weight was slightly larger (48 kg in previous model vs. 45 kg in present model), and median albumin was slightly smaller (39 g/L in previous model vs. 43 g/L in present model). After correcting for these differences, the estimated clearance for the previous model in the FeDeriCa population is 0.204 L/d.

The $t_{1/2}$ was determined to be 24.3 days in the popPK analysis with 28% inter-individual variability. Significant covariates influencing the CL were LBW, serum albumin, and Asian ethnicity (see Table 16)

Dose proportionality and time dependencies

In the Perjeta MAA it was demonstrated that pertuzumab has linear PK with respect to dose-proportionality and time-independence at a dose range of 2 to 25 mg/kg when weight-based dosing was studied, and from an 840 mg loading dose followed by 420 mg maintenance dose to 1050 mg dose when fixed, non-weight-based dosing was studied. Pertuzumab exposure appear to increase proportionally with SC dose in the Phase I study. The dose-proportional data was used to select the PH FDC SC loading dose of 1200 mg.

After a single injection of 600 mg pertuzumab in the PH FDC SC formulation, the AUC_{inf} of pertuzumab was 2010 day*ug/mL (mean CV% 25.5).

In the Phase I study, the loading dose 1200 mg of pertuzumab was not tested in the FDC formulation, only in co-mixed formulation. AUC_{inf} of pertuzumab administered in the co-mixed formulation with trastuzumab, was 4630 day*ug/mL (mean CV% 25.5) and 6160 day*ug/mL (mean CV% 22.7), depending on the concentration of the rHuPH20.

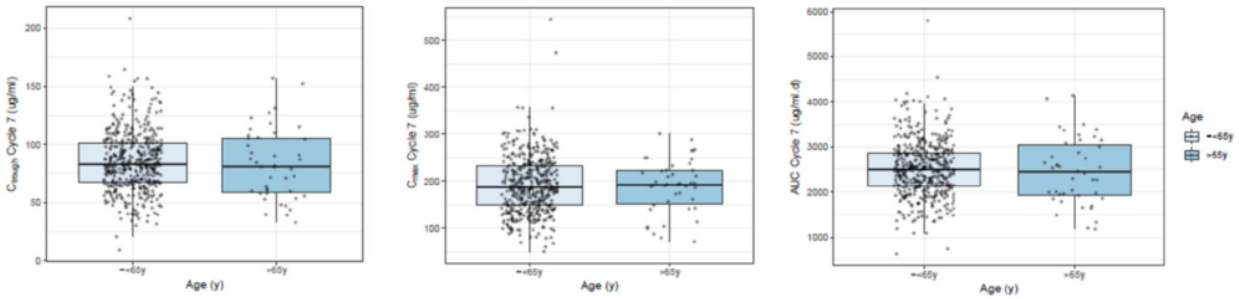
In the FeDeriCa study, mean Cycle 7 AUC_{0-21} for pertuzumab was determined to be 2530 day*ug/mL (mean CV% 26.2).

Special populations

Age

The FeDeriCa pertuzumab pop PK analysis dataset included data from 489 patients with a median age of 51 years (range: 25–80 years). A total of 446 patients (91.2%, 224 in the PH FDC SC arm and 222 in the P+H IV arm) were ≤65 years of age and 43 patients (8.8%, 19 in the PH FDC SC arm and 24 in the P+H IV arm) were >65 years of age. Median model predicted pertuzumab Cycle 7 C_{trough} for patients ≤65 years was 82.7 µg/mL versus 80.8 µg/mL for patients >65 years in FeDeriCa study. Figure 7 shows the current final pop PK model predicted pertuzumab steady state exposure (Cycle 7 C_{trough}, C_{max}, and AUC) following administration of PH FDC SC or P+H IV by age for all patients in the FeDeriCa PopPK analysis; age had no effect on pertuzumab steady state exposure. Following the PH FDC SC administration, median model predicted pertuzumab Cycle 7 C_{trough} for patients ≤65 years was 88.8 µg/mL versus 90.1 µg/mL for patients >65 years.

Figure 7 Model-Predicted Pertuzumab Exposures in Cycle 7 Stratified by Age.



AUC=area under the curve over 21 days in Cycle 7, C_{max}=maximum concentration, C_{trough}=trough concentration. Boxplots show the median (solid bold line), the interquartile range (shaded boxes), 1.5 times the interquartile range (whiskers). Points are jittered in the x-axis direction for clarity.
Source: PopPK/ER Report Figure 4-20

Table 11. Number of Elderly Subjects by Age Groups in the Pharmacokinetic Studies

Studies		Analysis population	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Phase I BO30185	Part 1	Healthy Male Volunteer	0/42	0/42	0/42
	Part 2	EBC Patients	4/40	2/40	0/40
Phase III WO40324 (FeDeriCa)	P+H IV	ITT population	30/252	3/252	0/252
		PPP population	24/203	1/203	0/203
	PH FDC SC	ITT population	22/248	4/248	0/248
		PPP population	22/206	3/206	0/206

EBC= early breast cancer; ITT= intention to treat; PPP= per protocol PK.

Impaired hepatic function

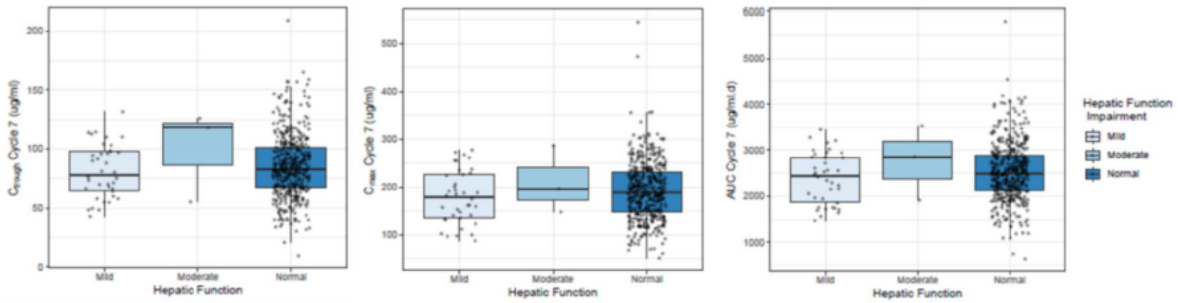
No dedicated clinical studies have been conducted in patients with hepatic impairment for pertuzumab. The FeDeriCa pertuzumab PopPK analysis dataset included the following data:

- 38 patients (7.8%, 20 in the PH FD SC arm and 18 in the P+H IV arm) categorised with mild hepatic impairment
- 3 patients (0.6%, 1 in the PH FDC SC arm and 2 in the P+H IV arm) categorised with moderate hepatic impairment
- 448 (91.6%, 222 in the PH FDC SC arm and 226 in the P+H IV arm) patients categorised with normal hepatic function

The current pertuzumab final pop PK model indicated no apparent relationship between pertuzumab CL and baseline ALT, AST, total bilirubin, and hepatic function category. This is consistent with the previous pop PK analysis. Figure 8 shows the current final pop PK model predicted pertuzumab steady state exposure (Cycle 7

C_{trough}, C_{max}, and AUC) following administration of PH FDC SC or P+H IV by hepatic function for all patients in the FeDeriCa pop PK analysis

Figure 8 Model-Predicted Pertuzumab Exposures in Cycle 7 Stratified by Hepatic Function



AUC=area under the curve over 21 days in Cycle 7, C_{max}=maximum concentration, C_{trough}=trough concentration. Boxplots show the median (solid bold line), the interquartile range (shaded boxes), 1.5 times the interquartile range (whiskers). Points are jittered in the x-axis direction for clarity.

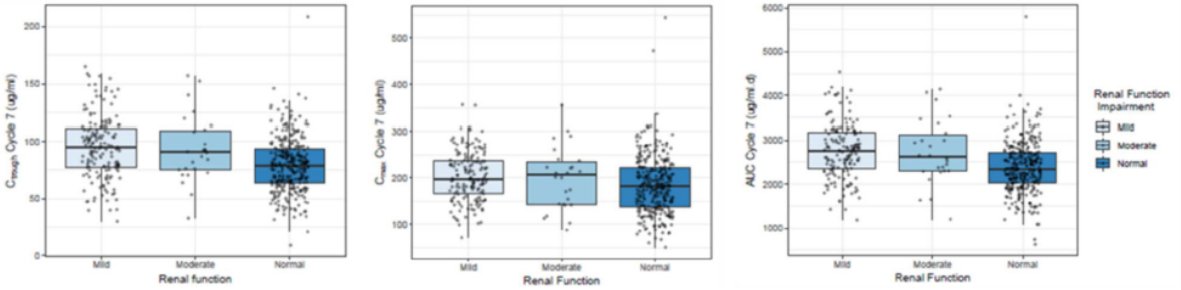
Impaired renal function

No dedicated clinical studies have been conducted in patients with renal impairment for pertuzumab. The FeDeriCa pertuzumab pop PK analysis dataset included the following data:

- 158 patients (32.3%, 77 in the PH FDC SC arm and 81 in the P+H IV arm) categorised with mild renal impairment
- 26 patients (5.3%, 14 in the PH FDC SC arm and 12 in the P+H IV arm) categorised with moderate renal impairment
- 305 patients (62.4%, 152 in the PH FDC SC arm and 153 in the P+H IV arm) categorised with normal renal function

The current pertuzumab pop PK model indicated no apparent relationship between pertuzumab CL and CLcr or renal function category. This is consistent with the previous pop PK analyses. Figure 9 shows the current final pop PK model predicted pertuzumab steady-state exposure (Cycle 7 C_{trough}, C_{max}, and AUC) following administration of PH FDC SC or P+H IV by renal function for all patients in the FeDeriCa PopPK analysis.

Figure 9 Model-Predicted Pertuzumab Exposures in Cycle 7 Stratified by Renal Function



AUC=area under the curve over 21 days in Cycle 7, C_{max}=maximum concentration, C_{trough}=trough concentration. Boxplots show the median (solid bold line), the interquartile range (shaded boxes), 1.5 times the interquartile range (whiskers). Points are jittered in the x-axis direction for clarity.

Pharmacokinetic interaction studies

No dedicated DDI studies have been conducted.

Based on data from the previous pivotal phase III WO20698 (CLEOPATRA) study in patients with HER2-positive MBC, no significant drug-drug interactions (DDIs) were observed between pertuzumab and trastuzumab (in the presence of docetaxel), or between pertuzumab and docetaxel (in the presence of trastuzumab) were observed.

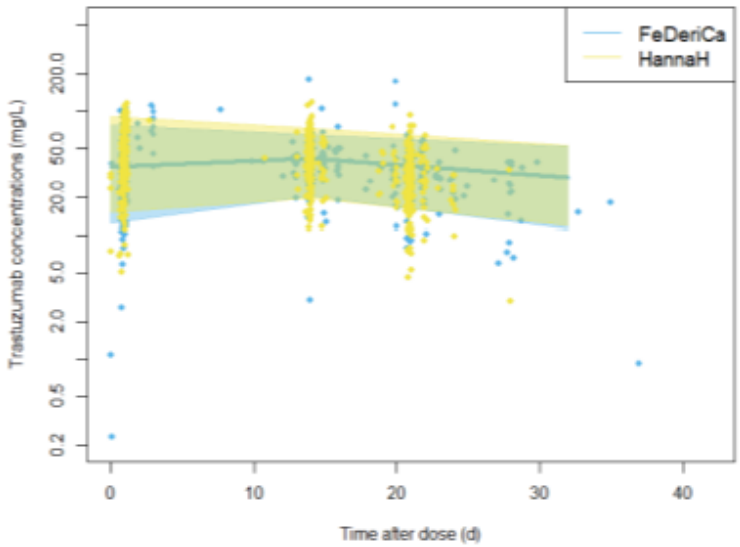
Pertuzumab-Trastuzumab PK Drug-Drug Interaction

In part 1 of study BO30185, two types of Perjeta SC injections were assessed: Perjeta given as a single-agent injection (for eventual use in co-administration with Herceptin SC single-agent injection) and Perjeta SC co-mixed with Herceptin SC in a single injection. If there were a PK interaction between Perjeta and Herceptin when co-mixed, the development of PH FDC SC would not be feasible.

To satisfy an exploratory analysis of a potential PK drug-drug interaction between pertuzumab and trastuzumab following administration of the PH FDC SC, a Visual Predictive Check (VPC) and Numerical Predictive Check (NPC) approach was applied.

A comparison of trastuzumab concentrations between HANNAH SC patients and FeDeriCa PH FDC SC patients after the first dose is shown below.

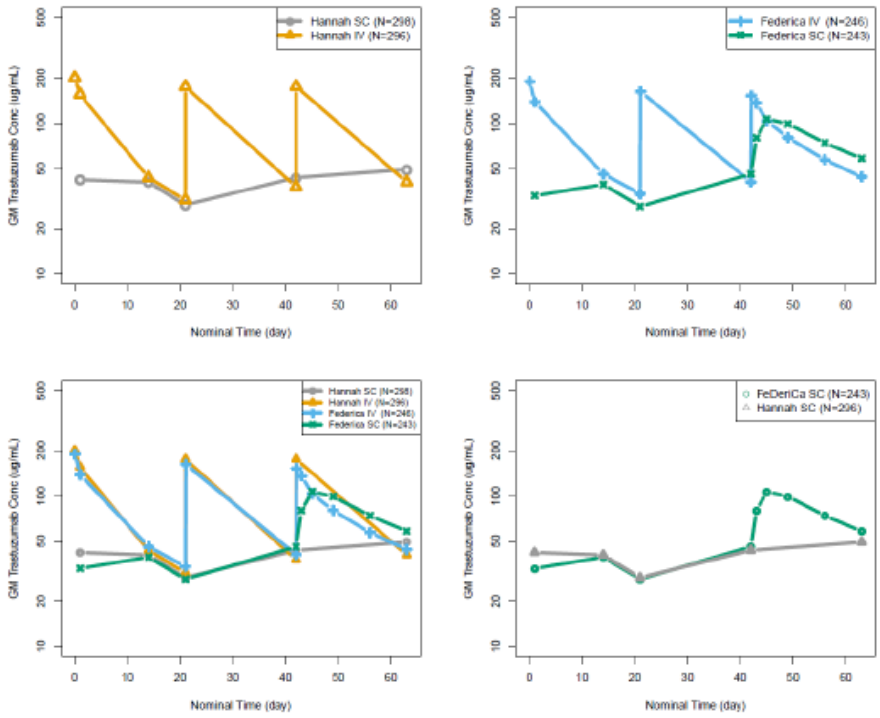
Figure 4-21: Observed trastuzumab concentrations versus time after the first dose in in FeDeriCa and HANNAH



Note: The solid blue and solid yellow lines represent the median value for observed trastuzumab concentrations with nominal time ≤ 21d stratified into the following time bins according to actual time after first dose: 0-3d, 10-18d, and >18d. Points represent samples from FeDeriCa (blue) and HANNAH (yellow). Shaded regions represent 5th to 95th percentile confidence intervals.
Source: 2019-09-03-TDM-DDI.R

The below figure compares the geometric mean trastuzumab curves for the first three cycles for HANNAH SC and FeDeriCa PH FDC SC patients, as well as the IV regimens from both studies.

Figure 8-11: Observed geometric mean trastuzumab concentrations versus nominal time after dose for the first three cycles



Note: GM = geometric mean, N = number of patients, IV = intravenous, SC = subcutaneous. The points and connecting lines indicate observed geometric mean trastuzumab concentrations according to nominal time. In the HannaH study, the first dose was administered in Cycle 1 with intensive PK sampling in Cycle 7 and 12 . No intensive sampling was done in HannaH after the third dose for comparison with the FeDeriCa. In the FeDeriCa study, the first dose was administered in Cycle 5 with intensive PK sampling in Cycle 7 and 12.
Source: 2019-09-03-TDM-DDI.R

There was no apparent impact of trastuzumab on the PK of pertuzumab when the two antibodies were delivered SC co-mixed.

Immunogenicity

In the phase 1 trial, the overall baseline prevalence for ADAs to pertuzumab and trastuzumab, and anti-rHuPH20 antibodies was 2/88 patients (2.3%), 6/88 patients (6.8%), and 6/87 patients (6.9%), respectively. These data may reflect a combination of pre-existing ADAs and/or untreated positive rate based on the statistical design of the assay cutpoints.

The overall incidence of ADAs to pertuzumab and trastuzumab, and anti-rHuPH20 antibodies in all cohorts was 27/88 patients (30.7%), 9/88 patients (10.2%), and 4/88 patients (4.5%), respectively. Exploratory analyses indicated that the occurrence of ADAs to pertuzumab and trastuzumab and/or anti-rHuPH20 antibodies did not appear to impact PK or have any clinical consequences with respect to safety (i.e., hypersensitivity or anaphylaxis events).

In the phase 3 trial (FeDeriCa), the incidence of treatment-emergent anti-drug antibodies (ADAs) was comparable between the P+H IV and PH FDC SC treatment arms. In the P+H IV arm, the incidence of treatment emergent ADAs to pertuzumab and trastuzumab was 3.0% (7/237 patients) and 0.4% (1/237 patients), respectively. In the PH FDC SC FDC arm, the incidence of treatment-emergent ADAs to

pertuzumab and trastuzumab, and anti-rHuPH20 antibodies was 4.8% (11/231 patients), 0.9% (2/232 patients), and 0.9% (2/225 patients), respectively. The exploratory analyses indicated that the occurrence of treatment-emergent ADAs to pertuzumab, trastuzumab, and/or anti-rHuPH20 antibodies did not appear to have any clinical consequences with respect to PK, efficacy or safety.

2.4.3. Pharmacodynamics

Mechanism of action

Trastuzumab and pertuzumab are both recombinant humanised monoclonal antibodies based upon the human IgG1(κ) framework sequence composed of two light chains and two heavy chains with functional differentiation based on their different CDRs. Via their respective distinct CDR regions, trastuzumab recognises sub-domain IV, the juxtamembrane region, while pertuzumab recognises sub-domain II, the dimerisation region, of the HER2 extracellular domain.

Binding of trastuzumab to the HER2 sub-domain IV inhibits ligand-independent HER2 signalling by blocking its homodimerisation and prevents the proteolytic cleavage of its extracellular domain subsequent constitutive activation of associated intracellular signalling pathways. As a result, trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2.

Binding of pertuzumab to the HER2 subdomain II 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 supporting cell growth arrest and apoptosis, respectively.

Pertuzumab and trastuzumab bind to distinct epitopes on the HER2 receptor without competing with each other and have complementary mechanisms for disrupting HER2 signalling. This results in augmented anti-proliferative activity *in vitro* and *in vivo* when pertuzumab and trastuzumab are given in combination. Additionally, the Fc portion of both their IgG1 framework provides for potent activation of ADCC. In addition, *in vitro,* both trastuzumab and pertuzumab mediate ADCC activity only on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Primary and Secondary pharmacology

No specific PD data were collected in the clinical studies BO30185 and WO40324. Accordingly, only exposure-response relationships will be described in this section.

Rationale for pharmacokinetic endpoint C_{trough}

The rationale for C_{trough} as a primary endpoint is based on historical *in vitro*, nonclinical, and clinical data. Nonclinical xenograft models have demonstrated that maximum tumour growth inhibition is achieved at concentrations of at least 20 µg/mL.

As C_{trough} represents target saturation, demonstrating non-inferiority in C_{trough} is to ensure the same degree of receptor saturation as IV administration and therefore the same degree of efficacy and comparable safety regardless of the route of administration.

Based on data from the Phase I Study BO30185, other PK parameters, such as AUC are highly correlated with C_{trough}, and are therefore expected to be similar between IV and SC administration. Due to slower absorption following SC dosing, the C_{max} is not expected to exceed the maximum exposure previously observed in EBC clinical trials following IV administration.

Therefore, a dose of pertuzumab and trastuzumab within the PH FDC SC that is statistically non-inferior to that of IV administration is believed to maintain the same degree of efficacy observed in studies with P+ H IV administration.

The applicant has received an endorsement for the design of the study and the proposed endpoints during the SA procedure EMA/CHMP/SAWP/645161/2016.

Exposure-response relationship

The E-R efficacy endpoint evaluated was total pathological complete response (tpCR). The basic exploratory plot for efficacy endpoints was tpCR rate versus pertuzumab exposure (C_{trough}, AUC), with mean exposure and tpCR rate stratified by pertuzumab exposure quartile. The relationships were summarised with simple linear logistic regression. Covariate analysis was conducted whenever E-R relationship was observed. Covariate analysis was done in a stepwise fashion, using $p<0.05$ in the forward step and $p<0.01$ in the backward step.

The exposure-efficacy analyses data set included 243 patients with model-predicted pertuzumab Cycle 7 C_{trough} in the PH FDC SC arm of FeDeriCa study. Five patients were excluded because they were not included in the population PK analysis set and did not have exposure estimates. A summary of the baseline covariates for patients in the exposure-efficacy data set, overall and by quartile of model predicted pertuzumab Cycle 7 C_{trough}, is provided in Table 12.

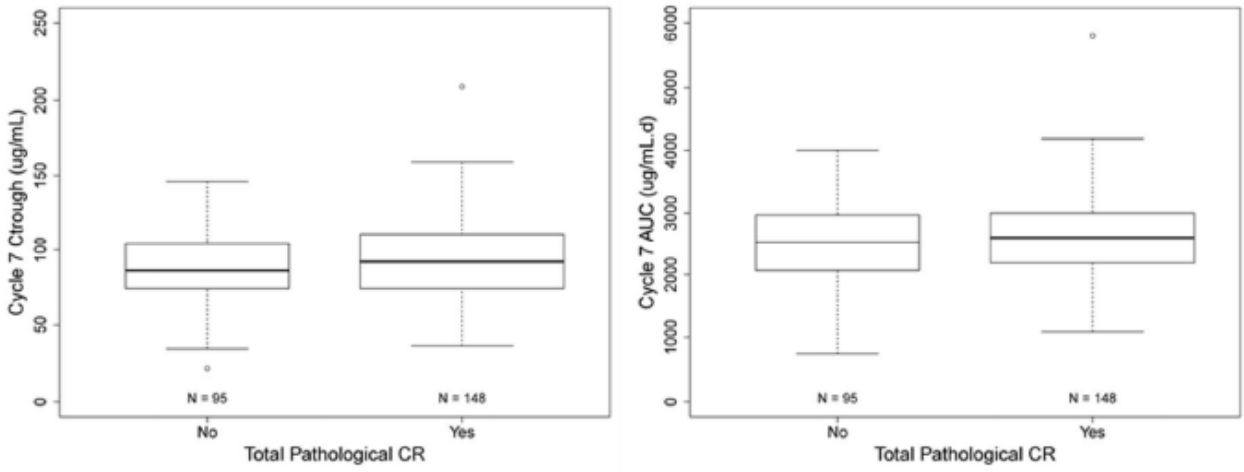
Table 12 Baseline covariates, overall and by quartile of model predicted pertuzumab Cycle 7 C C_{trough}, for the exposure-efficacy data set

Covariate	Model Predicted Pertuzumab Cycle 7 C_{trough} values (µg/mL)				
	Q1 64 [21 to 74] (n=63)	Q2 82 [75 to 89] (n=60)	Q3 98 [90 to 109] (n=60)	Q4 122 [110 to 209] (n=60)	All 89 [21 to 209] (n=243)
Age (y)	52 [33, 80]	52 [27, 74]	51 [29, 69]	51 [25, 75]	51 [25, 80]
Albumin (g/L)	43 [36, 50]	43 [36, 49]	44 [37, 49]	44 [35, 57]	44 [35, 57]
Sex					
Male	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Female	63 (100%)	60 (100%)	60 (100%)	60 (100%)	243 (100%)
Race					
White	39 (61.9%)	43 (71.7%)	42 (70.0%)	39 (65.0%)	163 (67.1%)
Black or African American	2 (3.2%)	1 (1.7%)	0 (0%)	0 (0%)	3 (1.2%)
Asian	15 (23.8%)	8 (13.3%)	13 (21.7%)	14 (23.3%)	50 (20.6%)
Other	7 (11.1%)	8 (13.3%)	5 (8.3%)	7 (11.7%)	27 (11.1%)
ECOG					
Missing	1 (1.6%)	1 (1.7%)	0 (0%)	1 (1.7%)	3 (1.2%)
0	55 (87.3%)	54 (90.0%)	58 (96.7%)	53 (88.3%)	220 (90.5%)
1	7 (11.1%)	5 (8.3%)	2 (3.3%)	6 (10.0%)	20 (8.2%)
Chemotherapy (COMT)					
AC + docetaxel	37 (58.7%)	32 (53.3%)	32 (53.3%)	24 (40%)	125 (51.4%)
ddAC + paclitaxel	26 (41.3%)	28 (46.7%)	28 (46.7%)	36 (60%)	118 (48.6%)
Clinical stage (CLIN)					
II-IIIA	50 (79.4%)	41 (68.3%)	52 (86.7%)	51 (85%)	194 (79.8%)
IIIB-IIIC	13 (20.6%)	19 (31.7%)	8 (13.3%)	9 (15%)	49 (20.2%)
Hormone Receptor Status (ERPR)					
Positive	38 (60.3%)	43 (71.7%)	34 (56.7%)	32 (53.3%)	147 (60.5%)
Negative	25 (39.7%)	17 (28.3%)	25 (41.7%)	28 (46.7%)	95 (39.1%)
Unknown	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)	1 (0.4%)

Note: AC = doxorubicin plus cyclophosphamide, ddAC = dose-dense doxorubicin plus cyclophosphamide, ECOG = Eastern Cooperative Oncology Group Performance Status, Q1 to Q4 = model-predicted Pertuzumab Cycle 7 C_{trough} quartile 1 through 4, Q1: 21 to 74 µg/mL, Q2: 75 to 89 µg/mL, Q3: 90 to 109 µg/mL, Q4: 110 to 209 µg/mL, Numbers in square brackets indicate the range of Pertuzumab Cycle 7 C_{trough}. Median (range) shown for quartiles of model predicted Cycle 7 C_{trough} for continuous covariates. Tabulated values are count (%) for categorical covariates.

A boxplot of model predicted Cycle 7 C_{trough} by tpCR is shown in Figure 10

Figure 10 Boxplot of Model-Predicted Cycle 7 Pertuzumab Exposures by tpCR Response



AUC=area under the curve over a dosing interval; CR = complete response, C_{trough}=trough concentration. Boxplot shows the median (solid bold line), the interquartile range (shaded boxes), 1.5 times the interquartile range (whiskers), and points outside the whiskers (solid points).

Table 13 describes the tpCR data stratified by Cycle 7 C_{trough} quartile and shows a slightly higher tpCR rate for patients in higher pertuzumab exposure quartile groups. Of note, the baseline characteristics (such as albumin, ECOG, clinical stage, hormone receptor status) were well balanced across different pertuzumab exposure quartile groups. Positive ERPR hormone receptor status was largest in the second exposure quartile, the percentages did not differ significantly across the groups (p=0.19). Between the first and fourth quartile, there was a 1.9-fold difference in median C_{trough} while tpCR rate increased modestly (8%). For the four exposure quartile groups, the difference in tpCR rate from the overall mean tpCR rate in the IV arm ranged from -7.6% to 7.4%, respectively, and the 95% CI for all quartile groups included zero. This indicates that the tpCR rates in these patients are comparable to P+H IV arm.

Table 13 Total pathological complete response events and rate stratified by model-predicted pertuzumab cycle 7 C_{trough} Quartile in PH FDC SC arm

	Model predicted Pertuzumab Cycle 7 C_{trough} Quartile (µg/mL)				
	Q1 (n=63)	Q2 (n=60)	Q3 (n=60)	Q4 (n=60)	All[a] (n=243)
Median C_{trough}, µg/mL (range)	64 [21 to 74]	82 [75 to 89]	98 [90 to 109]	122 [110 to 209]	89 [21 to 209]
tpCR	38 (60.3%) 95% CI: (48.2%, 72.4%)	32 (53.3%) 95% CI: (40.7%, 66.0%)	37 (61.7%) 95% CI: (49.4%, 74.0%)	41 (68.3%) 95% CI: (56.6%, 80.1%)	148 (60.9%) (95% CI: 54.8, 67.0%)
ΔtpCR	-0.7% [-14.2%, 12.9%]	-7.6% [-21.5%, 6.2%]	0.7% [-13.1%,14.4%]	7.4% [-6.3%, 21.0%]	-

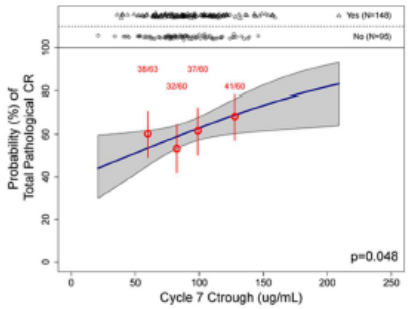
C_{trough}=trough concentration, N=number of patients, Q1 to Q4= model-predicted Pertuzumab Cycle 7 C_{trough} quartile 1 through 4, Q1: 21 to 74 µg/mL, Q2: 75 to 89 µg/mL, Q3: 90 to 109 µg/mL, Q4: 110 to 209 µg/mL, tpCR=total pathological complete response, ΔtpCR=difference from overall rate in IV arm with 95% CI.

[a] For comparison, rate of tpCR was 150/246 or 61.0% in the P+H IV arm.

Note: Numbers in square brackets indicate the range of Pertuzumab Cycle 7 C_{trough}. The comparison analysis of tpCR rate for each quartile group with overall rate in the PH FDC SC arm was performed as well and the results are similar with those obtained in the comparison with overall rate in the P+H IV arm.

Figure 11 shows the univariate logistic regression plot for tpCR in PH FDC SC arm. Multivariate testing showed that hormone receptor status (ERPR, oestrogen receptor [ER] or progesterone receptor [PgR]) was a statistically significant covariate on the intercept of the logistic regression relationship. Lower tpCR rate was observed for patients with positive ERPR. However, after adjusting ERPR status at baseline, there was no statistically significant relationship between model-predicted pertuzumab exposure (i.e., Cycle 7 C_{trough}) and tPCR rate (p=0.069).

Figure 11 Logistic Regression Pertuzumab Exposure-Response Plots for tpCR Observed in PH FDC SC arm in the FeDeriCa Study



CR=complete response, C_{trough}=model predicted pertuzumab Cycle 7 trough concentration, the p-value is the significance level of the slope of the regression fit. Red points indicate the mean concentration and response probability per exposure quartile. Vertical error bars indicate 90% confidence bounds. Numbers above each bar indicates subjects with the event and the total number of subjects in the quartile group. The blue line represents the fit of a logistic regression model. The shaded grey region indicates 90% confidence bands for the model fit. Points above the plot indicate exposures in subjects with a response (Yes) versus exposures in subjects with no response (No).

Logistic regression of tpCR using the exposure metric Cycle 7 serum pertuzumab C_{trough} suggested that increased model-predicted pertuzumab exposures were associated with slightly higher rates of tpCR (p = 0.048). When Cycle 7 serum pertuzumab C_{trough} values were stratified into quartiles and correlated with tpCR

rates, minor increases in tpCR rates were observed over the Cycle 7 serum pertuzumab C_{trough} quartiles. After adjusting the baseline ERPR status, which was identified as a statistically significant covariate on the intercept of the logistic regression relationship (lower tpCR rate was observed for patients with positive ERPR), there was no statistically significant relationship between model-predicted pertuzumab exposures and tpCR rates (p = 0.069).

All quartiles in the E-R analysis reached concentrations higher than the pre-specified PK/PD target of 20 µg/mL. Despite the fact that concentrations between quartiles differed, the CIs overlapped, thus suggesting similarity in the tpCR rates between different exposure quartiles.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of pertuzumab is in general adequately described. The PK of pertuzumab (and trastuzumab) was investigated in one Phase I and one Phase III clinical studies, and a popPK modelling was provided. The results give a rather good picture of absorption, distribution, and half-life values.

The approved IV loading dose of pertuzumab 840 mg was not included in the study as a control. The loading dose for PH FDC SC formulation was estimated based on dose-proportionality, and it was determined to be 1200 mg. This was deemed acceptable in the scientific advice EMA/CHMP/SAWP/791149/2017.

The applicant chose the 2000U/ml concentration of rHuPH20 for the PH FDC SC formulation. The decision to choose this concentration was mainly based on the available clinical experience with rHuPH20.

The applicant has provided adequate justification that the selected C_{trough} is the actual steady state C_{trough}.

The Cycle 7 $AUC_{0\text{-}tau}$ for pertuzumab and trastuzumab in PH FDC SC and P+H IV arms are highly comparable as it is evident from the GMR and 90% CI, which values are all centred around 1. As a result, the exposure of these formulations is deemed comparable. No comparison was done with IV loading doses of pertuzumab and SC loading dose in the PH FDC SC. In the Phase III data, it was observed that the mean C_{trough} following a loading dose is higher in the SC formulation, but not significantly. Due to the fact that no safety concerns arise due to increased exposure after a loading dose this concentration difference is deemed acceptable.

The Cycle 5 C_{trough} of trastuzumab in the PH FDC SC arm was lower compared to P+H IV arm. However, due to the fact that the C_{trough} pre-dose Cycle 8 was non-inferior, and efficacy concerns are not raised, the Cycle 5 C_{trough} is deemed comparable, and the differences clinically insignificant.

PK Drug-Drug interactions (DDIs) between co-mixed or co-formulated pertuzumab and trastuzumab

Administration of pertuzumab and trastuzumab as single agents resulted in similar exposure results compared to co-mixed and co-formulated administration. The applicant had compared the trastuzumab SC concentrations from HANNAH and FeDeriCa studies. In FeDeriCa study trastuzumab was administered in the FDC SC together with pertuzumab. Thus, the pertuzumab could have influenced the PK of trastuzumab. To address this, the applicant took the model from the HANNAH study, where trastuzumab's PK was modelled for it as a single agent, and imputed the data from FeDeriCa study to assess, if the trastuzumab PK still follows the same pattern. Based on the GOF plots, VPCs, the observed PK of trastuzumab in PH FDC SC is similar to the one predicted by the model based on the HANNAH study. As a result, no significant PK interactions are expected between these two agents.

Since the drug is administered subcutaneously, no influence of food is anticipated.

The applicant has performed popPK modelling of data from the clinical programme, using standard methodology. One of the issues identified evaluating goodness-of-fit plots is that there was a single low observation, diverting the smooth line of the agreement between predicted and observed concentrations. The applicant explains, that the estimate did not match outlier criteria throughout the modelling process, and thus was retained, which is acceptable.

According to the developed pertuzumab s/c PopPK, patients of Asian ethnicity have an increased CL of pertuzumab (12.3 %). However, the exposure, efficacy and safety results for subjects of Asian ethnicity are similar to non-Asians.

The routes and patterns of excretion were not investigated in detail. This is acceptable considering the nature of the product. This is a recombinant humanised monoclonal antibody of IgG1 protein, and it is not expected that this protein should be different from other proteins.

Patients with impaired liver function were not studied for this application. This is in line with the IV formulation which was also not studied in patients with hepatic impairment, this is reflected in the SmPC.

It was observed that patients with lower LBW and increased albumin concentration resulted in higher PH FDC SC exposure. The developed popPK model identified that CL is decreased in patients with higher albumin by 6% when albumin is at the 95th percentile and increased by 16% when albumin is at the 5th percentile, while other covariates are fixed to typical values. Similarly, CL could decrease by 34% when LBW is at the 5th percentile. However, when analysed according to key safety endpoints, no clear trend of increased SAEs or AEs was observed in patients with different LBW or albumin concentration.

There was an observed numerical difference in the C_{trough} depending on the status of the ADAs. The higher influence could be inferred in the IV formulation group for pertuzumab, for trastuzumab, in both SC and IV groups there was a single patient with ADA. Therefore, given the low numbers, no conclusions can be drawn. The patients who developed ADAs reached the target C_{trough} concentrations.

Pharmacodynamics

Both drugs discussed in this application have a well-known and established MoA. IV formulations of these medicines have been widely used. For the exposure-response assessment, the applicant evaluated the tpCR with regards to different C_{trough}. There was a trend toward a higher tpCR rate with increasing pertuzumab Cycle 7 C_{trough} in the PH FDC SC arm, which was statistically significant (p=0.048). However, after adjusting for baseline estrogen receptor or progesterone receptor (ERPR) status, there was no statistically significant relationship between model-predicted pertuzumab exposures and tpCR rate (p=0.069).

Patients at lower quartile of albumin have a somewhat lower median exposure compared to patients in higher albumin quartile. However, when analysed according to tpCR, no impact of lower albumin concentrations was found.

Lean body weight (LBW) has a significant impact on CL. However, the applicant has demonstrated that body weight is not a significant covariate for tpCR. Specific studies for drug-drug interactions were not performed for the PH FDC SC, and that is deemed acceptable, since neither pertuzumab, nor trastuzumab are likely to exhibit DDIs.

2.4.5. Conclusions on clinical pharmacology

The primary endpoint of the FeDeriCa trial was met, indicating that the fixed dose combination of pertuzumab and trastuzumab for SC administration (Phesgo) is pharmacokinetically non-inferior to its IV counterparts.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

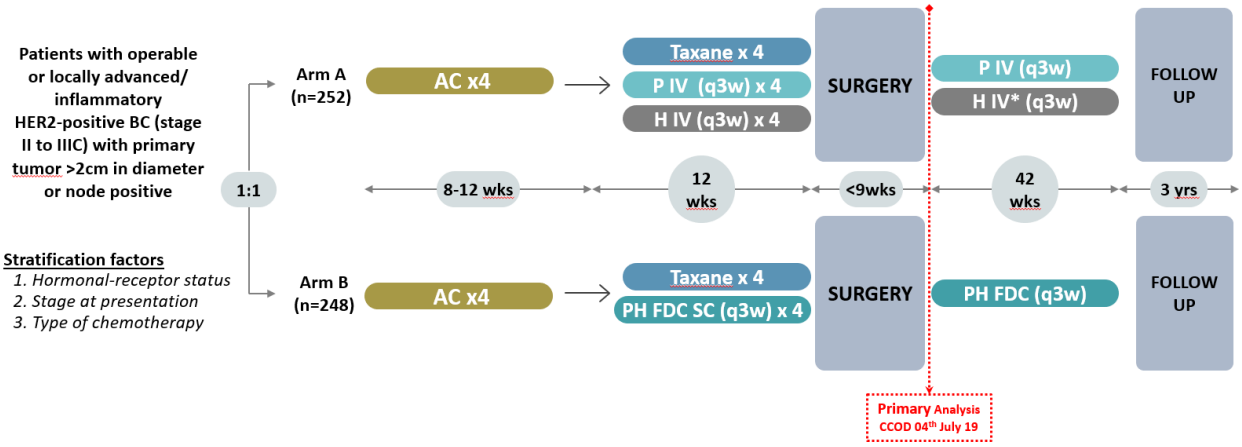
Relevant aspects have already been depicted and discussed in the previous section.

2.5.2. Main study(ies)

WO40324 – FeDeriCa

FeDeriCa is an ongoing pivotal phase III, two-arm, open-label randomised study investigating the pharmacokinetics, efficacy, and safety of PH FDC SC compared with P+H IV, in combination with chemotherapy, in patients with HER2-positive EBC in the neoadjuvant/adjuvant settings. A schematic diagram of the study design is shown in below.

FeDeriCa study design:



Methods

Study Participants

A total of 500 patients with HER2+ operable or locally advanced/inflammatory breast cancer with a tumour size of >2 cm or node positive were randomised in 1:1 ratio to receive either P+H IV (Arm A, n=252) or PH FDC SC (Arm B, n=248) as part of their neoadjuvant treatment. The primary analysis was conducted once all patients completed neoadjuvant therapy and had surgery (or had withdrawn from the study treatment). After

the surgery, patients continued to receive the same HER2-directed therapy in the adjuvant phase as per randomisation.

Key inclusion criteria

- Age ≥18 years at time of signing ICF
- ECOG performance status 0 or 1
- Female and male patients with Stage II-IIIC (T2-T4 plus any N, or any T plus N1-3, M0), locally advanced, inflammatory, or early-stage, unilateral, and histologically confirmed invasive BC
    - Patients with inflammatory BC had to be able to have a core-needle biopsy
- Primary tumour >2 cm in diameter, or N+ disease (clinically or on imaging, and node positivity confirmed with cytology and/or histopathology)
- HER2-positive BC confirmed by a central laboratory prior to study enrolment. HER2-positive status was determined based on pre-treatment breast biopsy material and defined as 3+ by immunohistochemistry (IHC) and/or positive by HER2 amplification by *in situ* hybridisation (ISH) with a ratio of ≥2 for the number of HER2 gene copies to the number of signals for chromosome 17 copies
    - Patients with multifocal tumours (more than one tumour confined to the same quadrant as the primary tumour) were eligible provided at least one focus was sampled and centrally confirmed as HER2-positive
- Hormone receptor status of the primary tumour, centrally confirmed. Hormone receptor-positive status could be determined by either known ER-positive and/or known PgR-positive status. Hormone receptor-negative status had to be determined by both known ER-negative and known PgR-negative status
- Baseline LVEF ≥55% measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)

Key exclusion criteria

- Stage IV (metastatic) BC
- Patients with a history of invasive BC
- Patients with a history of concurrent or previously treated non-breast malignancies except for appropriately treated 1) non-melanoma skin cancer and/or 2) *in situ* carcinomas, including cervix, colon, and skin
- A patient with previous invasive non-BC was eligible provided he/she were disease-free for more than 5 years.
- Patients who had received any previous systemic therapy (including chemotherapy, immunotherapy, HER2-targeted agents, endocrine therapy (selective ER modulators, aromatase inhibitors, and antitumor vaccines) for treatment or prevention of BC, or radiation therapy for treatment of cancer
- Patients with multicentric (multiple tumours involving more than one quadrant) BC, unless all tumours were HER2-positive
- Patients with bilateral BC
- Patients who had undergone an excisional biopsy of primary tumour and/or axillary lymph nodes

- Axillary lymph node dissection (ALND) prior to initiation of neoadjuvant therapy
- Sentinel lymph node biopsy (SLNB) prior to neoadjuvant therapy
- Serious cardiac illness or medical conditions
- Current severe, uncontrolled systemic disease that could interfere with planned treatment (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound-healing disorders)
- Any serious medical condition or abnormality in clinical laboratory tests that, in the Investigator's judgment, precluded the patient's safe participation in and completion of the study
- Known hypersensitivity to study drugs, excipients, and/or murine proteins
- Current chronic daily treatment with corticosteroids (dose >10 mg methylprednisolone or equivalent excluding inhaled steroids)

Treatments

The investigational medicinal products (IMPs) in this study were Perjeta® IV, Herceptin® IV, Herceptin® SC, and PH FDC SC.

The non-investigational medicinal products (NIMPs) in this study were doxorubicin, cyclophosphamide, paclitaxel, docetaxel, granulocyte-colony stimulating factor (G-CSF), and adjuvant hormone therapy.

Once eligibility for the study was confirmed, the investigator selected one of the two protocol-approved neoadjuvant chemotherapy regimens with which to treat the patient. Patients in both study arms received 8 cycles of neoadjuvant chemotherapy, either:

- **ddAC x 4 Q2W → paclitaxel x 12 Q1W:** Doxorubicin 60mg/m^2 IV and cyclophosphamide 600mg/m^2 IV, Q2W for four cycles (ddAC, Cycles 1-4) with G-CSF support as per local clinical practice. This is followed (2 weeks later) by paclitaxel 80 mg/m^2 QW for 12 weeks; or
- **AC x 4 Q3W → docetaxel x 4 Q3W:** Doxorubicin 60mg/m^2 IV and cyclophosphamide 600mg/m^2 IV (AC) Q3W for 4 cycles (Cycles 1-4). AC is followed (3 weeks later) by docetaxel 75 mg/m^2 IV, escalating to 100 mg/m^2 IV if no dose-limiting toxicity occurs (at the discretion of the investigator).

Once the investigator's choice of chemotherapy was made and eligibility confirmed, the patient was randomised to one of the two treatment arms.

During the neoadjuvant treatment period, P+H IV (Arm A; sequential administration) or PH FDC SC (Arm B) was administered Q3W for 4 cycles at Cycles 5-8 concurrently with the taxane component of chemotherapy. Loading doses for the first cycle (i.e., study Cycle 5) and maintenance doses for subsequent cycles (i.e., study Cycle 6 onwards) were as follows:

- **Arm A (P+H IV)**: loading doses Perjeta 840 mg IV and Herceptin 8 mg/kg IV; maintenance doses Perjeta 420 mg IV and Herceptin 6 mg/kg IV
- **Arm B (PH FDC SC)**: loading dose 1200 mg pertuzumab plus 600 mg trastuzumab (15 mL); maintenance dose 600 mg pertuzumab plus 600 mg trastuzumab (10 mL)

Patients in both cohorts were scheduled to undergo surgery after 8 cycles of neoadjuvant therapy, and no earlier than 14 days following the last infusion or injection of neoadjuvant therapy.

After surgery, patients continued to receive the same HER2-targeted therapy in the adjuvant setting (cycles 9-22) as per randomisation until a total of 18 cycles of HER2-targeted therapy have been given. Treatment could be stopped in case of investigator-assessed radiographic or clinical progression, or recurrence of disease, or unmanageable toxicity.

Crossover was not permitted as part of this study. However, patients in the P+H IV arm, from Cycle 9 onward, could switch from Herceptin IV to Herceptin SC in countries were Herceptin SC was routinely used, at the discretion of the Investigator.

Adjuvant endocrine therapy for patients with hormone-receptor positive disease and postoperative radiotherapy were to be given as clinically indicated and as per local practice.

All patients will be followed until approximately 3 years after the last patient's last treatment, and the end of study is expected approximately 4.5 years after last patient in.

Objectives

Primary objective

To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough} of pertuzumab SC within PH FDC SC compared with Perjeta IV

Secondary objectives

- To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum trastuzumab C_{trough} of trastuzumab SC within PH FDC SC compared with Herceptin IV
- To evaluate the efficacy of PH FDC SC + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy, according to tpCR (i.e., ypT0/is ypN0), iDFS, iDFS-SPNBC, EFS, EFS-SPNBC, DRFI and OS
- To evaluate the safety of PH FDC SC compared with Perjeta IV and Herceptin IV, according to the incidence and severity of AEs and AEs, and laboratory test abnormalities, as well as through primary and secondary cardiac endpoints

Exploratory objectives

- To characterise the pharmacokinetics of pertuzumab and trastuzumab following administration of PH FDC SC
- To compare the pharmacokinetics (including PK parameters such as AUC and C_{max}) following administration of PH FDC SC versus Perjeta IV and Herceptin IV (in combination with chemotherapy)
- To assess the pertuzumab PK profile and observed C_{trough} at Cycle 7 (predose Cycle 8) and Cycle 12 (postsurgery) following PH FDC SC administration
- To compare the pertuzumab exposure in Cycle 5 between Perjeta IV 840 mg and PH FDC SC (pertuzumab SC 1200 mg)
- To evaluate potential relationships between pertuzumab exposure and the efficacy and safety of PH FDC SC via a pertuzumab exposure-response analysis
- To assess the impact of a potential PK drug-drug interaction (DDI) between pertuzumab and trastuzumab following administration of PH FDC SC

- To evaluate the efficacy of PH FDC SC + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy, according to bpCR (i.e., ypT0/is, ypNx), German Breast Group (GBG) pCR (i.e., ypT0 ypN0) and clinical response (CR, PR, SD or PD) prior to surgery.
- To evaluate the immune response to pertuzumab, trastuzumab, and rHuPH20 with PH FDC SC compared with Perjeta IV and Herceptin IV
- To evaluate potential effects of ADAs
- To explore potential association of tissue-based biomarkers or biomarker profiles to pCR
- To explore changes in biomarker levels or biomarker profiles pre- and post treatment based on tumour tissue
- To assess blood-based biomarkers at baseline and longitudinally to explore changes over time and potential relationship to pCR and long-term efficacy endpoints

Outcomes/endpoints

Primary endpoint:

- Serum pertuzumab C_{trough} during Cycle 7 (pre-dose Cycle 8); assessed pre-dose on Cycle 8, Day 1 (up to 21 weeks)

Secondary Pharmacokinetic endpoint:

- Serum trastuzumab C_{trough} during Cycle 7 (pre-dose Cycle 8); assessed pre-dose on Cycle 8, Day 1 (up to 21 weeks)

Secondary efficacy endpoints:

- Total pathological complete response (tpCR) of PH FDC SC + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy. tpCR was defined as eradication of invasive disease in the breast and axilla (i.e., ypT0/isypN0), according to local pathologist assessment; assessed following completion of surgery (up to 33 weeks)
- Time-to-event endpoints: invasive disease-free survival (iDFS); iDFS including second primary non-BC; event free survival (EFS); EFS including second primary non-BC; overall survival (OS)

Secondary safety endpoints:

- Incidence and severity of adverse events and serious adverse event (SAEs)
- Laboratory test abnormalities
- Primary cardiac endpoints: incidence of a symptomatic ejection fraction decrease NYHA Class III or IV and a drop in left ventricular ejection fraction (LVEF) of at least 10 percentage points from baseline and to below 50%, cardiac death
- Secondary cardiac endpoint: incidence of an asymptomatic or mildly symptomatic left ventricular systolic dysfunction of NYHA Class II

Sample size

PK sample size calculations were based on the coefficient of variation (CV)% for the C_{trough} of trastuzumab observed from previous studies in MBC and EBC patients after Q3W treatment. With a CV of 60% assumed, a minimum or 130 patients per arm (*i.e.*, a total of 260 patients) was needed to demonstrate C_{trough} non-inferiority with a power of 80% if the true means of the two formulations did not differ by more than 5%. An additional 240 patients were also to be recruited to provide a substantial database to assess tpCR and safety profile comparability. Therefore, a total of approximately 500 patients (~250 patients per arm) was to provide a sufficient sample size to test the primary PK hypothesis as well as assess efficacy and safety profile comparability.

Randomisation

Patients were randomised using the method of stratified permuted blocks in a 1:1 ratio to receive either treatment Arm A or Arm B. Accounting for the three following stratification factors, each with two levels, patients were stratified using a fixed block of 6:

- Hormonal Receptor Status [Oestrogen receptor (ER)-positive or progesterone receptor (PgR)-positive, ER-negative and PgR-negative]
- Clinical stage at presentation (Stage II−IIIA, Stage IIIB−IIIC)
- Type of chemotherapy (ddAC followed by paclitaxel, AC followed by docetaxel)

Blinding (masking)

The study was open labelled

Statistical methods

Analysis populations:

- Per Protocol PK Analysis Population: The primary and secondary PK analysis were performed on the Per Protocol PK analysis population. Patients were assigned to treatment groups as treated. The Per Protocol PK analysis population included all patients enrolled who adhered to the protocol. Exclusions from the Per Protocol PK analysis population were made for the following reasons:
    - Patients were missing the C_{trough} pre-dose Cycle 8 PK sample.
    - Patients had a C_{trough} sample collected with at least 2 days deviation from the planned date on Day 21 (*i.e.*, before Day 19 or after Day 23).
    - Patients were given a dose amount that deviated from the planned dose by > 20% within 3 cycles (from Cycle 5).
    - Patients had a dose delay of more than 7 days.
    - A subcutaneous injection site other than thigh was used.
    - Cycle 8 pre-dose and post-dose samples were switched in the IV arm.

- There was an assay error impacting C_{trough} measurement.

Excluded cases were to be thoroughly investigated and documented, including the reason for exclusion. All decisions on exclusions from the analysis were made prior to database closure.

- Intention-to-Treat Population: All efficacy analyses were performed on the intention-to-treat (ITT) population. The ITT population was defined as all randomised patients. Patients were assigned to treatment groups as randomised.
- Safety Analysis Population: The safety analysis population included all patients who received at least one dose of study medication (*i.e.*, chemotherapy, Perjeta IV, Herceptin IV, Herceptin SC, or PH FDC SC) and was grouped according to actual treatment received. Patients who did not receive any of their study medication were excluded from the safety-evaluable population.

Analysis of pharmacokinetic endpoints: The primary endpoint of this study was the observed pertuzumab trough concentration (C_{trough}) at Cycle 7 (*i.e.*, the measured pre-dose concentration value at Cycle 8), following 3 cycles of Perjeta IV and Herceptin IV or PH FDC SC. The non-inferiority of the SC and IV dose of pertuzumab was assessed if the lower bound of the 90% confidence interval (CI) for the geometric mean ratio was equal or greater than 0.8.

The non-inferiority of the SC and IV dose of pertuzumab and trastuzumab were tested in a hierarchical order to adjust for multiple statistical testing and control the type I error at a one-sided 5% significance level.

The following hypotheses were tested:

- H0: The SC dose is inferior to the IV dose (i.e., the C_{trough}SC/C_{trough}IV geometric mean ratio (GMR) of the SC dose relative to the IV dose is not greater than 0.8) versus
- H1: The SC dose is non-inferior to the IV dose (i.e. the C_{trough}SC/C_{trough}IV GMR of the SC dose relative to the IV dose is equal or greater than 0.8)

The hierarchical testing procedure followed the steps below:

1. Test the primary endpoint, Cycle 7 pertuzumab serum C_{trough}SC/C_{trough}IV, at a one-sided 5% significance level.

If positive, continue to Step 2; otherwise, stop.

2. Test the secondary endpoint, Cycle 7 trastuzumab serum C_{trough}SC/C_{trough}IV, at a one-sided 5% significance level.

The non-inferiority of the SC and IV dose was assessed by a one-sided testing procedure. The null hypothesis was rejected and non-inferiority concluded if the lower bound of the 90% CI of the GMR was ≥ 0.8.

The secondary PK endpoint of this study was the observed trastuzumab trough concentration (C_{trough}) at Cycle 7 (i.e., the measured pre-dose concentration value at Cycle 8), following 3 cycles of Perjeta IV and Herceptin IV or PH FDC SC. The non-inferiority of the SC and IV dose of trastuzumab were assessed using the same criteria as for the primary analysis and were tested in a hierarchical order to adjust for multiple statistical testing and control the Type I error at a one-sided 5% significance level.

Type I error control: The type I error is controlled within the two PK endpoints, primary endpoint, Cycle 7 pertuzumab serum C_{trough}SC/C_{trough}IV and the secondary endpoint Cycle 7 trastuzumab serum C_{trough}SC/C_{trough}IV, with a closed testing procedure. All other secondary and exploratory endpoints will not be analysed outside the closed testing procedure and are therefore considered exploratory.

Analysis of efficacy endpoint: The main efficacy secondary endpoint was the rate of tpCR in the breast and nodes evaluated after surgery following a scheduled 8 cycles of neoadjuvant treatment. Rates of tpCR were calculated in each treatment the P+H IV arm and were assessed using the difference between PH FDC SC tpCR rate and IV tpCR rate and corresponding 95% Clopper Pearson CIs. The difference between the PH FDC SC tpCR rate and IV tpCR rates along with corresponding 95% Hauck-Anderson CIs were also calculated.

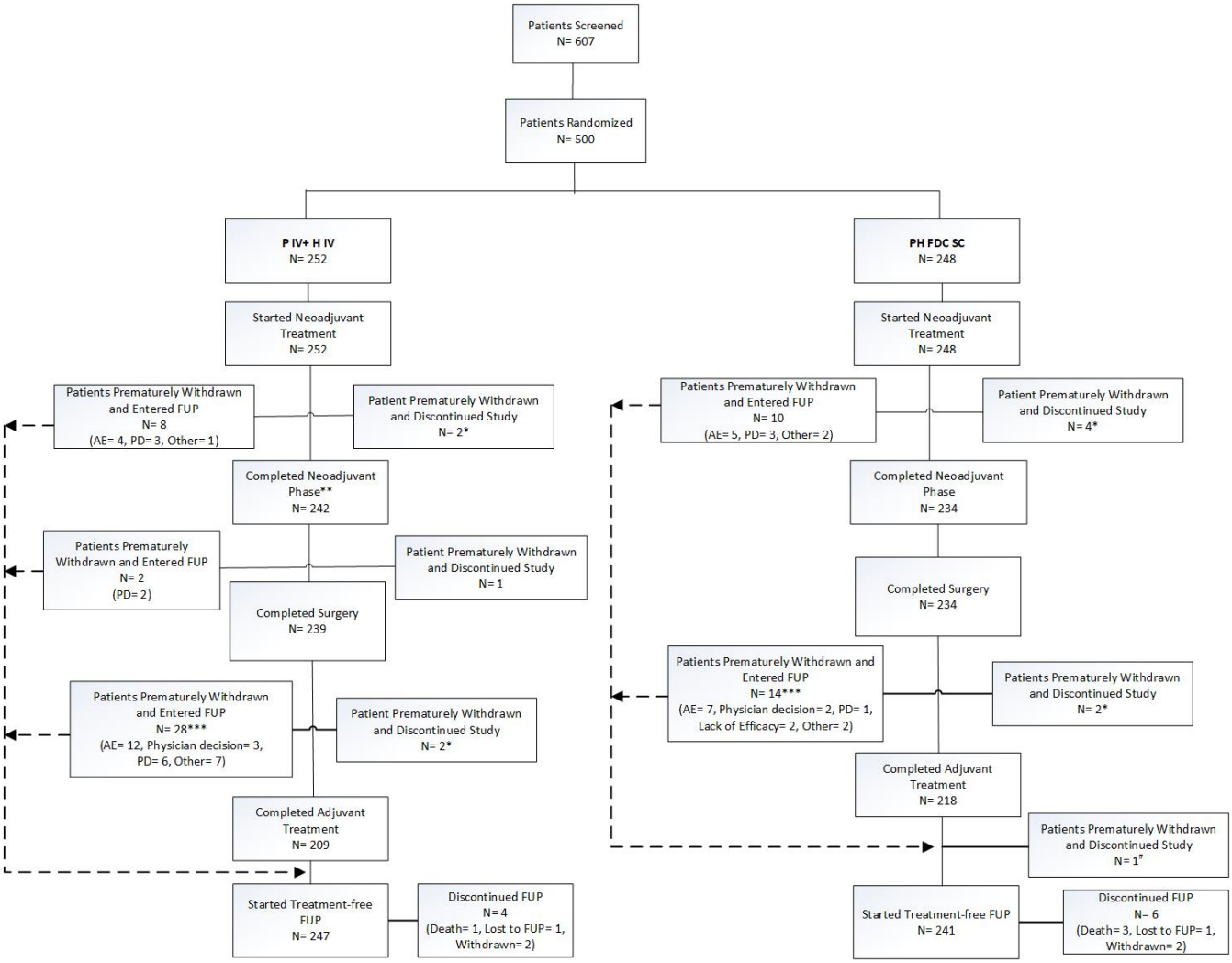
Acknowledging that tpCR is an exploratory endpoint and not type I error controlled, non-inferiority was assessed using the criteria that if the lower limit of the one-sided 97.5% confidence interval for the difference in tpCR rate (using the continuity correction of Anderson and Hauck) was above the non-inferiority margin of -12.5% (absolute percentage points), then this could reliably reflect the largest pathologic complete response (pCR) difference that could be considered unlikely. The non-inferiority margin of -12.5% in Study WO40324 (FeDeriCa) is based on Study BO22227 (HannaH) and is consistent with the EMEA guideline (choice of the non-inferiority margin, January 2006) which considers -12.5% an acceptable margin, still demonstrating clinical benefit of a product.

Statistical methods used to compare groups for primary outcome(s) include definition of the populations for main analysis, error probabilities, adjustment for multiplicity, brief description of the statistical techniques used, interim analyses.

The last update of the SAP (Version 3) occurred before database lock.

Results

Participant flow



** Includes one patient that discontinued study due to a fatal event*
*** 3 patients discontinued the study prior to undergoing surgery in P+H IV*
**** 8 patients in P+H IV arm and 4 in PH FDC SC arm discontinued the study in adjuvant phase (after surgery) but prior to undergoing adjuvant treatment*
 # 1 patient in the PH FDC SC arm withdrew immediately after completing all the adjuvant treatment hence this patient is counted both in completed and discontinued adjuvant phase

Recruitment

Patient enrolment took place over 6 months, from 14-JUN-2018 (first patient in) to 24-DEC-2018 (last patient in).

The clinical cutoff date (CCOD) occurred on 4-JUL-2019, and the database lock (DBL) occurred on 29-AUG-2019.

Conduct of the study

Protocol amendments

The first version of the protocol is dated 2-FEB-2018. There was only one amendment and version 2 is dated 12-OCT-2018. The main changes to the protocol and their rationale are summarised below:

- Sections 3.1, 3.3.3, 3.3.4, 4.1, 4.1.1, and 4.5.10 have been updated to clarify that the size of the tumour allowed for entry into the study is > 2 cm and not ≥ 2cm. This change to > 2 cm aligns with Stage II as inclusion criteria.
- Section 4.1.1 has been changed to give more clarity on "node-positive" and also to clarify that suspicious lymph nodes must be confirmed by cytology and/or histopathology.
- The observation period for Herceptin SC has been added to Section 4.3.2.1, along with instructions for slowing or interrupting the injection if the patient experiences injection-related symptoms, as this was missing in Version 1.
- Additional instructions have been added to Sections 4.3.2.1, 4.3.2.2, and 5.1.1.1 to allow for extra observation time (at the investigator's discretion, if deemed necessary) after administration of Herceptin SC, Herceptin IV, and the fixed-dose combination of pertuzumab and trastuzumab for SC injection (the FDC), taking into account different local requirements for observation time for Herceptin SC and IV.
- Sections 4.3.2.3 and 4.3.2.4 have been updated to provide additional guidance for the management of hypersensitivity reactions that occur following docetaxel and paclitaxel administrations, respectively.
- Sections 4.5.7.2, 4.5.10, and footnote 'h' of Appendices 1 and 2 have been updated to clarify that tumour staging at baseline is not mandatory and should only be performed if clinically indicated.
- Additional details and explanations about the PK sampling process have been added to Section 4.5.9.1, as this level of detail was not included in Version 1. Further clarifications on time windows for sampling have also been provided in Section 4.5.9.2 and are reflected in updates to Appendices 5 and 6.
- The definition for pathological complete response (and evaluation) in Section 4.5.11 has been updated to align with the U.S. Food and Drug Administration and European Medicines Agency guidance for industry on pCR endpoints.
- Symptomatic left ventricular systolic dysfunction (LVSD) and/or left ventricular ejection fraction (LVEF) decline were added as reasons for discontinuing anti-HER2 therapy in Section 5.2.5.1 (Symptomatic LVSD and/or LVEF Decline) to align with Section 4.7.1 (Study Treatment Discontinuation).
- The guidelines for taxane dose delays and modifications have been updated to provide instructions for patients who experience a Grade ≥ 3 enterocolitis event (see Section 5.2.4 and Table 8).
- LVEF assessment before surgery has been added to Appendices 1 and 2 to ensure adequate cardiac function prior to surgery and avoid risks due to anaesthesia.
- Wording was added to Appendices 1-4 to allow for an additional pregnancy test at the Month 7 follow-up visit, if deemed necessary by the investigator, due to the 7-month Herceptin wash out period.

SAP amendments

VERSION 2, 19-JUL-2019:

Two changes concerning exploratory efficacy endpoints:

- Removing Per Protocol PK analysis population from exploratory efficacy analysis in Section 4.5.5: This line was to be removed in previous version but due to error was retained in the final version 1. This was changed in version 2 to align with initial strategy described in section 4.5.
- Addition of text 'the non-inferiority margin' to make the clear that the preestablished non-inferiority margin is -12.5% (absolute percentage points).

VERSION 3, 23-AUG-2019:

- Addition of two new exclusion criteria in section 4.1.1 Per Protocol PK analysis population:
  - If pre-dose and post-dose samples were switched
  - Assay error impacting C_{trough} measurement.
- Additional minor changes have been made to improve clarity and consistency.

Protocol deviations

Table 14 Major Protocol Deviations by Randomised Treatment: ITT Population

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
No. of Patients with at least one Major Protocol Deviation	78 (31.0%)	65 (26.2%)
Protocol Deviations		
Number of Major - Inclusion Criteria Deviations	17	11
Number of Major - Exclusion Criteria Deviations	3	3
Number of Major - Medication Deviations	7	8
Number of Major - Procedural Deviations	63	61
No. Violating at least one Inclusion Criterion		
Signed Informed Consent	0	0
Age Criteria	0	0
Cancer Staging	1	1
Primary tumor > 2cm or node positive	0	1
HER2-positive breast cancer centrally confirmed	0	1
Hormone receptor status of primary tumor centrally confirmed	0	0
Agreement to undergo mastectomy or breast conserving surgery after neo therapy	0	0
Availability of tumor tissue block for central HER2	0	0
Adequate baseline LVEF	1	0
Contraception requirements met	8	5
Pregnancy - baseline test	7	3
Unrelated major surgery within 4 wks	0	0
No. Violating at least one Exclusion Criterion		
Breast Cancer - Stage 4	0	0
Hx of invasive BC	0	0
Hx of concurrent or previous non BC	0	0
Previous systemic tx for BC or rx	0	0
Hx of DCIS or LCIS w/ systemic tx or radiation	0	0
High risk pt w/ chemopreventative drug in past	0	0
Multicentric BC but not all HER2	0	0
Bilateral BC	0	0
Excisional biopsy of primary tumor and/or axillary LN	0	0
Axillary lymph node dissection (ALND) prior to initiation of neoadjuvant therapy	0	0
Sentinel lymph node biopsy (SLNB) prior to neoadjuvant therapy	1	1
Treatment with any investigational drug within 28 days prior to randomization	0	0
Serious cardiac illness or medical conditions	0	0
Inadequate bone marrow function	0	0
Impaired liver function	2	2
Inadequate renal function	0	0
Current severe, uncontrolled systemic disease	0	0
Pregnant or breastfeeding	0	0
Any serious medical condition or abnormality in clinical laboratory tests	0	0
Known active liver disease	0	0
Concurrent, serious, uncontrolled infections, or known infection with HIV	0	0
Known hypersensitivity to study drugs, excipients, and/or murine proteins	0	0
Current chronic daily treatment with corticosteroids	0	0
History of other malignancy within 5 years	0	0

No. Violating at least one Medication Criterion		
Dosage: HER2 tx not held or stopped according to LVEF algorithm	1	0
Dosage: Over dosage (>10% higher than expected dose)	0	0
Dosage: Overdosage - Anthracycline	0	1
Dosage: Overdosage - Herceptin	2	0
Dosage: Over dosage - Other chemotherapy	0	0
Dosage: Overdosage - Perjeta	1	0
Dosage: Over dosage Trastuzumab	0	0
Dosage: Over dosage FDC	0	0
Dosage: HER2 treatment beyond 18 cycles	0	0
Incorrect drug administered	3	3
Chemo without HER2 treatment	0	0
Prohibited concomitant medication (anti-cancer)	0	0
Prohibited concomitant medication (other)	0	1
Incorrect place of SC administration (thigh)	0	3
No. Violating at least one Procedural Criterion		
2 or more consecutive LVEF assessments missed	1	0
>9 weeks between HER2 treatment	4	2
End of anthracycline LVEF (prior to C5) not done	3	4
Failure to follow the cardiac safety procedures	0	0
Failure to follow toxicity management guidelines for high grade	0	1
Failure to report efficacy data	0	0
Not repeating LVEF as per cardiac algorithm	2	0
PK/ATA sample not done or C8 pre dose PK sample outside of window	29	34
Assessments outside of baseline window or not done - mammogram, LVEF	2	2
No confirmation of status of suspicious axillary node by FNA/biopsy	8	5
Not marking (clipping/tattooing) tumor at baseline	5	6
Missing complete Biochem or Haem panel prior to treatment cycle	3	4
Incorrect staging entered in IxRS	6	3

Denominator for percentages is the number of patients in the ITT population.
Patients may have deviations for more than one reason, therefore the same patient may be counted in different categories.

Protocol deviations occurred in a similar proportion of patients from both arms of the FeDeriCa trial. Most of those deviations were procedural and related to adherence to the protocol-defined schedule of PK assessments.

Baseline data

Demographics

All patients except two were female; both males were randomised to the P+H IV arm. Median age was 51 years (49 years P+H IV vs. 52 years PH FDC SC). The majority of patients were White (65.1% P+H IV and 66.5% PH FDC SC) or Asian (21.4% P+H IV and 20.6% PH FDC SC). The vast majority of patients had a baseline ECOG performance status of 0 (93.3% P+H IV vs. 91.5% PH FDC SC). Overall, 59 patients (11.8%) were aged ≥65 years (13.1% P+H IV and 10.5% PH FDC SC), of whom 7 (1.4%) were ≥75 years old (3 patients [1.2%] P+H IV and 4 patients [1.6%] PH FDC SC). See Table 15

The number of pre-menopausal patients was higher in the P+H IV arm (57.1% P+H IV vs. 47.6% PH FDC SC); and the number of post-menopausal patients was higher in the PH FDC SC arm (42.1% P+H IV vs. 52.4% PH FDC SC).

Table 15 Demographics and baseline characteristics by randomised treatment (ITT population)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)	Total (N=500)
Age (yr.)			
n	252	248	500
Mean (SD)	50.34 (10.79)	51.66 (10.72)	50.99 (10.76)
Median	49.00	52.00	51.00
Range	27.0 - 76.0	25.0 - 81.0	25.0 - 81.0
Age (yr.)			
n	252	248	500
<35	14 (5.6%)	16 (6.5%)	30 (6.0%)
35-39	24 (9.5%)	17 (6.9%)	41 (8.2%)
40-49	93 (36.9%)	70 (28.2%)	163 (32.6%)
50-64	88 (34.9%)	119 (48.0%)	207 (41.4%)
65-74	30 (11.9%)	22 (8.9%)	52 (10.4%)
>=75	3 (1.2%)	4 (1.6%)	7 (1.4%)
Sex			
n	252	248	500
Female	250 (99.2%)	248 (100%)	498 (99.6%)
Male	2 (0.8%)	0	2 (0.4%)
Ethnicity			
n	252	248	500
Hispanic or Latino	32 (12.7%)	42 (16.9%)	74 (14.8%)
Not Hispanic or Latino	200 (79.4%)	189 (76.2%)	389 (77.8%)
Not Reported	16 (6.3%)	13 (5.2%)	29 (5.8%)
Unknown	4 (1.6%)	4 (1.6%)	8 (1.6%)
Race			
n	252	248	500
American Indian or Alaska native	10 (4.0%)	10 (4.0%)	20 (4.0%)
Asian	54 (21.4%)	51 (20.6%)	105 (21.0%)
Black or African American	3 (1.2%)	3 (1.2%)	6 (1.2%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	164 (65.1%)	165 (66.5%)	329 (65.8%)
Multiple	2 (0.8%)	3 (1.2%)	5 (1.0%)
Unknown	19 (7.5%)	16 (6.5%)	35 (7.0%)
Weight (kg) at baseline			
n	252	248	500
Mean (SD)	67.92 (14.39)	68.89 (15.98)	68.41 (15.19)
Median	66.00	65.00	65.01
Range	40.0 - 126.0	40.5 - 136.0	40.0 - 136.0
Height (cm) at baseline			
n	252	248	500
Mean (SD)	161.89 (7.32)	161.51 (6.41)	161.70 (6.88)
Median	162.00	161.00	162.00
Range	145.0 - 185.0	146.0 - 179.0	145.0 - 185.0
BMI (WHO Classification) [1]			
n	252	248	500
Underweight	3 (1.2%)	7 (2.8%)	10 (2.0%)
Normal	120 (47.6%)	112 (45.2%)	232 (46.4%)
Overweight	80 (31.7%)	75 (30.2%)	155 (31.0%)
Obese	49 (19.4%)	54 (21.8%)	103 (20.6%)
Smoking Status			
n	252	248	500
Ever smoked	64 (25.4%)	68 (27.4%)	132 (26.4%)
Never smoked	188 (74.6%)	180 (72.6%)	368 (73.6%)
Menopausal Status at Screening			
n	252	248	500
Pre-menopausal	144 (57.1%)	118 (47.6%)	262 (52.4%)
Post-menopausal	106 (42.1%)	130 (52.4%)	236 (47.2%)
Unknown	2 (0.8%)	0	2 (0.4%)
Baseline ECOG Performance Status			
n	252	248	500
0	235 (93.3%)	227 (91.5%)	462 (92.4%)
1	16 (6.3%)	19 (7.7%)	35 (7.0%)
Unknown	1 (0.4%)	2 (0.8%)	3 (0.6%)

Denominator for percentages is the number of patients in the ITT population.
[1] BMI (kg/m2): Underweight <18.5; Normal 18.5-<25.0; Overweight 25.0-<30.0; Obese >=30.0

Clinical characteristics

Sixty-eight (27.0%) P+H IV vs. 74 (29.8%) PH FDC SC patients were assessed as HER2 IHC2+, and 175 (69.4%) P+H IV vs. 170 (68.5%) PH FDC SC patients assessed as HER2 IHC3+. The majority of patients had invasive carcinoma of no special type (77.0% P+H IV vs. 79.4% PH FDC SC), and most patients had histological grade 2 disease (47.2% P+H IV vs. 46.8% PH FDC SC). The majority of patients had hormone

receptor positive disease (61.5% P+H IV vs. 60.9% PH FDC SC); just over half the patients received AC→docetaxel (52.4% P+H IV vs. 51.6% PH FDC SC); and the majority of patients had Stage II–IIIA disease (79.8% each). See Table 16

Table 16 Disease characteristics at baseline by randomised treatment (ITT Population)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
Time since initial diagnosis [Weeks]		
n	250	247
Mean (SD)	6.25 (2.82)	6.50 (3.12)
Median	5.71	5.71
Min - Max	1.9 - 24.4	2.3 - 28.1
Site of primary tumor		
n	252	248
Right	124 (49.2%)	114 (46.0%)
Left	128 (50.8%)	134 (54.0%)
Histologic subtype		
n	252	248
Invasive carcinoma of no special type (NST)	194 (77.0%)	197 (79.4%)
Invasive lobular carcinoma	16 (6.3%)	13 (5.2%)
Invasive micropapillary carcinoma	2 (0.8%)	1 (0.4%)
Mucinous carcinoma	3 (1.2%)	2 (0.8%)
Apocrine carcinoma	3 (1.2%)	2 (0.8%)
Other	34 (13.5%)	33 (13.3%)
Histological grade		
n	252	248
GX	2 (0.8%)	4 (1.6%)
G1	9 (3.6%)	3 (1.2%)
G2	119 (47.2%)	116 (46.8%)
G3	80 (31.7%)	90 (36.3%)
No residual tumor	0	0
Unknown	42 (16.7%)	35 (14.1%)
Primary tumor estrogen receptor status (Central Lab)		
n	252	248
Estrogen receptor positive	152 (60.3%)	150 (60.5%)
Estrogen receptor negative	100 (39.7%)	97 (39.1%)
Estrogen receptor unknown	0	1 (0.4%)
Primary tumor progesterone receptor status (Central Lab)		
n	252	248
Progesterone receptor positive	116 (46.0%)	98 (39.5%)
Progesterone receptor negative	135 (53.6%)	149 (60.1%)
Progesterone receptor unknown	1 (0.4%)	1 (0.4%)
HER2 Immunohistochemistry (Central Lab)		
n	252	248
0	3 (1.2%)	0
1+	6 (2.4%)	2 (0.8%)
2+	68 (27.0%)	74 (29.8%)
3+	175 (69.4%)	170 (68.5%)
Unknown	0	2 (0.8%)

HER2 ISH (Central Lab)		
n	252	248
ISH+	252 (100%)	247 (99.6%)
ISH-	0	1 (0.4%)
Unknown	0	0
Clinical staging - Primary tumor		
n	252	248
TX	0	0
Tis	0	0
T1a	1 (0.4%)	0
T1b	2 (0.8%)	1 (0.4%)
T1c	11 (4.4%)	10 (4.0%)
T2	166 (65.9%)	154 (62.1%)
T3	37 (14.7%)	42 (16.9%)
T4a	9 (3.6%)	3 (1.2%)
T4b	17 (6.7%)	31 (12.5%)
T4c	2 (0.8%)	1 (0.4%)
T4d	7 (2.8%)	6 (2.4%)
Clinical staging - Regional lymph nodes		
n	252	248
NX	2 (0.8%)	0
N0	109 (43.3%)	101 (40.7%)
N1	107 (42.5%)	102 (41.1%)
N2a	13 (5.2%)	25 (10.1%)
N2b	2 (0.8%)	3 (1.2%)
N3a	8 (3.2%)	5 (2.0%)
N3b	6 (2.4%)	5 (2.0%)
N3c	5 (2.0%)	7 (2.8%)
Clinical stage at presentation		
n	252	248
II-IIIA	202 (80.2%)	196 (79.0%)
IIIB-IIIC	50 (19.8%)	52 (21.0%)

Denominator for percentages is the number of patients in the ITT population. Unknown includes not applicable.

Table 17 Randomised stratification factors by randomised treatment (IxRS): ITT Population

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
Hormonal receptor status (based on central assessment):		
ER negative and PgR negative	97 (38.5%)	96 (38.7%)
ER positive or PgR positive	155 (61.5%)	151 (60.9%)
Unknown	0	1 (0.4%)
Type of chemotherapy		
ddAC followed by paclitaxel	120 (47.6%)	120 (48.4%)
AC followed by docetaxel	132 (52.4%)	128 (51.6%)
Clinical stage at presentation		
Stage II-IIIA	201 (79.8%)	198 (79.8%)
Stage IIIB-IIIC	51 (20.2%)	50 (20.2%)

Numbers analysed

Three analysis populations were defined for the study:

- The intention-to-treat (ITT) population included all randomised patients.
- The Safety Analysis population included all patients who received at least one dose of study medication, according to the treatment actually received.
- The Per Protocol PK (PPP) analysis population included all enrolled patients who adhered to the pre-specified criteria in the protocol for PK assessments.

Most patients (242 [96.0%] P+H IV and 234[94.4%] PH FDC SC patients) completed the neoadjuvant treatment phase. Of these, 239 in the P+H IV arm and all 234 patients in the PH FDC SC arm underwent primary surgery.

The PPP analysis population was comprised of 203 patients in the P+H IV arm and 206 patients in the PH FDC SC arm. Out of the 252 (P+H IV arm) and 248 (PH FDC SC arm) patients randomised, a total of 239 (P+H IV arm) and 234 (PH FDC SC arm) had predose Cycle 8 PK measurements. Of these, 36 patients in the P+H IV arm and 28 patients in the PH FDC SC arm were excluded from the PPP population due to at least one predefined PK protocol violation. The most common reasons for exclusion in both arms were delays in Day 21 C_{trough} sample collection (13 patients in P+H IV arm and 17 patients in the PH FDC SC arm), or due to a dose delay of more than 7 days (17 patients in P+H IV arm and 9 patients in the PH FDC SC arm).

Table 18 Analysis populations by randomised treatment: all patients

Analysis Populations Reason for Exclusions	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
Randomized Patients	252	248
No. of Patients with Pre-dose Cycle 8 PK measurement	239	234
Per Protocol PK Analysis Population [1]	203	206
No. Excluded due to Violation of PK Protocol	36	28
Patients with a Ctrough sample collected with at least 2 days deviation from the planned on Day 21	13	17
Patients given a dose amount that deviates from the planned dose by >20%	2	1
Patients with a dose delay of more than 7 days	17	9
Patients with a subcutaneous injection site other than thigh is used	0	2
For Cycle8 IV PK samples check if Pre-dose and Post-dose samples were switched	6	0
Assay error impacting Ctrough measurement	0	0
Intent-to-treat Population [2]	252	248
No. Excluded from ITT population	0	0
Safety Analysis Population [3]	252	248
No excluded as Patient did not receive at least one dose of any study medication	0	0

[1] Per Protocol PK analysis population will include all patients enrolled who adhered to the protocol.
[2] ITT includes all randomized patients.
[3] Safety analysis population include all patients who receive at least one dose of study medication.

Outcomes and estimation

Primary and secondary PK endpoints were presented in detail in the Pharmacokinetics section and summarised below.

Primary endpoint: Serum pertuzumab C_{trough} during Cycle 7 (pre-dose Cycle 8); assessed pre-dose on Cycle 8, Day 1 (up to 21 weeks).

The geometric mean of serum pertuzumab C_{trough} for the PH FDC SC arm was 88.7 µg/mL compared with 72.4 µg/mL for the P+H IV arm. The resulting geometric mean ratio (GMR) of Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough}, SC/C_{trough} IV values was 1.22 (90% CI: 1.14, 1.31).

The observed lower limit of the two-sided 90% CI of 1.14, was above the prespecified non-inferiority margin of 0.8.

The coefficients of variation for Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough} were 34.1% in the P+H IV arm vs. 33.6% in the PH FDC SC arm, showing comparable variability between the two treatment arms.

Secondary pharmacokinetic endpoint: Serum trastuzumab C_{trough} during Cycle 7 (pre-dose Cycle 8)

The geometric mean of serum trastuzumab C_{trough} for the PH FDC SC arm was 57.5 µg/mL compared with 43.2 µg/mL for the P+H IV arm. The resulting GMR Cycle 7 corresponding lower limit of the two-sided 90% CI of 1.24 was greater than the prespecified non-inferiority margin of 0.8.

The coefficients of variation for Cycle 7 (pre-dose Cycle 8) serum trastuzumab C_{trough} were 34.7% in the P+H IV arm vs. 37.0% in the PH FDC SC arm, showing comparable variability between the two treatment arms.

Main efficacy endpoint: Total pathological complete response (tpCR)

In the ITT population, most patients in both arms achieved tpCR in the breast and axilla and this was comparable between the two arms. The tpCR rate was 59.5% (150/252) with 95% CI: 53.18% - 65.64% in the P+H IV arm and 59.7% (148/248) with 95% CI: 53.28%- 65.84% in the PH FDC SC arm. This resulted in a difference of 0.15% (95% CI: -8.67, 8.97) in the tpCR rate. See Table 19

Table 19 Summary of total pathological complete response (tpCR) (ITT population)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)		Pertuzumab + Trastuzumab FDC SC Arm (N=248)
tpCR(absence of invasive neoplastic cells in breast and in the axillary lymph nodes)	150 (59.5%)		148 (59.7%)
Exact 95% CI for tpCR Rate [1]	(53.18, 65.64)		(53.28, 65.84)
Difference in tpCR Rate (SC minus IV arm)		0.15	
95% CI for the difference in tpCR [2]		(-8.67, 8.97)	

[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
[2] Continuity correction of Anderson and Hauck (1986) has been used in this calculation.

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At surgery, 51.6% of patients in the P+H IV arm and 52.4% of patients in the PH FDC SC arm had no residual tumour in the breast. For patients who did not achieve tpCR, the majority had T1 tumours (23.8% vs. 24.2%) and N1 status (11.9% vs. 11.3%) in the P+H IV and PH FDC SC arms, respectively.

At surgery, the most common histopathological type was invasive carcinoma of no special type (27.8% vs. 26.6%) and most tumours were Grade 2 (14.7% vs. 16.1%), unifocal (38.1% vs. 31.0%) and ≥ 5 mm (26.2% vs. 23.4%) in the P+H IV vs. PH FDC SC arms, respectively.

Ancillary analyses

Subgroup analyses

In both arms, the rate of tpCR was higher in patients who were: hormone receptor negative (66.0% and 70.8%), had Stage II-IIIA disease (61.7% and 61.1%) and who received ddAC followed by paclitaxel (63.3% and 66.7%) in the P+H IV and PH FDC SC arms, respectively. See Table 20

Table 20 Subgroup analyses: tpCR by stratification factors

Subgroup	P+H IV arm N=252	PH FDC SC arm N=248
Hormone Receptor Status		
HR positive (ER and/or PgR positive)	86/155 (55.5%)	79/151 (52.3%)
HR negative (ER and/or PgR negative)	64/97 (66.0%)	68/96 (70.8%)
Clinical Stage at Presentation		
Stage II-IIIA	124/201 (61.7%)	121/198 (61.1%)
Stage IIIB-IIIC	26/51 (51.0%)	27/50 (54.0%)
Type of Chemotherapy		
ddAC followed by paclitaxel	76/120 (63.3%)	80/120 (66.7%)
AC followed by docetaxel	74/132 (56.1%)	68/128 (53.1%)

Total pathological CR rates were numerically higher for obese patients in the P+H IV arm (63.3% P+H IV vs. 48.1% PH FDC SC) and for Asian patients in the PH FDC SC arm (48.1% P+H IV vs. 60.8% PH FDC SC).

In general, tpCR rates were comparable within biomarker subgroups between both treatment arms. tpCR rates in HER2 IHC3+ patients were 61.7% (95% CI: 54.08, 68.95) in the P+H IV arm and 63.5% (95% CI: 55.81, 70.76) in the PH FDC SC arm. In HER2 IHC2+ patients, the tpCR rate was 58.8% (95% CI: 46.23, 70.63) in the P+H IV arm and 50.0% (95% CI: 38.14, 61.86) in the PH FDC SC arm. Patients with mutated PIK3CA had slightly lower tpCR rates compared to those with a non-mutated gene within each treatment arm and the tpCR rates were comparable between treatment arms.

Patients with a higher HER2 gene copy number (*i.e.*, ≥6) had higher tpCR rates compared to patients with a lower HER2 gene copy number (*i.e.*, ≥4 and <6) (61.1% vs. 46.2% in the P+H IV arm and 61.5% vs. 37.5% in the PH FDC SC arm), and this was balanced across treatment arms.

Table 21 Total pathological complete response by subgroup and treatment regimen (ITT population)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)				Pertuzumab + Trastuzumab FDC SC Arm (N=248)			
Subgroup	Patients per group	Responders	tpCR Rate	95% CI of Respond Rate [1]	Patients per group	Responders	tpCR Rate	95% CI of Respond Rate [1]
All	252	150	59.5	(53.18, 65.64)	248	148	59.7	(53.28, 65.84)
Age								
<65	219	131	59.8	(53.00, 66.37)	222	134	60.4	(53.60, 66.84)
>=65	33	19	57.6	(39.22, 74.52)	26	14	53.8	(33.37, 73.41)
CENTRAL - Clinical stage at presentation								
Stage II-IIIA	201	124	61.7	(54.59, 68.44)	198	121	61.1	(53.94, 67.94)
Stage IIIB-IIIC	51	26	51.0	(36.60, 65.25)	50	27	54.0	(39.32, 68.19)
Type of chemotherapy								
ddAC followed by paclitaxel	120	76	63.3	(54.05, 71.94)	120	80	66.7	(57.48, 75.01)
AC followed by docetaxel	132	74	56.1	(47.16, 64.68)	128	68	53.1	(44.11, 62.00)
CENTRAL - Hormone receptor status								
Positive (ER and/or PgR positive)	155	86	55.5	(47.30, 63.46)	151	79	52.3	(44.04, 60.50)
Negative (ER and PgR negative)	97	64	66.0	(55.66, 75.30)	96	68	70.8	(60.67, 79.67)
Unknown	0	0	NE	NE	1	1	100	(2.50, 100.00)
Histological subtype								
Invasive carcinoma of no special type (NST)	194	114	58.8	(51.49, 65.77)	197	117	59.4	(52.18, 66.31)
Invasive lobular carcinoma	16	10	62.5	(35.43, 84.80)	13	9	69.2	(38.57, 90.91)
Invasive micropapillary carcinoma	2	1	50.0	(1.26, 98.74)	1	0	NE	(0.00, 97.50)
Mucinous carcinoma	3	1	33.3	(0.84, 90.57)	2	1	50.0	(1.26, 98.74)
Apocrine carcinoma	3	3	100	(29.24, 100.00)	2	1	50.0	(1.26, 98.74)
Other	34	21	61.8	(43.56, 77.83)	33	20	60.6	(42.14, 77.09)
Histological grade at baseline								
GX	2	2	100	(15.81, 100.00)	4	2	50.0	(6.76, 93.24)
G1	9	4	44.4	(13.70, 78.80)	3	2	66.7	(9.43, 99.16)
G2	119	73	61.3	(51.98, 70.13)	116	66	56.9	(47.38, 66.06)
G3	80	49	61.3	(49.70, 71.94)	90	59	65.6	(54.80, 75.26)
Unknown	42	22	52.4	(36.42, 68.00)	35	19	54.3	(36.65, 71.17)
Menopausal status at Randomization								
Pre-menopausal	144	88	61.1	(52.64, 69.12)	118	69	58.5	(49.04, 67.47)
Post-menopausal	106	61	57.5	(47.57, 67.09)	130	79	60.8	(51.82, 69.21)
Unknown	2	1	50.0	(1.26, 98.74)	0	0	NE	NE
Race								
American Indian or Alaska native	10	8	80.0	(44.39, 97.48)	10	6	60.0	(26.24, 87.84)
Asian	54	26	48.1	(34.34, 62.16)	51	31	60.8	(46.11, 74.16)
Black or African American	3	2	66.7	(9.43, 99.16)	3	3	100	(29.24, 100.00)
White	164	99	60.4	(52.44, 67.91)	165	99	60.0	(52.10, 67.54)
Multiple	2	1	50.0	(1.26, 98.74)	3	2	66.7	(9.43, 99.16)
Unknown	19	14	73.7	(48.80, 90.85)	16	7	43.8	(19.75, 70.12)
BMI (WHO Classification) [2]								
Underweight	3	3	100	(29.24, 100.00)	7	3	42.9	(9.90, 81.59)
Normal	120	71	59.2	(49.82, 68.05)	112	70	62.5	(52.85, 71.47)
Overweight	80	45	56.3	(44.70, 67.32)	75	49	65.3	(53.46, 75.96)
Obese	49	31	63.3	(48.29, 76.58)	54	26	48.1	(34.34, 62.16)

[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
[2] BMI (kg/m2): Underweight <18.5; Normal 18.5-<25.0; Overweight 25.0-<30.0; Obese >=30.0

Exploratory analyses

Table 22 Summary of breast pathological complete response (ITT population)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)		Pertuzumab + Trastuzumab FDC SC Arm (N=248)
bpCR(absence of invasive neoplastic cells in breast)	163 (64.7%)		160 (64.5%)
Exact 95% CI for bpCR Rate [1]	(58.44, 70.58)		(58.21, 70.47)
Difference in bpCR Rate (SC minus IV arm)		-0.17	
95% CI for the difference in bpCR [2]		(-8.77, 8.44)	

bpCR, defined as eradication of invasive disease in the breast (i.e., ypT0/is, ypNx).
[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
[2] Continuity correction of Anderson and Hauck (1986) has been used in this calculation.

Table 23 Summary of German breast group pathological complete response (ITT population)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)		Pertuzumab + Trastuzumab FDC SC Arm (N=248)
GBG pCR(absence of invasive and in situ disease in breast and invasive disease in the axillary lymph nodes)	124 (49.2%)		127 (51.2%)
Exact 95% CI for GBG pCR Rate [1]	(42.88, 55.55)		(44.80, 57.59)
Difference in GBG pCR Rate (SC minus IV arm)		2.00	
95% CI for the difference in GBG pCR [2]		(-6.98, 10.99)	

GBG pCR, defined as eradication of invasive and in situ disease in the breast and invasive disease in axilla (i.e., ypT0 ypN0).
[1] Confidence Interval for one sample binomial proportion using Pearson-Clopper method.
[2] Continuity correction of Anderson and Hauck (1986) has been used in this calculation.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table: Summary of efficacy for trial FeDeriCa

Title: A phase III, randomized, multicentre, open-label, two-arm study to evaluate the pharmacokinetics, efficacy, and safety of subcutaneous administration of the fixed-dose combination of pertuzumab and trastuzumab in combination with chemotherapy in patients with HER2-positive early breast cancer.		
Study identifier	WO40324, Eudract number 2017-004897-32, NCT03493854, "FeDeriCa"	
Design	Phase III, randomised (1:1), open-label, two-arm	
	Duration of main phase:	13 months (14-JUN-2018 to 4-JUL-2019)
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Non-inferiority	

Treatments groups	Arm A (P+H IV)		Neoadjuvant phase: AC x 4 → P+H IV Q3W x 4 concurrent with taxane Adjuvant phase: P+H IV Q3W x 14 n=252
	Arm B (PH FDC SC)		Neoadjuvant phase: AC x 4 → PH FDC SC Q3W x 4 concurrent with taxane Adjuvant phase: PH FDC SC Q3W x 14 n=248
Endpoints and definitions	Secondary efficacy endpoint [a,b]	tpCR	Total pathologic complete response, i.e. ypT0/is ypN0 evaluated after surgery following the neoadjuvant phase of treatment
Clinical cut-off	4-JUL-2019		
Database lock	29-AUG-2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat is defined as all randomised patients, when all patients had completed 8 cycles (chemotherapy + anti-HER2 treatment) of neoadjuvant therapy and had had surgery		
Descriptive statistics and estimate variability	Treatment group	Arm A (P+H IV)	Arm B (PH FDC SC)
	Number of subjects	252	248
	tpCR, number of subjects (rate)	150 (59.5%)	148 (59.7%)
	95% CI tpCR rate	53.18, 65.64	53.28, 65.84
Effect estimate per comparison	tpCR rate	Comparison groups	Arm B (PH FDC SC) minus Arm A (P+H IV)
		Difference in tpCR rate (SC minus IV arm)	0.15
		Δ 95% CI for the difference in tpCR[c]	−8.67, 8.97
Notes	[a] PK was the primary endpoint of the study, so all efficacy analyses were considered secondary or exploratory [b] All subsequent secondary endpoints are time-to-event and will be reported at the end of the study [c] Continuity correction of Anderson and Hauck (1986) has been used for the calculation of the 95% CI		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
FeDeriCa	52/500 = 10.4%	7/500 = 1.4%	0/500

Non-Controlled trials	Not applicable	Not applicable	Not applicable

Supportive study(ies)

Not applicable.

2.5.3. Discussion on clinical efficacy

This is an application for a fixed dose combination of pertuzumab and trastuzumab co-formulated with recombinant human hyaluronidase PH20 (rHuPH20, a permeation enhancer), for subcutaneous administration (PH FDC SC). Pertuzumab and trastuzumab in PH FDC SC are identical to those contained in the currently approved mono-components Perjeta and Herceptin. This product was developed to offer patients a less invasive and faster administration of pertuzumab and trastuzumab compared to IV infusions or SC administration of trastuzumab and IV infusion of pertuzumab.

The proposed indications for PH FDC SC are the same as those approved for pertuzumab in the EU, i.e. in combination with trastuzumab and chemotherapy for early and metastatic HER2-positive breast cancer.

This application is primarily based on a pharmacokinetic bridging approach and efficacy and safety are presented as supportive. There is only one clinical efficacy study, FeDeriCa (WO40324), an ongoing pivotal Phase III, global, two-arm, open-label, multicentre, randomised study. The applicant submitted also a Phase I Study, BO30185, which was performed for dose selection. This study and selected dose for phase III trial are discussed in section 2.4.

Design and conduct of clinical studies

The overall design of the FeDeriCa trial –targeted population, open-label nature, stratification factors for randomisation, definition of primary and secondary endpoints, choice of control arm, chemotherapy backbones– has been extensively discussed in scientific advice meetings between 2016 and 2017. As was the case with the HannaH study, which led to the approval of trastuzumab for SC administration in 2013, the selection of the EBC setting in FeDeriCa allows for a much more homogeneous treatment-naïve population, further granting faster delivery of PK, efficacy and safety results.

It has long been debated whether pCR truly can be a surrogate for overall survival, the most persuasive – albeit longest to collect– efficacy outcome of Oncology trials, or at least whether it relates to post-adjuvant endpoints after curative-intent treatment (IDFS, DFS, EFS). The evolving definition of pCR (e.g. including or excluding *in situ* disease, only considering the breast and not lymph nodes, among others) and other factors that increase heterogeneity (e.g. tumour biological profile) have complicated overall agreement. Currently, it is considered that tpCR (ypT0/is ypN0), the most widely accepted definition of pCR, can predict survival in the most aggressive subtypes of breast cancer, i.e., triple-negative and HER2-enriched. The tpCR comparison is exploratory and hence not type I error controlled. The non-inferiority margin of -12.5% in FeDeriCa is based on study HannaH (SC vs. IV trastuzumab in EBC) and consistent with EMA guidelines for the choice of non-inferiority margin, hence clinically acceptable.

Up to surgery, the study had progressed as expected during the neoadjuvant setting, with very few patients withdrawn for conceivable reasons. Recruitment finished faster than anticipated. The updated patient disposition tree showed that overall discontinuation of anti-HER2 treatment because of AEs during both phases was balanced between treatment arms.

The low proportion of elderly patients in the FeDeriCa trial seems to reflect the distribution of age of HER2+ EBC in clinical practice.

Upon the CHMP's request, the applicant was recommended to providing long-term efficacy data from FeDeriCa in Q4 2023 (final CSR), noting that an important proportion of patients (98%) is available for treatment-free follow-up.

64 patients (36 patients from the P+H IV arm and 28 from the PH FDC SC arm) were excluded from the PPP population due to at least one predefined PK protocol violation.

Efficacy data and additional analyses

The distribution of baseline demographic and disease characteristics in the two arms of the study is balanced. Although the only two male subjects were randomised to the control arm, extrapolation of overall study results to male patients is anticipated.

Since PK endpoints were prioritised in hierarchical testing, efficacy was assessed as a secondary endpoint. Clinical efficacy, as measured by local assessment of tpCR, using the definition recommended by the EMA (absence of invasive neoplastic cells in the resected breast and axillary lymph nodes, that is, ypT0/is ypN0), showed comparable results in both arms: 59.5% in the P+H IV arm and 59.7% in the PH FDC SC arm, with 95% CIs almost fully overlapped. Importantly, these data are analogous to similar anthracycline regimens with dual HER2 blockade in recent neoadjuvant trials (involving trastuzumab and pertuzumab) that used akin pCR definitions (BERENICE, TRAIN-2, GEPAR-SEPTO and TRYPHAENA). Regarding the difference in tpCR rates between SC and IV arms (0.15%, 95% CI -8.67, 8.97), the maximum potential efficacy loss (-8.67%) from the SC vs. the IV route falls under the clinically acceptable defined threshold of -12.5%.

Subgroup analysis on tpCR did not identify a particular subgroup of patients with significantly different results across arms. As expected, numerically higher tpCR rates were observed in the HR- subgroup vs. the HR+ subgroup: 66.0% vs. 55.5% in the P+H IV arm and 70.8% vs. 52.3% in the PH FDC SC arm. Likewise, earlier stages (II-IIIA) had also a superior trend to accomplish complete response as compared to more advanced stages (IIIB-IIIC): 61.7% vs. 51.0% in the P+H IV arm and 61.1% vs. 54.0% in the PH FDC SC arm. Of note, the dose dense scheme (ddAC → paclitaxel) also achieved higher tpCR rates as compared to the AC → docetaxel regimen: 63.3% vs. 56.1% in the P+H IV arm and 66.7% vs. 53.1% in the PH FDC SC arm.

Slight variations in the pathological definition of complete response (bpCR and GBG pCR) were consistent with the main efficacy outcome. bpCR is a less conservative definition of complete response that only takes the breast into account, i.e. regardless of lymph node status. On the other hand, GBG pCR entails a stricter definition that excludes responders that have residual carcinoma *in situ:* only ypT0 ypN0 is regarded as complete response. These exploratory efficacy endpoints were not considered for sensitivity analysis for the main efficacy endpoint (tpCR). As expected, bpCR exhibited higher rates than tpCR, whereas those according to GBG pCR definition were lower. Importantly, the results of each endpoint were comparable between the IV and SC arms, hence reflecting the main efficacy analysis.

Overall incidence of ADAs was low and comparable between treatment arms (see Clinical Safety). Due to low numbers of ADAs, no conclusion can be drawn on their effect on efficacy.

2.5.4. Conclusions on the clinical efficacy

The main efficacy outcome of the FeDeriCa trial shows comparable tpCR rates between the P+H IV and PH FDC SC arms. Although short-term efficacy in the early breast cancer setting can be extrapolated to the metastatic setting in the HER2-enriched subtype, the applicant is expected to provide results from the time-to-event endpoints (final CSR from FeDeriCa expected in Q4 2023).

2.6. Clinical safety

Both trastuzumab (IV and SC formulation) and pertuzumab (IV formulation only) are EMA-approved anti-HER2 treatments with a known safety profile and extensive post-marketing PSUR follow-up.

The main safety concern from trastuzumab is congestive heart failure (CHF) and asymptomatic cardiac dysfunction. Hence all candidates for treatment with this drug, especially those with prior anthracycline and cyclophosphamide exposure, should undergo baseline cardiac assessment including left ventricular ejection fraction (LVEF) determination. Other common adverse drug reactions (ADRs) from trastuzumab are infusion-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary events (i.e. interstitial lung disease). The safety profile of trastuzumab SC is consistent with the known safety profile for trastuzumab IV with no new safety findings.

Pertuzumab (IV formulation) is only licensed for use in combination with trastuzumab, thus its potential adverse reactions must be always considered as an addition to those from trastuzumab. The most common ADRs (≥30%) from pertuzumab are diarrhoea, alopecia, nausea, fatigue, neutropenia, and vomiting.

In the context of a full marketing authorisation application, the applicant has submitted PK, efficacy and safety data for pertuzumab/trastuzumab fixed dose combination for subcutaneous injection (PH FDC SC) in the currently approved therapeutic indications for pertuzumab IV.

The safety evaluation of PH FDC SC to treat patients with HER2+ BC is based on data from two clinical studies: FeDeriCa (phase III) and study BO30185 (phase I), both done in the EBC setting and summarised in Table 24 below. Owing to differences in trial design, it was not considered clinically meaningful to pool the safety data from the two studies. The main focus of the safety assessment will be FeDeriCa study.

Table 24 **Summary of studies contributing to safety evaluation**

Study No. (Phase)	Study Design, Control Type	Population	No. of Subjects/ Patients	Dose, Route, and Regimen
WO40324 FeDeriCa (Phase III)	Randomised, multicentre, open-label, two-arm (IV vs SC)	Patients with HER2-positive early breast cancer	500 patients Arm A: 252 patients Arm B: 248 patients	**Arm A[a]: P+H IV** Loading dose: Herceptin IV: 8 mg/kg Perjeta: 840 mg Maintenance dose Herceptin IV: 6 mg/kg (Q3W) Perjeta: 420 mg (Q3W) Neoadjuvant Perjeta + Herceptin IV for 4 cycles (Q3W) concurrently with taxane chemotherapy after anthracycline-based chemotherapy followed by surgery Adjuvant Perjeta with either Herceptin IV or Herceptin SC for 14 cycles **Arm B: PH FDC SC** Loading dose 1200 mg pertuzumab plus 600 mg trastuzumab plus 30,000 U rHuPH20 Maintenance dose 600 mg pertuzumab plus 600 mg trastuzumab plus 20,000 U rHuPH20 (Q3W) Neoadjuvant PH FDC SC for 4 cycles (Q3W) concurrently with taxane chemotherapy after anthracycline-based chemotherapy Adjuvant PH FDC SC for 14 cycles
BO30185b (Phase I)	Open-label, two-part, multicentre	Part 1: HMVs Part 2: Patients with EBC who had completed standard (neo)-adjuvant breast cancer therapy	Part 1 48 HMVs (8 cohorts, 6 HMVs/cohort) Part 2c 40 female patients with EBC Cohort B: 20 patients Cohort C: 20 patients	Part 1 Cohort 1: 420 mg Perjeta (control) Cohort 2: 400 mg pertuzumab SC Cohort 3: 600 mg pertuzumab SC Cohort 4: 1200 mg pertuzumab SC Cohort 5: 600 mg Herceptin SC (control) Cohort 6d: 400 mg pertuzumab SC plus 600 mg Herceptin SC (co-mixed) Cohort 7d: 1200 mg pertuzumab SC plus 600 mg Herceptin SC (co-mixed) Cohort 8e: 1200 mg pertuzumab SC plus 600 mg Herceptin SC (co-mixed) Part 2c Cohort B: co-mixed SC injection of 600 mg pertuzumab and 600 mg trastuzumab (with 1000 U/mL rHuPH20) Cohort Cb: co-formulated PH FDC SC injection of 600 mg pertuzumab and 600 mg trastuzumab (with 2000 U/mL rHuPH20)

EBC = early breast cancer; HER2 = human epidermal growth factor receptor 2; HMV = healthy male volunteer; IV = intravenous; P+H IV = Perjeta plus Herceptin intravenous; PH FDC SC = fixed dose combination of pertuzumab and trastuzumab for subcutaneous administration; rHuPH20 = recombinant human hyaluronidase; Q3W = every 3 weeks; SC = subcutaneous.

[a] After surgery (from cycle 9 onwards), patients in Arm A continued Perjeta and were allowed to switch from Herceptin IV to Herceptin SC, at the discretion of the investigator, in countries where Herceptin SC is routinely used.

[b] Safety data from Part 2 Cohort C (PH FDC SC) are presented herein.

[c] Cohort A (co-administered pertuzumab SC and trastuzumab SC, each agent administered separately) was not required.

[d] Both pertuzumab SC and Herceptin SC contained 2000 U/mL rHuPH20.

[e] Pertuzumab SC contained no rHuPH20; Herceptin SC contained 2000 U/mL rHuPH20.

The safety population of FeDeriCa is constituted by 252 patients from the P+H IV arm and 248 patients from the PH FDC SC arm.

The primary analysis in the pivotal FeDeriCa study was conducted once all patients had completed the neoadjuvant therapy and underwent surgery (clinical cut-off date 04-JUL-2019).

Upon request, the applicant provided an updated safety database once all patients from the trial have finished receiving adjuvant anti-HER2 treatment, with a cut-off date 10-JUL-2020. The following safety assessment focuses on this late database, since it allowed for comparing safety performance of both arms along the adjuvant phase, where dual HER2-targeted treatment is no longer confounded by chemotherapy.

Patient exposure

The median number of cycles to anti-HER2 to treatment was 18 cycles for both the P+H IV and PH FDC SC arms (range: 1-18 cycles for both arms), which is in line with the expected number of cycles as per protocol (up to max. 18 cycles).

The below table depicts exposure to dual anti-HER2 treatment (FeDeriCa study):

Summary of Exposure to Overall Planned HER2 Targeted Therapy (Neoadjuvant + Adjuvant Phase): Safety Population
Protocol: WO40324 (CCOD:10JUL2020 DBL:06AUG2020)

	Pertuzumab IV + Trastuzumab IV Arm			Pertuzumab + Trastuzumab FDC SC Arm
	Pertuzumab IV (N=247)	Trastuzumab IV (N=246)	Trastuzumab SC [1] (N=65)	Pertuzumab and Trastuzumab FDC SC (N=243)
Completed assigned therapy				
Yes	209 (84.6%)	150 (61.0%)	0	217 (89.3%)
No	38 (15.4%)	96 (39.0%)	65 (100%)	26 (10.7%)
Number of cycles				
n	247	246	65	243
Mean	16.4	13.1	12.8	16.8
SD	4.2	6.5	3.1	3.9
Median	18.0	18.0	14.0	18.0
Min - Max	1 - 18	1 - 18	1 - 14	1 - 18
Treatment duration [Weeks]				
n	247	246	65	243
Mean	51.8	40.7	36.1	53.0
SD	13.8	22.0	9.5	12.8
Median	56.3	55.3	39.1	56.3
Min - Max	0 - 66	0 - 66	0 - 43	0 - 65
Dose intensity [%] [2]				
n	4062	3227	835	4092
Mean	99.97	99.50	100.00	100.02
SD	1.29	3.25	0.00	1.56
Median	100.00	100.00	100.00	100.00
Min - Max	21.7 - 100.0	82.8 - 115.9	100.0 - 100.0	100.0 - 200.0
Total cumulative dose [mg]				
n	247	246	65	243
Mean	7690.82	5465.70	7707.69	21343.21
SD	1857.93	2915.94	1868.18	4749.13
Median	8400.00	6082.40	8400.00	22800.00
Min - Max	182.0 - 9240.0	466.0 - 12769.0	600.0 - 8400.0	1800.0 - 24000.0
Number of patients with at least one dose delay [3]				
n	247	246	65	243
Yes	120 (48.6%)	112 (45.5%)	16 (24.6%)	112 (46.1%)
No	127 (51.4%)	134 (54.5%)	49 (75.4%)	131 (53.9%)
Number of patients with at least one dose delay - Due to AE				
n	247	246	65	243
Yes	80 (32.4%)	78 (31.7%)	7 (10.8%)	68 (28.0%)
No	167 (67.6%)	168 (68.3%)	58 (89.2%)	175 (72.0%)
Number of cycles of study drug received	247 (100%)	246 (100%)	65 (100%)	243 (100%)

Cycle number [4]				
1-	3 (1.2%)	2 (0.8%)	1 (1.5%)	6 (2.5%)
2-	1 (0.4%)	1 (0.4%)	2 (3.1%)	2 (0.8%)
3-	1 (0.4%)	1 (0.4%)	1 (1.5%)	1 (0.4%)
4-	12 (4.9%)	69 (28.0%)	0	4 (1.6%)
5-	0	5 (2.0%)	0	1 (0.4%)
6-	2 (0.8%)	0	1 (1.5%)	0
7-	4 (1.6%)	3 (1.2%)	0	2 (0.8%)
8-	0	1 (0.4%)	0	1 (0.4%)
9-	1 (0.4%)	2 (0.8%)	2 (3.1%)	0
10-	3 (1.2%)	2 (0.8%)	0	0
11-	1 (0.4%)	1 (0.4%)	1 (1.5%)	1 (0.4%)
12-	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
13-	1 (0.4%)	0	6 (9.2%)	2 (0.8%)
14-	0	0	51 (78.5%)	1 (0.4%)
15-	1 (0.4%)	1 (0.4%)	0	0
16-	5 (2.0%)	5 (2.0%)	0	1 (0.4%)
17-	2 (0.8%)	2 (0.8%)	0	3 (1.2%)
18-	209 (84.6%)	150 (61.0%)	0	217 (89.3%)

[1] Subset of patients who switched from Trastuzumab IV to Trastuzumab SC in the Adjuvant Phase (i.e. from Cycle 5) and continued with Pertuzumab IV.
[2] Dose intensity = 100% * actual amount of drug received per cycle / planned dose per cycle.
[3] For HER2 treatment dose modification was not allowed however a dose delay of up to 6 weeks due to adverse event was permitted.
[4] Pertuzumab IV + Trastuzumab IV or Pertuzumab and Trastuzumab FDC SC will be given for 4 cycles in Neoadjuvant phase and another 14 cycles in the Adjuvant phase.

Adverse events

The overview of Adverse Events in the Safety Population of FeDeriCa study is presented in the below table.

Table 25 Overall summary of adverse events by treatment regimen: safety population

Protocol: WO40324 (CCOD:10JUL2020 DBL:06AUG2020)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)			Pertuzumab + Trastuzumab FDC SC Arm (N=248)		
	Phase			Phase		
	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
Total number of patients with at least one adverse event (AE)	249 (98.8%)	218 (86.5%)	251 (99.6%)	248 (100%)	221 (89.1%)	248 (100%)
Total number of patients with at least one:						
AE with fatal outcome	1 (0.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)	0	2 (0.8%)
Serious AE	43 (17.1%)	8 (3.2%)	50 (19.8%)	39 (15.7%)	10 (4.0%)	47 (19.0%)
Related Serious AE (any)	26 (10.3%)	2 (0.8%)	29 (11.5%)	26 (10.5%)	4 (1.6%)	29 (11.7%)
Grade 3 to 5 AE	131 (52.0%)	37 (14.7%)	149 (59.1%)	124 (50.0%)	28 (11.3%)	133 (53.6%)
AE to monitor	203 (80.6%)	116 (46.0%)	216 (85.7%)	204 (82.3%)	111 (44.8%)	220 (88.7%)
Anaphylaxis and hypersensitivity	3 (1.2%)	1 (0.4%)	4 (1.6%)	2 (0.8%)	2 (0.8%)	4 (1.6%)
NCI-CTCAE Grade >=3	1 (0.4%)	0	1 (0.4%)	0	0	0
Infusion/ Administration related reactions within 24 hours	32 (12.7%)	12 (4.8%)	38 (15.1%)	24 (9.7%)	43 (17.3%)	55 (22.2%)
NCI-CTCAE Grade >=3	3 (1.2%)	0	3 (1.2%)	0	0	0
Serious Rash / Skin Reactions	0	0	0	0	1 (0.4%)	1 (0.4%)
NCI-CTCAE Grade >=3	0	0	0	0	0	0
Diarrhoea	138 (54.8%)	53 (21.0%)	149 (59.1%)	148 (59.7%)	43 (17.3%)	153 (61.7%)
NCI-CTCAE Grade >=3	10 (4.0%)	3 (1.2%)	13 (5.2%)	18 (7.3%)	0	18 (7.3%)
Cardiac dysfunction	36 (14.3%)	33 (13.1%)	66 (26.2%)	33 (13.3%)	20 (8.1%)	53 (21.4%)
NCI-CTCAE Grade >=3	3 (1.2%)	8 (3.2%)	12 (4.8%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
Interstitial lung disease (ILD)	2 (0.8%)	1 (0.4%)	3 (1.2%)	2 (0.8%)	3 (1.2%)	5 (2.0%)
NCI-CTCAE Grade >=3	0	0	0	0	0	0
Neutropenia / Febrile neutropenia	131 (52.0%)	49 (19.4%)	142 (56.3%)	118 (47.6%)	31 (12.5%)	123 (49.6%)
NCI-CTCAE Grade >=3	88 (34.9%)	9 (3.6%)	92 (36.5%)	79 (31.9%)	10 (4.0%)	82 (33.1%)
Serious Mucositis	4 (1.6%)	0	4 (1.6%)	3 (1.2%)	0	3 (1.2%)
NCI-CTCAE Grade >=3	4 (1.6%)	0	4 (1.6%)	2 (0.8%)	0	2 (0.8%)
Pregnancy and Neonatal related [2]	4 (1.6%)	4 (1.6%)	8 (3.2%)	3 (1.2%)	2 (0.8%)	5 (2.0%)
NCI-CTCAE Grade >=3	2 (0.8%)	1 (0.4%)	3 (1.2%)	0	1 (0.4%)	1 (0.4%)
AE leading to study drug discontinuation (any)	24 (9.5%)	9 (3.6%)	32 (12.7%)	17 (6.9%)	5 (2.0%)	22 (8.9%)
AE leading to HER2 targeted therapy discontinuation	5 (2.0%)	9 (3.6%)	15 (6.0%)	6 (2.4%)	5 (2.0%)	12 (4.8%)
AE leading to any chemotherapy drug discontinuation	23 (9.1%)	0	23 (9.1%)	14 (5.6%)	0	14 (5.6%)
Total number of patients with at least one:						
AE leading to any chemotherapy drug dose modification [1]	45 (17.9%)	0	45 (17.9%)	41 (16.5%)	0	41 (16.5%)
Related AE (any)	247 (98.0%)	139 (55.2%)	248 (98.4%)	246 (99.2%)	162 (65.3%)	247 (99.6%)
Related to HER2 targeted therapy	152 (60.3%)	118 (46.8%)	183 (72.6%)	144 (58.1%)	149 (60.1%)	188 (75.8%)
Related to any chemotherapy drug	247 (98.0%)	63 (25.0%)	248 (98.4%)	246 (99.2%)	61 (24.6%)	247 (99.6%)

Denominator for percentages is the number of patients in the Safety population.
Overall count includes AEs from post screening, Neoadjuvant, Adjuvant and Follow up phases.
Note: (any) means any study drug.
[1] Dose Modification includes Dose Increase, Dose Decrease, Dose Interruption.
Note for HER2 treatment dose modification was not allowed however a dose delay of up to 6 weeks due to adverse event was permitted.
[2] Includes Exposure during pregnancy / Exposure during breast feeding / Pregnancy complications / Oligohydramnios / Congenital abnormalities related AE's.

Program: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/LPLV_Safety/prod/program/t_ae_ovr.sas
Output: root/clinical_studies/RO7198574/CDPT3514/WO40324/data_analysis/LPLV_Safety/prod/output/t_ae_ovr_ALL_SE_10JUL2020_40324.out

NB. Additional details for AEs highlighted by red boxes are included in sections 2.6.1, 2.7 and 3.6.

A summary of the most common Adverse Events (≥5%) in the Safety Population of FeDeriCa study is presented below.

Table 26 Most common Adverse Events (⩾5%): Safety Population

Protocol: WO40324 (CCOD:10JUL2020 DBL:06AUG2020)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)			Pertuzumab + Trastuzumab FDC SC Arm (N=248)		
	Phase			Phase		
MedDRA Preferred Term	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
Alopecia	184 (73.0%)	2 (0.8%)	184 (73.0%)	195 (78.6%)	1 (0.4%)	196 (79.0%)
Diarrhoea	138 (54.8%)	53 (21.0%)	149 (59.1%)	148 (59.7%)	43 (17.3%)	153 (61.7%)
Nausea	153 (60.7%)	20 (7.9%)	156 (61.9%)	149 (60.1%)	16 (6.5%)	152 (61.3%)
Anaemia	103 (40.9%)	19 (7.5%)	108 (42.9%)	83 (33.5%)	17 (6.9%)	91 (36.7%)
Asthenia	76 (30.2%)	22 (8.7%)	83 (32.9%)	73 (29.4%)	27 (10.9%)	79 (31.9%)
Arthralgia	33 (13.1%)	52 (20.6%)	78 (31.0%)	31 (12.5%)	45 (18.1%)	67 (27.0%)
Fatigue	56 (22.2%)	20 (7.9%)	63 (25.0%)	64 (25.8%)	18 (7.3%)	72 (29.0%)
Neutropenia	63 (25.0%)	15 (6.0%)	67 (26.6%)	53 (21.4%)	14 (5.6%)	58 (23.4%)
Stomatitis	60 (23.8%)	8 (3.2%)	61 (24.2%)	61 (24.6%)	4 (1.6%)	63 (25.4%)
Neutrophil count decreased	46 (18.3%)	22 (8.7%)	55 (21.8%)	41 (16.5%)	9 (3.6%)	42 (16.9%)
Radiation skin injury	0	53 (21.0%)	53 (21.0%)	0	50 (20.2%)	50 (20.2%)
Rash	39 (15.5%)	21 (8.3%)	55 (21.8%)	27 (10.9%)	19 (7.7%)	45 (18.1%)
Myalgia	42 (16.7%)	12 (4.8%)	52 (20.6%)	50 (20.2%)	22 (8.9%)	68 (27.4%)
Headache	49 (19.4%)	28 (11.1%)	68 (27.0%)	36 (14.5%)	18 (7.3%)	46 (18.5%)
Constipation	51 (20.2%)	11 (4.4%)	54 (21.4%)	54 (21.8%)	6 (2.4%)	57 (23.0%)
Vomiting	46 (18.3%)	7 (2.8%)	50 (19.8%)	47 (19.0%)	6 (2.4%)	50 (20.2%)
Decreased appetite	44 (17.5%)	10 (4.0%)	51 (20.2%)	39 (15.7%)	6 (2.4%)	43 (17.3%)
Alanine aminotransferase increased	48 (19.0%)	5 (2.0%)	50 (19.8%)	30 (12.1%)	13 (5.2%)	39 (15.7%)
Mucosal inflammation	50 (19.8%)	1 (0.4%)	50 (19.8%)	39 (15.7%)	1 (0.4%)	39 (15.7%)
Cough	31 (12.3%)	11 (4.4%)	41 (16.3%)	32 (12.9%)	12 (4.8%)	41 (16.5%)
Dysgeusia	35 (13.9%)	6 (2.4%)	35 (13.9%)	41 (16.5%)	4 (1.6%)	43 (17.3%)
Peripheral sensory neuropathy	35 (13.9%)	6 (2.4%)	40 (15.9%)	37 (14.9%)	5 (2.0%)	41 (16.5%)
Insomnia	27 (10.7%)	13 (5.2%)	35 (13.9%)	33 (13.3%)	12 (4.8%)	43 (17.3%)
Hot flush	22 (8.7%)	19 (7.5%)	38 (15.1%)	13 (5.2%)	28 (11.3%)	41 (16.5%)
Pyrexia	39 (15.5%)	7 (2.8%)	42 (16.7%)	26 (10.5%)	9 (3.6%)	34 (13.7%)
Neuropathy peripheral	31 (12.3%)	14 (5.6%)	40 (15.9%)	25 (10.1%)	9 (3.6%)	33 (13.3%)
Dry skin	28 (11.1%)	8 (3.2%)	34 (13.5%)	31 (12.5%)	8 (3.2%)	38 (15.3%)
Aspartate aminotransferase increased	38 (15.1%)	6 (2.4%)	40 (15.9%)	24 (9.7%)	8 (3.2%)	29 (11.7%)
Nasopharyngitis	20 (7.9%)	20 (7.9%)	38 (15.1%)	17 (6.9%)	16 (6.5%)	32 (12.9%)
Epistaxis	35 (13.9%)	5 (2.0%)	37 (14.7%)	27 (10.9%)	6 (2.4%)	31 (12.5%)
Dizziness	22 (8.7%)	13 (5.2%)	32 (12.7%)	15 (6.0%)	20 (8.1%)	33 (13.3%)
Dyspepsia	27 (10.7%)	3 (1.2%)	30 (11.9%)	31 (12.5%)	9 (3.6%)	35 (14.1%)
Leukopenia	33 (13.1%)	10 (4.0%)	36 (14.3%)	20 (8.1%)	10 (4.0%)	25 (10.1%)
Upper respiratory tract infection	19 (7.5%)	12 (4.8%)	24 (9.5%)	22 (8.9%)	16 (6.5%)	34 (13.7%)

White blood cell count decreased	28 (11.1%)	16 (6.3%)	35 (13.9%)	19 (7.7%)	5 (2.0%)	20 (8.1%)
Procedural pain	24 (9.5%)	2 (0.8%)	25 (9.9%)	29 (11.7%)	5 (2.0%)	32 (12.9%)
Pruritus	13 (5.2%)	13 (5.2%)	25 (9.9%)	6 (2.4%)	22 (8.9%)	27 (10.9%)
Oedema peripheral	18 (7.1%)	8 (3.2%)	26 (10.3%)	15 (6.0%)	8 (3.2%)	23 (9.3%)
Infusion related reaction	36 (14.3%)	5 (2.0%)	38 (15.1%)	9 (3.6%)	0	9 (3.6%)
Paraesthesia	12 (4.8%)	11 (4.4%)	22 (8.7%)	19 (7.7%)	7 (2.8%)	25 (10.1%)
Pain in extremity	15 (6.0%)	11 (4.4%)	25 (9.9%)	8 (3.2%)	15 (6.0%)	21 (8.5%)
Injection site reaction	1 (0.4%)	1 (0.4%)	2 (0.8%)	17 (6.9%)	33 (13.3%)	40 (16.1%)
Dyspnoea	11 (4.4%)	6 (2.4%)	15 (6.0%)	23 (9.3%)	7 (2.8%)	30 (12.1%)
Back pain	11 (4.4%)	5 (2.0%)	14 (5.6%)	17 (6.9%)	13 (5.2%)	27 (10.9%)
Abdominal pain upper	15 (6.0%)	6 (2.4%)	20 (7.9%)	17 (6.9%)	5 (2.0%)	20 (8.1%)
Weight decreased	11 (4.4%)	5 (2.0%)	15 (6.0%)	21 (8.5%)	5 (2.0%)	26 (10.5%)
Muscle spasms	6 (2.4%)	12 (4.8%)	18 (7.1%)	7 (2.8%)	16 (6.5%)	22 (8.9%)
Ejection fraction decreased	9 (3.6%)	15 (6.0%)	24 (9.5%)	7 (2.8%)	8 (3.2%)	16 (6.5%)
Hypokalaemia	19 (7.5%)	4 (1.6%)	22 (8.7%)	16 (6.5%)	1 (0.4%)	16 (6.5%)
Musculoskeletal pain	10 (4.0%)	12 (4.8%)	20 (7.9%)	9 (3.6%)	9 (3.6%)	18 (7.3%)
Nail discolouration	17 (6.7%)	0	17 (6.7%)	20 (8.1%)	2 (0.8%)	22 (8.9%)
Malaise	14 (5.6%)	6 (2.4%)	18 (7.1%)	16 (6.5%)	6 (2.4%)	17 (6.9%)
Abdominal pain	13 (5.2%)	2 (0.8%)	15 (6.0%)	18 (7.3%)	6 (2.4%)	22 (8.9%)
Erythema	8 (3.2%)	5 (2.0%)	13 (5.2%)	10 (4.0%)	14 (5.6%)	22 (8.9%)
Urinary tract infection	11 (4.4%)	6 (2.4%)	16 (6.3%)	13 (5.2%)	7 (2.8%)	18 (7.3%)
Nail disorder	14 (5.6%)	3 (1.2%)	17 (6.7%)	14 (5.6%)	5 (2.0%)	17 (6.9%)
Haemorrhoids	10 (4.0%)	1 (0.4%)	11 (4.4%)	20 (8.1%)	2 (0.8%)	22 (8.9%)
Bone pain	12 (4.8%)	1 (0.4%)	13 (5.2%)	17 (6.9%)	3 (1.2%)	19 (7.7%)
Paronychia	6 (2.4%)	6 (2.4%)	12 (4.8%)	14 (5.6%)	7 (2.8%)	20 (8.1%)
Dermatitis	4 (1.6%)	10 (4.0%)	14 (5.6%)	10 (4.0%)	8 (3.2%)	18 (7.3%)
Rhinorrhoea	9 (3.6%)	4 (1.6%)	12 (4.8%)	14 (5.6%)	7 (2.8%)	17 (6.9%)
Febrile neutropenia	14 (5.6%)	0	14 (5.6%)	16 (6.5%)	0	16 (6.5%)
Oropharyngeal pain	8 (3.2%)	7 (2.8%)	14 (5.6%)	11 (4.4%)	5 (2.0%)	15 (6.0%)
Palmar-plantar erythrodysaesthesia syndrome	13 (5.2%)	0	13 (5.2%)	17 (6.9%)	0	17 (6.9%)
Influenza like illness	6 (2.4%)	8 (3.2%)	11 (4.4%)	9 (3.6%)	8 (3.2%)	15 (6.0%)
Lacrimation increased	13 (5.2%)	2 (0.8%)	14 (5.6%)	13 (5.2%)	1 (0.4%)	14 (5.6%)
Breast pain	6 (2.4%)	7 (2.8%)	13 (5.2%)	6 (2.4%)	9 (3.6%)	15 (6.0%)
Hypertension	1 (0.4%)	14 (5.6%)	15 (6.0%)	6 (2.4%)	7 (2.8%)	13 (5.2%)
Rhinitis	7 (2.8%)	7 (2.8%)	13 (5.2%)	9 (3.6%)	6 (2.4%)	14 (5.6%)
Gastrooesophageal reflux disease	11 (4.4%)	3 (1.2%)	13 (5.2%)	11 (4.4%)	1 (0.4%)	12 (4.8%)
Onycholysis	12 (4.8%)	1 (0.4%)	13 (5.2%)	9 (3.6%)	2 (0.8%)	11 (4.4%)
Dry eye	7 (2.8%)	3 (1.2%)	9 (3.6%)	13 (5.2%)	1 (0.4%)	14 (5.6%)
Anxiety	2 (0.8%)	6 (2.4%)	8 (3.2%)	9 (3.6%)	6 (2.4%)	15 (6.0%)
Cystitis	7 (2.8%)	6 (2.4%)	13 (5.2%)	6 (2.4%)	2 (0.8%)	8 (3.2%)
Oedema	8 (3.2%)	5 (2.0%)	13 (5.2%)	6 (2.4%)	1 (0.4%)	7 (2.8%)
Gastritis	5 (2.0%)	0	5 (2.0%)	10 (4.0%)	3 (1.2%)	13 (5.2%)
Respiratory tract infection	11 (4.4%)	2 (0.8%)	13 (5.2%)	1 (0.4%)	2 (0.8%)	2 (0.8%)

Investigator text for AEs encoded using MedDRA version 22.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
Table includes only AEs occurring in >=5% of patients in at least one treatment group.
Table includes AEs from Neoadjuvant, Adjuvant and Follow up phase.

Grade 3-4 AEs

A summary of the most common Grade 3-4 AEs (≥5%) in FeDeriCa study is presented below.

Table 27 Most common Grade 3-4 Adverse Events (⩾5%): Safety Population

Protocol: WO40324 (CCOD:10JUL2020 DBL:06AUG2020)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)			Pertuzumab + Trastuzumab FDC SC Arm (N=248)		
	Phase			Phase		
MedDRA Preferred Term	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
Neutropenia	35 (13.9%)	0	35 (13.9%)	34 (13.7%)	2 (0.8%)	36 (14.5%)
Neutrophil count decreased	31 (12.3%)	5 (2.0%)	33 (13.1%)	26 (10.5%)	5 (2.0%)	27 (10.9%)
Diarrhoea	10 (4.0%)	3 (1.2%)	13 (5.2%)	18 (7.3%)	0	18 (7.3%)
White blood cell count decreased	18 (7.1%)	1 (0.4%)	19 (7.5%)	10 (4.0%)	3 (1.2%)	10 (4.0%)
Febrile neutropenia	14 (5.6%)	0	14 (5.6%)	16 (6.5%)	0	16 (6.5%)

Investigator text for AEs encoded using MedDRA version 23.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
Overall count includes AEs from post screening, Neoadjuvant, Adjuvant and Follow up phases.

Cardiac AEs

Cardiac safety data for FeDeriCa are presented in the below tables.

Table 28 Cardiac Safety Summary Overall up to CCD: Safety Population

	pertuzumab IV + trastuzumab IV (N=252)			pertuzumab + trastuzumab FDC SC (N=248)		
	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
Primary Cardiac Event	0	1 (0.4%)	2 (0.8%)	2 (0.8%)	2 (0.8%)	4 (1.6%)
Heart failure (NYHA III/IV) and significant left ventricular ejection fraction (LVEF) decline [1]	0	1 (0.4%)	2 (0.8%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
Cardiac death (definite or probable)	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Secondary Cardiac Event	4 (1.6%)	15 (6.0%)	18 (7.1%)	2 (0.8%)	8 (3.2%)	12 (4.8%)
Identified by initial LVEF assessments [2]	4 (1.6%)	15 (6.0%)	18 (7.1%)	2 (0.8%)	8 (3.2%)	12 (4.8%)
Confirmed by second LVEF assessment	1 (0.4%)	0	10 (4.0%)	0	0	2 (0.8%)

Percentages are based on N in the column headings.

Secondary cardiac events are only counted for patients who have not experienced a primary cardiac event.

[1] Significant LVEF decline defined as a drop in LVEF of at least 10-percentage points from baseline and to below 50%.

[2] Defined by a drop in LVEF of at least 10-percentage points from baseline and to below 50%.

Overall count includes AEs from post screening, Neoadjuvant, Adjuvant and Follow up phases.

Table 29 Cardiac Dysfunction AEs: Safety Population

Protocol: WO40324 (CCOD:10JUL2020 DBL:06AUG2020)

		Pertuzumab IV + Trastuzumab IV Arm (N=252)			Pertuzumab + Trastuzumab FDC SC Arm (N=248)		
		Phase			Phase		
MedDRA System Organ Class MedDRA Preferred Term	Grade	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
- Any adverse events -	- Any Grade -	36 (14.3%)	33 (13.1%)	66 (26.2%)	33 (13.3%)	20 (8.1%)	53 (21.4%)
	Grade 1-2	33 (13.1%)	25 (9.9%)	54 (21.4%)	32 (12.9%)	18 (7.3%)	50 (20.2%)
	1	20 (7.9%)	19 (7.5%)	36 (14.3%)	27 (10.9%)	9 (3.6%)	36 (14.5%)
	2	13 (5.2%)	6 (2.4%)	18 (7.1%)	5 (2.0%)	9 (3.6%)	14 (5.6%)
	Grade 3-4	3 (1.2%)	7 (2.8%)	11 (4.4%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
	3	3 (1.2%)	6 (2.4%)	10 (4.0%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
	4	0	1 (0.4%)	1 (0.4%)	0	0	0
	Grade 5	0	1 (0.4%)	1 (0.4%)	0	0	0
General disorders and administration site conditions - Overall -	- Any Grade -	26 (10.3%)	15 (6.0%)	40 (15.9%)	22 (8.9%)	10 (4.0%)	32 (12.9%)
	Grade 1-2	25 (9.9%)	15 (6.0%)	39 (15.5%)	22 (8.9%)	10 (4.0%)	32 (12.9%)
	1	19 (7.5%)	14 (5.6%)	32 (12.7%)	21 (8.5%)	8 (3.2%)	29 (11.7%)
	2	6 (2.4%)	1 (0.4%)	7 (2.8%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
	Grade 3-4	1 (0.4%)	0	1 (0.4%)	0	0	0
	3	1 (0.4%)	0	1 (0.4%)	0	0	0
Oedema peripheral	- Any Grade -	18 (7.1%)	8 (3.2%)	26 (10.3%)	15 (6.0%)	8 (3.2%)	23 (9.3%)
	Grade 1-2	18 (7.1%)	8 (3.2%)	26 (10.3%)	15 (6.0%)	8 (3.2%)	23 (9.3%)
	1	13 (5.2%)	8 (3.2%)	21 (8.3%)	15 (6.0%)	6 (2.4%)	21 (8.5%)
	2	5 (2.0%)	0	5 (2.0%)	0	2 (0.8%)	2 (0.8%)
Oedema	- Any Grade -	8 (3.2%)	5 (2.0%)	13 (5.2%)	6 (2.4%)	1 (0.4%)	7 (2.8%)
	Grade 1-2	7 (2.8%)	5 (2.0%)	12 (4.8%)	6 (2.4%)	1 (0.4%)	7 (2.8%)
	1	6 (2.4%)	4 (1.6%)	10 (4.0%)	5 (2.0%)	1 (0.4%)	6 (2.4%)
	2	1 (0.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
	Grade 3-4	1 (0.4%)	0	1 (0.4%)	0	0	0
	3	1 (0.4%)	0	1 (0.4%)	0	0	0
Peripheral swelling	- Any Grade -	0	2 (0.8%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
	Grade 1-2	0	2 (0.8%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
	1	0	2 (0.8%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
Investigations - Overall -	- Any Grade -	9 (3.6%)	15 (6.0%)	24 (9.5%)	7 (2.8%)	8 (3.2%)	16 (6.5%)
	Grade 1-2	8 (3.2%)	8 (3.2%)	16 (6.3%)	7 (2.8%)	8 (3.2%)	16 (6.5%)
	1	3 (1.2%)	3 (1.2%)	7 (2.8%)	5 (2.0%)	2 (0.8%)	7 (2.8%)
	2	5 (2.0%)	5 (2.0%)	9 (3.6%)	2 (0.8%)	6 (2.4%)	9 (3.6%)
	Grade 3-4	1 (0.4%)	7 (2.8%)	8 (3.2%)	0	0	0
	3	1 (0.4%)	6 (2.4%)	7 (2.8%)	0	0	0
	4	0	1 (0.4%)	1 (0.4%)	0	0	0

Ejection fraction decreased	- Any Grade -	9 (3.6%)	15 (6.0%)	24 (9.5%)	7 (2.8%)	8 (3.2%)	16 (6.5%)
	Grade 1-2	8 (3.2%)	8 (3.2%)	16 (6.3%)	7 (2.8%)	8 (3.2%)	16 (6.5%)
	1	3 (1.2%)	3 (1.2%)	7 (2.8%)	5 (2.0%)	2 (0.8%)	7 (2.8%)
	2	5 (2.0%)	5 (2.0%)	9 (3.6%)	2 (0.8%)	6 (2.4%)	9 (3.6%)
	Grade 3-4	1 (0.4%)	7 (2.8%)	8 (3.2%)	0	0	0
	3	1 (0.4%)	6 (2.4%)	7 (2.8%)	0	0	0
	4	0	1 (0.4%)	1 (0.4%)	0	0	0
Cardiac disorders							
- Overall -	- Any Grade -	3 (1.2%)	4 (1.6%)	10 (4.0%)	3 (1.2%)	5 (2.0%)	7 (2.8%)
	Grade 1-2	2 (0.8%)	3 (1.2%)	7 (2.8%)	2 (0.8%)	3 (1.2%)	4 (1.6%)
	1	0	2 (0.8%)	4 (1.6%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
	2	2 (0.8%)	1 (0.4%)	3 (1.2%)	1 (0.4%)	2 (0.8%)	2 (0.8%)
	Grade 3-4	1 (0.4%)	0	2 (0.8%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
	3	1 (0.4%)	0	2 (0.8%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
	Grade 5	0	1 (0.4%)	1 (0.4%)	0	0	0
Cardiac failure	- Any Grade -	2 (0.8%)	2 (0.8%)	7 (2.8%)	2 (0.8%)	3 (1.2%)	4 (1.6%)
	Grade 1-2	1 (0.4%)	1 (0.4%)	4 (1.6%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
	1	0	0	2 (0.8%)	0	0	0
	2	1 (0.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
	Grade 3-4	1 (0.4%)	0	2 (0.8%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
	3	1 (0.4%)	0	2 (0.8%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
	Grade 5	0	1 (0.4%)	1 (0.4%)	0	0	0
Left ventricular dysfunction	- Any Grade -	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
	Grade 1-2	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
	1	0	0	0	1 (0.4%)	1 (0.4%)	2 (0.8%)
	2	1 (0.4%)	0	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
Diastolic dysfunction	- Any Grade -	0	1 (0.4%)	1 (0.4%)	0	0	0
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	0	0	0
	1	0	1 (0.4%)	1 (0.4%)	0	0	0
Ventricular compliance decreased	- Any Grade -	0	1 (0.4%)	1 (0.4%)	0	0	0
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	0	0	0
	1	0	1 (0.4%)	1 (0.4%)	0	0	0
Respiratory, thoracic and mediastinal disorders							
- Overall -	- Any Grade -	0	1 (0.4%)	1 (0.4%)	2 (0.8%)	0	2 (0.8%)
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	2 (0.8%)	0	2 (0.8%)
	1	0	1 (0.4%)	1 (0.4%)	0	0	0
	2	0	0	0	2 (0.8%)	0	2 (0.8%)
Nocturnal dyspnoea	- Any Grade -	0	0	0	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	0	0	0	1 (0.4%)	0	1 (0.4%)
	2	0	0	0	1 (0.4%)	0	1 (0.4%)
Orthopnoea	- Any Grade -	0	1 (0.4%)	1 (0.4%)	0	0	0
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	0	0	0
	1	0	1 (0.4%)	1 (0.4%)	0	0	0
Pulmonary oedema	- Any Grade -	0	0	0	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	0	0	0	1 (0.4%)	0	1 (0.4%)
	2	0	0	0	1 (0.4%)	0	1 (0.4%)

Investigator text for AEs encoded using MedDRA version 23.0. All counts represent patients.
Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.
To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
Percentages are based on N in the column headings.
Overall count includes AEs from post screening, Neoadjuvant, Adjuvant and Follow up phases.

Table 30 Summary of LVEF incidence: Safety Population

	pertuzumab IV + trastuzumab IV (N=252)			pertuzumab + trastuzumab FDC SC (N=248)		
	Neoadjuvant [3]	Adjuvant [4]	Overall	Neoadjuvant [3]	Adjuvant [4]	Overall
Baseline left ventricular ejection fraction (LVEF) (%)						
n			252			248
Mean (SD)			65.16 (5.24)			64.96 (5.3)
Median			65.00			65.00
Range			53.0-79.4			55.0-78.0
Change from baseline to worst value [1]						
n	89	160	249	81	163	245
Mean (SD)	-6.21 (6.21)	-8.62 (6.67)	-7.76 (6.60)	-5.35 (6.15)	-8.21 (6.01)	-7.26 (6.18)
Median	-5.00	-8.00	-7.00	-5.00	-7.00	-6.00
Range	-32.0-3.0	-35.0 – 4.0	-35.0- 4.0	-21.0 – 13.0	-35.0 – 7.0	-35.0-13.0
Treatment difference [2]				0.87	0.41	0.49
95% CI				-1 - 2.7	-1.0 – 1.8	-0.6-1.6
Worst value <40%						
Yes	0	4 (2.5%)	4 (1.6%)	1 (1.2%)	1 (0.6%)	2 (0.8%)
No	89 (100%)	156 (97.5%)	245 (98.4%)	80 (98.8%)	162 (99.4%)	243 (99.2%)
Number of patient with baseline value and ≥1 post-baseline treatment phase value [1]						
n	89	160	249	81	163	245
Increase or no change	17 (19.1%)	11 (6.9%)	28 (11.2%)	18 (22.2%)	13 (8.0%)	31 (12.7%)
Decrease of <10 points from baseline	51 (57.3%)	86 (53,8%)	137 (55.0%)	47 (58.0%)	92 (56.4%)	140 (57.1%)
Decrease of ≥10 points from baseline	21 (23.6%)	63 (39.4%)	84 (33.7%)	16 (19.8%)	58 (35.6%)	74 (30.2%)
45≤ LVEF <50	3 (3.4%)	9 (5.6%)	10 (4.0%)	1 (1.2%)	8 (4.9%)	10 (4.1%)
No of patients with at least 1 one significant LVEF drop (defined as a drop in LVEF of at least 10 EF points from baseline and to below 50%)	4 (4.5%)	16 (10.0%)	17 (6.8%)	3 (3.7%)	10 (6.1%)	13 (5.3%)

Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of HER2 treatment	19 (21.3%)	19 (11.9%)	19 (7.6%)	10 (12.3%)	8 (4.9%)	10 (4.1%)
LVEF <45 and Decrease of ≥10 points from baseline	1 (1.1%)	11 (6.9%)	12 (4.8%)	3 (3.7%)	2 (1.2%)	5 (2.0%)

[1] Lowest post-baseline Treatment phase value per patient.

[2] Treatment difference defined as PH FDC SC arm – PH IV arm.

[3] Percentages are based on the number of subjects who have worst post-baseline value in Neoadjuvant phase.

[4] Percentages are based on the number of subjects who have worst post-baseline value in Adjuvant phase.

Overall count includes AEs from post screening, Neoadjuvant, Adjuvant and Follow up phases.

Table 31 Overall Other Cardiac Events: Safety Population

	pertuzumab IV + trastuzumab IV (N=252)			pertuzumab + trastuzumab FDC SC (N=248)		
	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
Any other cardiac events	9 (3.6%)	3 (1.2%)	12 (4.8%)	8 (3.2%)	1 (0.4%)	9 (3.6%)
Acute coronary syndrome (PT)	0	0	0	0	0	0
Acute myocardial infarction	0	0	0	1 (0.4%)	0	1 (0.4%)
Severe rhythm disturbances requiring treatment	9 (3.6%)	3 (1.2%)	12 (4.8%)	7 (2.8%)	1 (0.4%)	8 (3.2%)

Overall count includes AEs from post screening, Neoadjuvant, Adjuvant and Follow up phases.

Hypersensitivity/anaphylaxis events and administration-related reactions

An overview of Administration Related Reactions occurring within 24h in FeDeriCa study is presented below.

Table 32 Administration Related Reactions occurred within 24h of HER2 treatment: Safety Population

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		Pertuzumab IV + Trastuzumab IV Arm (N=252)			Pertuzumab + Trastuzumab FDC SC Arm (N=248)		
		Phase			Phase		
MedDRA System Organ Class MedDRA Preferred Term	Grade	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
- Any adverse events -	- Any Grade -	32 (12.7%)	12 (4.8%)	39 (15.5%)	24 (9.7%)	43 (17.3%)	55 (22.2%)
	Grade 1-2	29 (11.5%)	12 (4.8%)	36 (14.3%)	24 (9.7%)	43 (17.3%)	55 (22.2%)
	1	15 (6.0%)	9 (3.6%)	20 (7.9%)	19 (7.7%)	41 (16.5%)	50 (20.2%)
	2	14 (5.6%)	3 (1.2%)	16 (6.3%)	5 (2.0%)	2 (0.8%)	5 (2.0%)
	Grade 3-4	3 (1.2%)	0	3 (1.2%)	0	0	0
	3	3 (1.2%)	0	3 (1.2%)	0	0	0
General disorders and administration site conditions							
- Overall -	- Any Grade -	2 (0.8%)	3 (1.2%)	5 (2.0%)	20 (8.1%)	35 (14.1%)	44 (17.7%)
	Grade 1-2	2 (0.8%)	3 (1.2%)	5 (2.0%)	20 (8.1%)	35 (14.1%)	44 (17.7%)
	1	0	3 (1.2%)	3 (1.2%)	17 (6.9%)	33 (13.3%)	41 (16.5%)
	2	2 (0.8%)	0	2 (0.8%)	3 (1.2%)	2 (0.8%)	3 (1.2%)
Injection site reaction	- Any Grade -	0	1 (0.4%)	1 (0.4%)	17 (6.9%)	32 (12.9%)	39 (15.7%)
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	17 (6.9%)	32 (12.9%)	39 (15.7%)
	1	0	1 (0.4%)	1 (0.4%)	14 (5.6%)	30 (12.1%)	36 (14.5%)
	2	0	0	0	3 (1.2%)	2 (0.8%)	3 (1.2%)
Injection site pain	- Any Grade -	0	0	0	0	4 (1.6%)	4 (1.6%)
	Grade 1-2	0	0	0	0	4 (1.6%)	4 (1.6%)
	1	0	0	0	0	3 (1.2%)	3 (1.2%)
	2	0	0	0	0	1 (0.4%)	1 (0.4%)
Asthenia	- Any Grade -	2 (0.8%)	0	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	2 (0.8%)	0	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
	1	0	0	0	1 (0.4%)	0	1 (0.4%)
	2	2 (0.8%)	0	2 (0.8%)	0	0	0
Oedema peripheral	- Any Grade -	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
	1	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
Application site pain	- Any Grade -	0	0	0	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	0	0	0	1 (0.4%)	0	1 (0.4%)
	1	0	0	0	1 (0.4%)	0	1 (0.4%)
Oedema	- Any Grade -	0	1 (0.4%)	1 (0.4%)	0	0	0
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	0	0	0
	1	0	1 (0.4%)	1 (0.4%)	0	0	0
Pyrexia	- Any Grade -	0	0	0	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	0	0	0	1 (0.4%)	0	1 (0.4%)
	1	0	0	0	1 (0.4%)	0	1 (0.4%)

Injury, poisoning and procedural complications							
- Overall -	- Any Grade -	26 (10.3%)	4 (1.6%)	27 (10.7%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
	Grade 1-2	24 (9.5%)	4 (1.6%)	25 (9.9%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
	1	13 (5.2%)	2 (0.8%)	13 (5.2%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
	2	11 (4.4%)	2 (0.8%)	12 (4.8%)	0	0	0
	Grade 3-4	2 (0.8%)	0	2 (0.8%)	0	0	0
	3	2 (0.8%)	0	2 (0.8%)	0	0	0
Infusion related reaction	- Any Grade -	26 (10.3%)	4 (1.6%)	27 (10.7%)	0	0	0
	Grade 1-2	24 (9.5%)	4 (1.6%)	25 (9.9%)	0	0	0
	1	13 (5.2%)	2 (0.8%)	13 (5.2%)	0	0	0
	2	11 (4.4%)	2 (0.8%)	12 (4.8%)	0	0	0
	Grade 3-4	2 (0.8%)	0	2 (0.8%)	0	0	0
	3	2 (0.8%)	0	2 (0.8%)	0	0	0
Injection related reaction	- Any Grade -	0	0	0	1 (0.4%)	1 (0.4%)	2 (0.8%)
	Grade 1-2	0	0	0	1 (0.4%)	1 (0.4%)	2 (0.8%)
	1	0	0	0	1 (0.4%)	1 (0.4%)	2 (0.8%)
Skin and subcutaneous tissue disorders							
- Overall -	- Any Grade -	1 (0.4%)	0	1 (0.4%)	3 (1.2%)	2 (0.8%)	5 (2.0%)
	Grade 1-2	1 (0.4%)	0	1 (0.4%)	3 (1.2%)	2 (0.8%)	5 (2.0%)
	1	1 (0.4%)	0	1 (0.4%)	2 (0.8%)	2 (0.8%)	4 (1.6%)
	2	0	0	0	1 (0.4%)	0	1 (0.4%)
Rash	- Any Grade -	1 (0.4%)	0	1 (0.4%)	2 (0.8%)	2 (0.8%)	4 (1.6%)
	Grade 1-2	1 (0.4%)	0	1 (0.4%)	2 (0.8%)	2 (0.8%)	4 (1.6%)
	1	1 (0.4%)	0	1 (0.4%)	2 (0.8%)	2 (0.8%)	4 (1.6%)
Pruritus	- Any Grade -	0	0	0	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	0	0	0	1 (0.4%)	0	1 (0.4%)
	2	0	0	0	1 (0.4%)	0	1 (0.4%)
Musculoskeletal and connective tissue disorders							
- Overall -	- Any Grade -	2 (0.8%)	1 (0.4%)	3 (1.2%)	0	2 (0.8%)	2 (0.8%)
	Grade 1-2	2 (0.8%)	1 (0.4%)	3 (1.2%)	0	2 (0.8%)	2 (0.8%)
	1	0	1 (0.4%)	1 (0.4%)	0	2 (0.8%)	2 (0.8%)
	2	2 (0.8%)	0	2 (0.8%)	0	0	0
Myalgia	- Any Grade -	2 (0.8%)	1 (0.4%)	3 (1.2%)	0	0	0
	Grade 1-2	2 (0.8%)	1 (0.4%)	3 (1.2%)	0	0	0
	1	0	1 (0.4%)	1 (0.4%)	0	0	0
	2	2 (0.8%)	0	2 (0.8%)	0	0	0
Muscle spasms	- Any Grade -	0	0	0	0	1 (0.4%)	1 (0.4%)
	Grade 1-2	0	0	0	0	1 (0.4%)	1 (0.4%)
	1	0	0	0	0	1 (0.4%)	1 (0.4%)
Soft tissue swelling	- Any Grade -	0	0	0	0	1 (0.4%)	1 (0.4%)
	Grade 1-2	0	0	0	0	1 (0.4%)	1 (0.4%)
	1	0	0	0	0	1 (0.4%)	1 (0.4%)
Nervous system disorders							
- Overall -	- Any Grade -	2 (0.8%)	0	2 (0.8%)	0	3 (1.2%)	3 (1.2%)
	Grade 1-2	1 (0.4%)	0	1 (0.4%)	0	3 (1.2%)	3 (1.2%)
	1	1 (0.4%)	0	1 (0.4%)	0	3 (1.2%)	3 (1.2%)
	Grade 3-4	1 (0.4%)	0	1 (0.4%)	0	0	0
	3	1 (0.4%)	0	1 (0.4%)	0	0	0
Dizziness	- Any Grade -	1 (0.4%)	0	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
	Grade 1-2	1 (0.4%)	0	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
	1	0	0	0	0	1 (0.4%)	1 (0.4%)
	2	1 (0.4%)	0	1 (0.4%)	0	0	0
Headache	- Any Grade -	1 (0.4%)	0	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
	Grade 1-2	0	0	0	0	1 (0.4%)	1 (0.4%)
	1	0	0	0	0	1 (0.4%)	1 (0.4%)
	Grade 3-4	1 (0.4%)	0	1 (0.4%)	0	0	0
	3	1 (0.4%)	0	1 (0.4%)	0	0	0
Dysgeusia	- Any Grade -	1 (0.4%)	0	1 (0.4%)	0	0	0
	Grade 1-2	1 (0.4%)	0	1 (0.4%)	0	0	0
	1	1 (0.4%)	0	1 (0.4%)	0	0	0
Paraesthesia	- Any Grade -	0	0	0	0	1 (0.4%)	1 (0.4%)
	Grade 1-2	0	0	0	0	1 (0.4%)	1 (0.4%)
	1	0	0	0	0	1 (0.4%)	1 (0.4%)
Vascular disorders							
- Overall -	- Any Grade -	0	3 (1.2%)	3 (1.2%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
	Grade 1-2	0	3 (1.2%)	3 (1.2%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
	1	0	2 (0.8%)	2 (0.8%)	0	1 (0.4%)	1 (0.4%)
	2	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Hot flush	- Any Grade -	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
	1	0	1 (0.4%)	1 (0.4%)	0	0	0
	2	0	0	0	1 (0.4%)	0	1 (0.4%)
Hypotension	- Any Grade -	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
	1	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
Hypertension	- Any Grade -	0	1 (0.4%)	1 (0.4%)	0	0	0
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	0	0	0
	2	0	1 (0.4%)	1 (0.4%)	0	0	0
Gastrointestinal disorders							
- Overall -	- Any Grade -	0	1 (0.4%)	1 (0.4%)	0	2 (0.8%)	2 (0.8%)
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	0	2 (0.8%)	2 (0.8%)
	1	0	1 (0.4%)	1 (0.4%)	0	2 (0.8%)	2 (0.8%)
Vomiting	- Any Grade -	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
	1	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)
Abdominal pain	- Any Grade -	0	0	0	0	1 (0.4%)	1 (0.4%)
	Grade 1-2	0	0	0	0	1 (0.4%)	1 (0.4%)
	1	0	0	0	0	1 (0.4%)	1 (0.4%)

Respiratory, thoracic and mediastinal disorders							
- Overall -	- Any Grade -	2 (0.8%)	1 (0.4%)	3 (1.2%)	0	0	0
	Grade 1-2	2 (0.8%)	1 (0.4%)	3 (1.2%)	0	0	0
	1	1 (0.4%)	1 (0.4%)	2 (0.8%)	0	0	0
	2	1 (0.4%)	0	1 (0.4%)	0	0	0
Cough	- Any Grade -	1 (0.4%)	0	1 (0.4%)	0	0	0
	Grade 1-2	1 (0.4%)	0	1 (0.4%)	0	0	0
	1	1 (0.4%)	0	1 (0.4%)	0	0	0
Dyspnoea	- Any Grade -	0	1 (0.4%)	1 (0.4%)	0	0	0
	Grade 1-2	0	1 (0.4%)	1 (0.4%)	0	0	0
	1	0	1 (0.4%)	1 (0.4%)	0	0	0
Rhinorrhoea	- Any Grade -	1 (0.4%)	0	1 (0.4%)	0	0	0
	Grade 1-2	1 (0.4%)	0	1 (0.4%)	0	0	0
	2	1 (0.4%)	0	1 (0.4%)	0	0	0
Cardiac disorders							
- Overall -	- Any Grade -	0	0	0	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	0	0	0	1 (0.4%)	0	1 (0.4%)
	1	0	0	0	1 (0.4%)	0	1 (0.4%)
Palpitations	- Any Grade -	0	0	0	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	0	0	0	1 (0.4%)	0	1 (0.4%)
	1	0	0	0	1 (0.4%)	0	1 (0.4%)
Immune system disorders							
- Overall -	- Any Grade -	1 (0.4%)	0	1 (0.4%)	0	0	0
	Grade 1-2	1 (0.4%)	0	1 (0.4%)	0	0	0
	2	1 (0.4%)	0	1 (0.4%)	0	0	0
Drug hypersensitivity	- Any Grade -	1 (0.4%)	0	1 (0.4%)	0	0	0
	Grade 1-2	1 (0.4%)	0	1 (0.4%)	0	0	0
	2	1 (0.4%)	0	1 (0.4%)	0	0	0
Psychiatric disorders							
- Overall -	- Any Grade -	0	0	0	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	0	0	0	1 (0.4%)	0	1 (0.4%)
	2	0	0	0	1 (0.4%)	0	1 (0.4%)
Insomnia	- Any Grade -	0	0	0	1 (0.4%)	0	1 (0.4%)
	Grade 1-2	0	0	0	1 (0.4%)	0	1 (0.4%)
	2	0	0	0	1 (0.4%)	0	1 (0.4%)

Investigator text for AEs encoded using MedDRA version 23.0. All counts represent patients.
Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient.
To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC.
Percentages are based on N in the column headings.
Overall count includes AEs from post screening, Neoadjuvant, Adjuvant and Follow up phases.

Serious adverse event/deaths/other significant events

SAEs

Serious Adverse Events by treatment regimen for FeDeriCa study are presented in the below table.

Table 33 Serious Adverse Events by treatment regimen: Safety Population

MedDRA System Organ Class MedDRA Preferred Term	Pertuzumab IV + Trastuzumab IV Arm (N=252)			Pertuzumab + Trastuzumab FDC SC Arm (N=248)		
	Phase			Phase		
	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
Total number of patients with at least one adverse event	43 (17.1%)	8 (3.2%)	50 (19.8%)	39 (15.7%)	10 (4.0%)	47 (19.0%)
Overall total number of events	60	8	71	54	11	69
Infections and infestations						
Total number of patients with at least one adverse event	16 (6.3%)	3 (1.2%)	19 (7.5%)	9 (3.6%)	4 (1.6%)	13 (5.2%)
Neutropenic sepsis	1 (0.4%)	0	1 (0.4%)	3 (1.2%)	0	3 (1.2%)
Sepsis	2 (0.8%)	0	2 (0.8%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
Mastitis	1 (0.4%)	1 (0.4%)	2 (0.8%)	0	1 (0.4%)	1 (0.4%)
Pneumonia	2 (0.8%)	1 (0.4%)	3 (1.2%)	0	0	0
Appendicitis	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Gastroenteritis	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Postoperative wound infection	2 (0.8%)	0	2 (0.8%)	0	0	0
Anal abscess	1 (0.4%)	0	1 (0.4%)	0	0	0
Cellulitis	1 (0.4%)	0	1 (0.4%)	0	0	0
Clostridium difficile colitis	1 (0.4%)	0	1 (0.4%)	0	0	0
Escherichia bacteraemia	0	0	0	1 (0.4%)	0	1 (0.4%)
Herpes zoster	0	0	0	0	1 (0.4%)	1 (0.4%)
Influenza	0	0	0	1 (0.4%)	0	1 (0.4%)
Lower respiratory tract infection	0	0	0	1 (0.4%)	0	1 (0.4%)
Pharyngitis	1 (0.4%)	0	1 (0.4%)	0	0	0
Postoperative abscess	0	1 (0.4%)	1 (0.4%)	0	0	0
Pseudomonas infection	0	0	0	1 (0.4%)	0	1 (0.4%)
Pyelonephritis acute	1 (0.4%)	0	1 (0.4%)	0	0	0
Respiratory tract infection	1 (0.4%)	0	1 (0.4%)	0	0	0
Skin infection	0	0	0	0	1 (0.4%)	1 (0.4%)
Urosepsis	1 (0.4%)	0	1 (0.4%)	0	0	0
Total number of events	17	3	20	11	4	15
Blood and lymphatic system disorders						
Total number of patients with at least one adverse event	14 (5.6%)	0	14 (5.6%)	11 (4.4%)	0	11 (4.4%)
Febrile neutropenia	10 (4.0%)	0	10 (4.0%)	9 (3.6%)	0	9 (3.6%)
Neutropenia	3 (1.2%)	0	3 (1.2%)	1 (0.4%)	0	1 (0.4%)
Anaemia	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Immune thrombocytopenia	0	0	1 (0.4%)	0	0	0
Total number of events	15	0	16	11	0	11
Cardiac disorders						
Total number of patients with at least one adverse event	2 (0.8%)	2 (0.8%)	6 (2.4%)	4 (1.6%)	4 (1.6%)	8 (3.2%)
Cardiac failure	2 (0.8%)	2 (0.8%)	6 (2.4%)	2 (0.8%)	3 (1.2%)	4 (1.6%)
Acute myocardial infarction	0	0	0	1 (0.4%)	0	1 (0.4%)
Arrhythmia	0	0	0	1 (0.4%)	0	1 (0.4%)
Cardiomyopathy	0	0	0	0	1 (0.4%)	1 (0.4%)
Pericardial effusion	0	0	0	0	0	1 (0.4%)
Total number of events	2	2	6	4	4	9
Gastrointestinal disorders						
Total number of patients with at least one adverse event	4 (1.6%)	0	4 (1.6%)	7 (2.8%)	0	7 (2.8%)
Diarrhoea	2 (0.8%)	0	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
Colitis	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Abdominal pain	0	0	0	1 (0.4%)	0	1 (0.4%)
Anal incontinence	0	0	0	1 (0.4%)	0	1 (0.4%)
Gastritis haemorrhagic	0	0	0	1 (0.4%)	0	1 (0.4%)
Gastrointestinal toxicity	0	0	0	1 (0.4%)	0	1 (0.4%)
Pancreatitis	0	0	0	1 (0.4%)	0	1 (0.4%)
Vomiting	1 (0.4%)	0	1 (0.4%)	0	0	0
Total number of events	4	0	4	7	0	7
General disorders and administration site conditions						
Total number of patients with at least one adverse event	6 (2.4%)	0	6 (2.4%)	3 (1.2%)	0	4 (1.6%)
Pyrexia	3 (1.2%)	0	3 (1.2%)	2 (0.8%)	0	2 (0.8%)
Chest pain	1 (0.4%)	0	1 (0.4%)	0	0	0
Fatigue	1 (0.4%)	0	1 (0.4%)	0	0	0
Lithiasis	0	0	0	1 (0.4%)	0	1 (0.4%)
Mucosal inflammation	1 (0.4%)	0	1 (0.4%)	0	0	0
Death	0	0	0	0	0	1 (0.4%)
Total number of events	7	0	7	3	0	4
Respiratory, thoracic and mediastinal disorders						
Total number of patients with at least one adverse event	3 (1.2%)	0	3 (1.2%)	5 (2.0%)	1 (0.4%)	7 (2.8%)
Pneumonitis	1 (0.4%)	0	1 (0.4%)	2 (0.8%)	0	2 (0.8%)
Pulmonary embolism	1 (0.4%)	0	1 (0.4%)	2 (0.8%)	0	2 (0.8%)
Acute respiratory failure	0	0	0	0	1 (0.4%)	1 (0.4%)
Pneumothorax	1 (0.4%)	0	1 (0.4%)	0	0	0
Pulmonary oedema	0	0	0	1 (0.4%)	0	1 (0.4%)
Dyspnoea	0	0	0	0	0	1 (0.4%)
Total number of events	3	0	3	5	1	7
Investigations						
Total number of patients with at least one adverse event	2 (0.8%)	0	2 (0.8%)	4 (1.6%)	0	4 (1.6%)
Neutrophil count decreased	1 (0.4%)	0	1 (0.4%)	3 (1.2%)	0	3 (1.2%)
Clostridium test positive	1 (0.4%)	0	1 (0.4%)	0	0	0
White blood cell count decreased	0	0	0	1 (0.4%)	0	1 (0.4%)
Total number of events	2	0	2	4	0	4
Injury, poisoning and procedural complications						
Total number of patients with at least one adverse event	2 (0.8%)	0	2 (0.8%)	3 (1.2%)	0	3 (1.2%)
Infusion related reaction	2 (0.8%)	0	2 (0.8%)	0	0	0
Femur fracture	0	0	0	1 (0.4%)	0	1 (0.4%)
Flap necrosis	0	0	0	1 (0.4%)	0	1 (0.4%)
Post procedural haematoma	0	0	0	1 (0.4%)	0	1 (0.4%)

Reproductive system and breast disorders						
Total number of patients with at least one adverse event	1 (0.4%)	1 (0.4%)	2 (0.8%)	2 (0.8%)	0	2 (0.8%)
Breast haematoma	0	1 (0.4%)	1 (0.4%)	0	0	0
Breast inflammation	0	0	0	1 (0.4%)	0	1 (0.4%)
Metrorrhagia	1 (0.4%)	0	1 (0.4%)	0	0	0
Uterine haemorrhage	0	0	0	1 (0.4%)	0	1 (0.4%)
Total number of events	1	1	2	2	0	2
Vascular disorders						
Total number of patients with at least one adverse event	2 (0.8%)	0	2 (0.8%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
Embolism	0	0	0	1 (0.4%)	0	1 (0.4%)
Haematoma	1 (0.4%)	0	1 (0.4%)	0	0	0
Hypertension	0	0	0	0	1 (0.4%)	1 (0.4%)
Iliac artery occlusion	1 (0.4%)	0	1 (0.4%)	0	0	0
Total number of events	2	0	2	1	1	2
Nervous system disorders						
Total number of patients with at least one adverse event	1 (0.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
Seizure	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Syncope	0	1 (0.4%)	1 (0.4%)	0	0	0
Total number of events	1	1	2	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Total number of patients with at least one adverse event	0	1 (0.4%)	1 (0.4%)	0	0	1 (0.4%)
Clear cell renal cell carcinoma	0	1 (0.4%)	1 (0.4%)	0	0	0
Angiosarcoma	0	0	0	0	0	1 (0.4%)
Total number of events	0	1	1	0	0	1
Endocrine disorders						
Total number of patients with at least one adverse event	1 (0.4%)	0	1 (0.4%)	0	0	0
Goitre	1 (0.4%)	0	1 (0.4%)	0	0	0
Total number of events	1	0	1	0	0	0
Musculoskeletal and connective tissue disorders						
Total number of patients with at least one adverse event	1 (0.4%)	0	1 (0.4%)	0	0	0
Periostitis	1 (0.4%)	0	1 (0.4%)	0	0	0
Total number of events	1	0	1	0	0	0
Psychiatric disorders						
Total number of patients with at least one adverse event	1 (0.4%)	0	1 (0.4%)	0	0	0
Depression	1 (0.4%)	0	1 (0.4%)	0	0	0
Total number of events	1	0	1	0	0	0
Renal and urinary disorders						
Total number of patients with at least one adverse event	0	0	0	1 (0.4%)	0	1 (0.4%)
Renal failure	0	0	0	1 (0.4%)	0	1 (0.4%)
Total number of events	0	0	0	1	0	1
Skin and subcutaneous tissue disorders						
Total number of patients with at least one adverse event	0	0	0	0	1 (0.4%)	1 (0.4%)
Erythema	0	0	0	0	1 (0.4%)	1 (0.4%)
Total number of events	0	0	0	0	1	1

Investigator text for AEs encoded using MedDRA version 23.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Overall count includes AEs from post screening, Neoadjuvant, Adjuvant and Follow up phases.

Deaths

An overview of AEs resulting in Death is presented below (FeDeriCA study).

Table 34 Adverse Events Resulting in Death by treatment regimen: Safety Population

Protocol: WO40324 (CCOD:10JUL2020 DBL:06AUG2020)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)			Pertuzumab + Trastuzumab FDC SC Arm (N=248)		
	Phase			Phase		
MedDRA SOC and Preferred Term	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
Total number of deaths	1 (0.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)	0	2 (0.8%)
Cardiac disorders / Acute myocardial infarction	0	0	0	1 (0.4%)	0	1 (0.4%)
Cardiac disorders / Cardiac failure	0	1 (0.4%)	1 (0.4%)	0	0	0
Infections and infestations / Urosepsis	1 (0.4%)	0	1 (0.4%)	0	0	0
General disorders and administration site conditions / Death	0	0	0	0	0	1 (0.4%)

Investigator text for AEs encoded using MedDRA version 23.0.
Percentages are based on N in the column headings.
Overall count includes AEs from post screening, Neoadjuvant, Adjuvant and Follow up phases.

Laboratory findings

*Data from laboratory findings corresponds to the data cut-off from the primary analysis (4-JUL-2019)

Table 35 Laboratory test results with highest NCI CTCAE grade post-baseline by treatment regimen: Safety Population (FeDeriCa)

Laboratory Test Direction of Abnormality	Highest CTC Grade	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
Albumin	n	251	247
Low	1	40 (15.9%)	34 (13.8%)
	2	8 (3.2%)	5 (2.0%)
	3	1 (0.4%)	0
	Any	49 (19.5%)	39 (15.8%)
Alkaline Phosphatase	n	191	181
High	1	32 (16.8%)	40 (22.1%)
	2	2 (1.0%)	1 (0.6%)
	Any	34 (17.8%)	41 (22.7%)
SGPT/ALT	n	252	248
High	1	146 (57.9%)	123 (49.6%)
	2	14 (5.6%)	12 (4.8%)
	3	6 (2.4%)	3 (1.2%)
	Any	166 (65.9%)	138 (55.6%)
SGOT/AST	n	252	248
High	1	129 (51.2%)	110 (44.4%)
	2	6 (2.4%)	1 (0.4%)
	3	2 (0.8%)	2 (0.8%)
	Any	137 (54.4%)	113 (45.6%)
Creatinine	n	252	248
High	1	187 (74.2%)	186 (75.0%)
	2	5 (2.0%)	8 (3.2%)
	3	1 (0.4%)	0
	Any	193 (76.6%)	194 (78.2%)
Glucose	n	251	247
Low	1	18 (7.2%)	21 (8.5%)
	2	3 (1.2%)	0
	3	1 (0.4%)	0
	Any	22 (8.8%)	21 (8.5%)
High	3	3 (1.2%)	4 (1.6%)
	Any	3 (1.2%)	4 (1.6%)
Hemoglobin	n	252	248
Low	1	131 (52.0%)	138 (55.6%)
	2	90 (35.7%)	76 (30.6%)
	3	10 (4.0%)	6 (2.4%)
	Any	231 (91.7%)	220 (88.7%)
High	1	10 (4.0%)	4 (1.6%)
	Any	10 (4.0%)	4 (1.6%)
Lymphocytes Abs	n	163	166
Low	1	29 (17.8%)	19 (11.4%)
	2	59 (36.2%)	67 (40.4%)
	3	45 (27.6%)	48 (28.9%)
	4	7 (4.3%)	4 (2.4%)
	Any	140 (85.9%)	138 (83.1%)
High	2	3 (1.8%)	3 (1.8%)
	Any	3 (1.8%)	3 (1.8%)
Neutrophils, Total, Abs	n	163	166
Low	1	27 (16.6%)	35 (21.1%)
	2	29 (17.8%)	22 (13.3%)
	3	16 (9.8%)	24 (14.5%)
	4	36 (22.1%)	25 (15.1%)
	Any	108 (66.3%)	106 (63.9%)
Platelet	n	252	248
Low	1	62 (24.6%)	60 (24.2%)
	2	2 (0.8%)	2 (0.8%)
	3	1 (0.4%)	0
	Any	65 (25.8%)	62 (25.0%)
Potassium	n	252	248
Low	2	36 (14.3%)	28 (11.3%)
	3	6 (2.4%)	11 (4.4%)
	4	1 (0.4%)	1 (0.4%)
	Any	43 (17.1%)	40 (16.1%)
High	1	17 (6.7%)	26 (10.5%)
	2	6 (2.4%)	3 (1.2%)
	3	0	2 (0.8%)
	4	0	1 (0.4%)
	Any	23 (9.1%)	32 (12.9%)
Sodium	n	252	248
Low	1	22 (8.7%)	31 (12.5%)
	3	4 (1.6%)	0
	4	0	1 (0.4%)
	Any	26 (10.3%)	32 (12.9%)
High	1	19 (7.5%)	13 (5.2%)
	2	4 (1.6%)	1 (0.4%)
	3	0	1 (0.4%)
	4	2 (0.8%)	1 (0.4%)
	Any	25 (9.9%)	16 (6.5%)

Bilirubin	n	252	248
High	1	11 (4.4%)	16 (6.5%)
	2	1 (0.4%)	3 (1.2%)
	4	1 (0.4%)	0
	Any	13 (5.2%)	19 (7.7%)
Total Leukocyte Count	n	252	248
Low	1	59 (23.4%)	68 (27.4%)
	2	66 (26.2%)	69 (27.8%)
	3	42 (16.7%)	42 (16.9%)
	4	20 (7.9%)	19 (7.7%)
	Any	187 (74.2%)	198 (79.8%)
High	Any	0	0

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
'n' denotes the number of patients with a post-baseline lab value within this time interval. For a patient with multiple post-baseline lab abnormalities, the highest (worst) grade of these abnormalities for the given lab test is reported. 'Any' is the number of patients with a post-baseline abnormality of any grade for the specified lab test.

Safety in special populations

Total number of AEs by Race, Region and Race is presented below (DCO: 4-JUL-2019) (FeDeriCa study):

Adverse Event by Baseline Characteristics (Race, Region and Age) by Treatment Regimen: Safety Population
Protocol: WO40324 (CCOD:04JUL2019 DBL:29AUG2019)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
Total number of patients with at least one AE:	251	248
Race		
American Indian or Alaska Native	10 (4.0%)	10 (4.0%)
Asian	54 (21.5%)	51 (20.6%)
Black or African American	3 (1.2%)	3 (1.2%)
White	163 (64.9%)	165 (66.5%)
Multiple	2 (0.8%)	3 (1.2%)
Unknown	19 (7.6%)	16 (6.5%)
Region		
Europe	167 (66.5%)	160 (64.5%)
Asia	53 (21.1%)	51 (20.6%)
North America	16 (6.4%)	17 (6.9%)
South America	15 (6.0%)	20 (8.1%)
Age		
<40	37 (14.7%)	33 (13.3%)
40-65	188 (74.9%)	193 (77.8%)
>65	26 (10.4%)	22 (8.9%)

Sex not included in baseline as only 2 male patients in the study.

A summary table of AEs profile by age group is presented below with data cut-off from the primary analysis (4-JUL-2019) (FeDeriCa study).

Table 36 Summary of AEs profile by age group (FeDeriCa)

MedDRA Terms	Age <65 (N=441)	Age 65-74 (N=52)	Age 75-84 (N=7)	Age 85+ (N=0)
Total No of patients with at least 1 event	440 (99.8%)	52 (100%)	7 (100%)	0
Total AEs	6878	757	107	0
Serious AEs – Total	67 (15.2%)	13 (25.0%)	5 (71.4%)	0
- Fatal	0	0	2 (28.6%)	0
- Hospitalisation/prolong existing hospitalisation	65 (14.7%)	12 (23.1%)	4 (57.1%)	0
- Life-threatening	4 (0.9%)	1 (1.9%)	2 (28.6%)	0
Disability/incapacity	1 (0.2%)	1 (1.9%)	2 (28.6%)	0

- Other (medically significant)	3 (0.7%)	1 (1.9%)	0	0
AE leading to drop-out	4 (0.9%)	0	1 (14.3%)	0
Psychiatric disorders	85 (19.3%)	8 (15.4%)	2 (28.6%)	0
Nervous system disorders	256 (58.0%)	30 (57.7%)	5 (71.4%)	0
Accidents and injuries	8 (1.8%)	2 (3.8%)	1 (14.3%)	0
Cardiac disorders	43 (9.8%)	7 (13.5%)	3 (42.9%)	0
Vascular disorders	96 (21.8%)	9 (17.3%)	1 (14.3%)	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	222 (50.3%)	27 (51.9%)	5 (71.4%)	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	N/A	N/A	N/A	N/A
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	41 (9.3%)	8 (15.4%)	2 (28.6%)	0
other AE appearing more frequently in older patients	N/A	N/A	N/A	N/A

The incidence and severity of AEs seems balanced between the IV and SC arms of FeDeriCa across categories of age, region and race, although patients ≥ 65 years have a higher risk to develop diarrhoea in both arms (67% vs. 55% in patients < 65 years).
Safety in patients ≥ 75 years is limited to data from 7 out of 500 patients, but this has been clarified at the SmPC. It is expected that long-term safety in elderly patients should remain comparable to their younger counterparts, but this will be confirmed by follow-up data to come.
Data provided by the applicant suggests that no dose adjustments are needed for the new fixed-dose combination in patients with low and high body weight.
Data in patients with moderate renal impairment is limited but suggests that no dose adjustments of Phesgo are necessary. Concerning hepatic impairment, no studies have been done, hence no specific dose recommendations can be made for these patients.

Immunological events

Table 37 Comparison of ADAs and Antibodies Incidence: FeDeriCa

	P+H IV arm incidence		PH FDC SC arm incidence	
	Treatment-emergent	Positive at any timepoint	Treatment-emergent	Positive at any timepoint
ADAs to pertuzumab	3.0% (7/237)	7.1% (18/252)	4.8% (11/231)	8.5% (21/248)
ADAs to trastuzumab	0.4% (1/237)	1.2% (3/252)	0.9% (2/232)	2.4% (6/248)
Anti-rHuPH20 antibodies	NA	NA	0.9% (2/225)	6.7% (16/240)

Table 38 Summary of tpCR by trastuzumab ADA status with a positive ADA sample at any timepoint: ITT population (FeDeriCa)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
ADA Negative	249	242
tpCR (n, %)	150 (60.2%)	143 (59.1%)
ADA Positive	3	6
tpCR (n, %)	0	5 (83.3%)

ADA: Anti-drug antibody

Table 39 Summary of tpCR by pertuzumab ADA status with a positive ADA sample at any timepoint: ITT population (FeDeriCa)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)	Pertuzumab + Trastuzumab FDC SC Arm (N=248)
ADA Negative	234	227
tpCR (n, %)	135 (57.7%)	136 (59.9%)
ADA Positive	18	21
tpCR (n, %)	15 (83.3%)	12 (57.1%)

ADA: Anti-drug antibody

At this point, the incidence of ADAs and NAbs in both arms of the study is too low to assess their potential impact on efficacy and safety. However, the applicant has guaranteed that more immunogenicity data are expected through an Integrated Summary of Immunogenicity to be submitted in February 2021.

Safety related to drug-drug interactions and other interactions

There was no evidence of drug-drug interactions between pertuzumab and trastuzumab when administered as the PH FDC SC formulation (FeDeriCa study) nor when administered as a co-mixed formulation in study BO30185 Part 1.

Discontinuation due to adverse events

Table 40 AEs leading to withdrawal of HER2-targeted therapy: Safety population (FeDeriCa)

	Pertuzumab IV + Trastuzumab IV Arm (N=252)			Pertuzumab + Trastuzumab FDC SC Arm (N=248)		
	Phase			Phase		
MedDRA System Organ Class MedDRA Preferred Term	Neoadjuvant	Adjuvant	Overall	Neoadjuvant	Adjuvant	Overall
Total number of patients with at least one adverse event	5 (2.0%)	9 (3.6%)	15 (6.0%)	6 (2.4%)	5 (2.0%)	12 (4.8%)
Overall total number of events	5	9	15	6	5	12
Investigations						
Total number of patients with at least one adverse event	2 (0.8%)	7 (2.8%)	9 (3.6%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
Ejection fraction decreased	1 (0.4%)	7 (2.8%)	8 (3.2%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
Alanine aminotransferase increased	1 (0.4%)	0	1 (0.4%)	0	0	0
Total number of events	2	7	9	1	1	2
Cardiac disorders						
Total number of patients with at least one adverse event	2 (0.8%)	0	2 (0.8%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
Cardiac failure	2 (0.8%)	0	2 (0.8%)	1 (0.4%)	2 (0.8%)	3 (1.2%)
Total number of events	2	0	2	1	2	3
Respiratory, thoracic and mediastinal disorders						
Total number of patients with at least one adverse event	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (0.8%)
Pneumonitis	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Pulmonary fibrosis	0	0	0	0	1 (0.4%)	1 (0.4%)
Total number of events	0	1	1	1	1	2
Nervous system disorders						
Total number of patients with at least one adverse event	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Peripheral sensory neuropathy	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Total number of events	0	1	1	1	0	1
General disorders and administration site conditions						
Total number of patients with at least one adverse event	0	0	0	0	1 (0.4%)	2 (0.8%)
Asthenia	0	0	0	0	1 (0.4%)	1 (0.4%)
Death 0	0	0	0	0	1 (0.4%)	
Total number of events 0	0	0	0	1	2	
Immune system disorders						
Total number of patients with at least one adverse event	1 (0.4%)	0	1 (0.4%)	0	0	0
Drug hypersensitivity	1 (0.4%)	0	1 (0.4%)	0	0	0
Total number of events	1	0	1	0	0	0
Infections and infestations						
Total number of patients with at least one adverse event	0	0	0	1 (0.4%)	0	1 (0.4%)
Appendicitis	0	0	0	1 (0.4%)	0	1 (0.4%)
Total number of events	0	0	0	1	0	1
Injury, poisoning and procedural complications						
Total number of patients with at least one adverse event	0	0	0	1 (0.4%)	0	1 (0.4%)
Infusion related reaction	0	0	0	1 (0.4%)	0	1 (0.4%)
Total number of events	0	0	0	1	0	1
Blood and lymphatic system disorders						
Total number of patients with at least one adverse event	0	0	1 (0.4%)	0	0	0
Immune thrombocytopenia	0	0	1 (0.4%)	0	0	0
Total number of events	0	0	1	0	0	0

Investigator text for AEs encoded using MedDRA version 23.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Overall count includes AEs from post screening, Neoadjuvant, Adjuvant and Follow up phases.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety profile of trastuzumab is extensively documented and most Breast Oncologists are acquainted with its toxicities and how to handle them, particularly concerning heart failure and other forms of cardiac dysfunction. The addition of pertuzumab to trastuzumab-based regimens in the neoadjuvant, adjuvant and metastatic settings of HER2+ breast cancer proved to improve efficacy without significantly compromising safety, with diarrhoea as main adverse event.

The safety objective of the FeDeriCa trial was to compare the incidence and severity of AEs between its two arms: P+H IV (n=252) and PH FDC SC (n=248). Of note, the study involved the administration of 4 cycles of pertuzumab + trastuzumab (IV or SC) combined with chemotherapy in the neoadjuvant phase and the remaining 14 cycles –without chemotherapy– in the adjuvant phase. At the initial submission, with a cut-off date 4-JUL-2019, safety results mainly concerned the neoadjuvant phase.

Upon request, the applicant provided an updated safety database once all patients from the trial had finished receiving anti-HER2 treatment, with a cut-off date 10-JUL-2020. According to exposure tables, the median number of cycles of pertuzumab + trastuzumab in both arms is 18, whereas median dose intensity remained at 100%.

AEs: The overall distribution of AEs, G3/4 AEs, G5 AEs, serious AEs and AEs leading to discontinuation across the neoadjuvant and adjuvant phases is comparable between the IV and SC arms of this open-label trial. Importantly, the proportions of each subcategory of AEs correspond to those seen in similar trials with dual HER2-blockade plus chemotherapy in the neoadjuvant setting of HER2+ EBC.

As expected, the only notable imbalance between arms corresponds to infusion/administration related reactions, with higher proportion of any grade events in the SC arm (22% vs. 15% in the IV arm), which occurred predominantly in the adjuvant phase.

The most common AEs (incidence ≥ 5%) occurred with similar frequency between arms. Evidently, typical AEs from chemotherapy (alopecia, nausea/vomiting, asthenia/fatigue, stomatitis, neutropenia, myalgia, peripheral sensory neuropathy) were more prevalent in the neoadjuvant phase of the trial.

AEs with significant incidence in the adjuvant phase in both arms of FeDeriCa included diarrhoea (21% IV, 17% SC); arthralgia (21% IV, 18% SC); and radiation skin injury (21% IV, 20% SC). Since arthralgia can be attributable to adjuvant endocrine treatment and radiation skin injury to adjuvant radiotherapy, it seems that diarrhoea was the main AE attributable to anti-HER2 treatment in the adjuvant phase.

G≥3 AEs: A little over half of the patients of each arm experimented G≥3 AEs across both phases of the study (59% IV, 54% SC). In the adjuvant phase, these high-grade AEs occurred more frequently in the IV arm (15% vs. 11% in the SC arm). With the exception of G3/4 diarrhoea (13 patients in the IV arm vs. 18 in the SC arm), G3/4 AEs with the highest incidence were of haematological nature and thus attributable to concomitant chemotherapy during the neoadjuvant phase. G3/4 cardiac events across both phases were reported in very few patients, 1 from the IV arm and 3 from the SC arm.

SAES: The proportion of patients who suffered SAEs were similar in the IV (20%) and SC (19%) arms across both phases of the trial. Most SAEs occurred in the neoadjuvant phase and were of haematological (like attributable to the chemotherapy backbone) or infectious nature.

In the adjuvant phase there were 8 patients with SAEs in the IV arm and 10 in the SC arm. From these, 2 patients in the IV arm and 3 in the SC arm were serious cardiac failure events. There were 2 events of serious diarrhoea in the IV arm and 1 in the SC arm, all in the neoadjuvant phase.

Deaths: In the primary analysis and 4-month safety update from FeDeriCa (data cut-off 4-NOV-2019) one death in each arm had been reported, both in the neoadjuvant phase:

-An elderly patient from the P+H IV arm who died from urosepsis after 2 cycles of P+H and 5 doses of paclitaxel.

-An elderly patient from the PH FDC SC arm who died from an acute myocardial infarction after 2 cycles of ddAC and before any anti-HER2 treatment.

The updated safety database with data cut-off on 10-JUL-2020 reports 6 additional deaths: 2 in the IV arm and 4 in the SC arm. 1 patient in the IV arm and 3 in the SC arm died from progressive disease in the follow-up phase of the trial. The other 2 patients died during the adjuvant phase: 1 patient from the IV arm died from cardiac failure related to anti-HER2 treatment and 1 from the SC arm died from sudden dyspnoea after hospitalisation for pneumonia.

Overall, it appears that only the patient who died from cardiac failure (NYHA class IV) in the IV arm from FeDeriCa suffered a G5 AE directly related to anti-HER2 treatment.

AESIs: Diarrhoea, likely associated to both taxanes and pertuzumab, occurred in about 60% of patients from each arm, although mostly low-grade and manageable, not leading to the suspension of anti-HER2 treatment in any patient. G3/4 diarrhoea occurred in 5% of patients from the IV arm and 7% of the SC arm, predominantly in the neoadjuvant phase of the trial.

Cardiac toxicity, the main safety concern of dual HER2-blockade, was similar between arms and as expected, but led to discontinuing anti-HER2 treatment in 10 patients from the IV arm [8 from ejection fraction decreased (EFD) and 2 from cardiac failure)] and 5 from the SC arm (2 and 3, respectively). The overall behaviour of LVEF across both phases of the trial is comparable between the two arms.

2 primary cardiac events (NYHA class III/IV heart failure with EFD<50% or cardiac death) occurred in the IV arm vs. 4 in the SC arm, whereas secondary cardiac events (NYHA class II heart failure) prevailed in the IV arm (18 vs. 12 in the SC arm). Of note, the overall incidence of EFD events in both arms was considerably higher in the late adjuvant phase of the trial: confirmatory assessment seems to have happened in the follow-up period.

Interstitial lung disease events, although rare (3 in the IV arm and 5 in the SC arm) and mild (none G≥3), led to permanent withdrawal of HER2-targeted therapy in 1 patient from the IV arm and 2 from the SC arm.

Infusion/administration related reactions: Reasonably, reactions related to the administration route of anti-HER2 treatment differed considerably between arms: while systemic G1-3 related reactions prevailed in the IV arm (11% vs. 0.8% in the SC arm), local injection site events were predominant in the SC arm (16% vs. 0.4% in the IV arm). However, hypersensitivity/anaphylaxis events were rare, occurring in 4 patients from each arm. Both trastuzumab and pertuzumab were discontinued in one patient from each arm because of anaphylaxis during or immediately after administration.

Discontinuations: The majority of patients from both arms of FeDeriCa completed the intended 18 cycles of dual HER2-targeted treatment in the neoadjuvant and adjuvant phases. As explained earlier, withdrawal of pertuzumab and/or trastuzumab due to AEs during both phases was balanced between arms (15 vs. 12 patients, respectively). The main reason for anti-HER2 treatment discontinuations in both arms was cardiac events such as EFD or cardiac failure (10 patients in the IV arm, 5 in the SC arm). In the IV arm, discontinuations due to AEs occurred predominantly in the adjuvant phase, whereas in the SC arm they were balanced between both phases.

Special populations: The incidence and severity of AEs seems balanced between the IV and SC arms of FeDeriCa across categories of age, region and race, although patients ≥ 65 years have a higher risk to develop diarrhoea in both arms (67% vs. 55% in patients < 65 years). Safety in patients ≥ 75 years is limited to data from 7 out of 500 patients, but this has been clarified at the SmPC.

Data in patients with moderate renal impairment is limited but suggests that no dose adjustments of Phesgo are necessary. Concerning hepatic impairment, no studies have been done, and therefore no specific dose recommendations can be made.

Immunogenicity: The incidence of ADAs and NAbs in both arms of the study is too low to assess their potential impact on efficacy and safety at this point. The applicant has committed to providing more immunogenicity data through an Integrated Summary of Immunogenicity in February 2021 (see RMP).

2.6.2. Conclusions on the clinical safety

Given the accepted PK-bridging (supported by the similarity of safety profile in FEDERICA and the IV safety database), the safety database for Phesgo is understood to be the totality of data from the pooled studies CLEOPATRA, NEOSPHERE, TRYPHAENA, APHINITY, and FEDERICA. The CHMP recommended to provide post-approval an updated ADR table for SmPC 4.8 displaying such ADR frequencies.

Except for AEs related to route of administration, the safety profile of Phesgo (pertuzumab + trastuzumab fixed dose for SC administration) across the neoadjuvant and adjuvant phases of the FeDeriCa trial is comparable to its IV counterparts, with no new safety signals identified. Chemotherapy-related AEs were prevalent in the neoadjuvant phase of the trial. AEs related to anti-HER2 treatment were more prevalent in the adjuvant phase, among which diarrhoea and cardiac events were most frequent, although with incidence and severity comparable to other trials in similar EBC settings.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Congestive heart failure / Left ventricular dysfunction Administration-related reactions
Important potential risks	Oligohydramnios Lack of efficacy due to immunogenicity Medication errors (altered safety and efficacy)
Missing information	None

Pharmacovigilance plan

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimisation activities				
WO40324 (FeDeriCa, Ongoing)	• To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough} of pertuzumab SC within Phesgo compared with Perjeta IV • To demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum trastuzumab C_{trough} of trastuzumab SC within Phesgo compared with Herceptin IV • To evaluate the efficacy of Phesgo + chemotherapy compared with Perjeta IV and Herceptin IV + chemotherapy	• Lack of efficacy due to immunogenicity	• Updated Immunogenicity Report	• February 2021
	• To evaluate the safety of Phesgo compared with Perjeta IV and Herceptin IV		• Final CSR	• Q4 2023

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Congestive heart failure / Left ventricular dysfunction	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** In Section 4.2 of the EU SmPC, "Left ventricular dysfunction" part and Section 4.4 "Left ventricular dysfunction (including congestive heart failure)" provides recommendations on risk management approach. **Other risk minimisation measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Oligohydramnios	**Routine risk communication:** Section 4.6 of the EU SmPC: Fertility, pregnancy and lactation **Routine risk minimisation activities recommending specific clinical measures to address the risk:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Global Enhanced Pharmacovigilance Pregnancy Program

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	In Section 4.6 of the EU SmPC: "Fertility, pregnancy and lactation" part provides recommendations on risk management approach. **Other risk minimisation measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimisation measures:** None	Questionnaire for pregnancy-related adverse events *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None
Risk of lack of efficacy due to immunogenicity	**Routine risk communication:** Section 4.8 of the EU SmPC: "Immunogenicity" part **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** Updated immunogenicity report for Study WO40324 Final CSR for Study WO40324
Administration-Related Reactions (ARRs)	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Guidance on observation period after administration has been adequately captured in Section 4.2 of E.U. SmPC. **Other risk minimisation measures beyond the Product Information:** Pack Size: Each carton contains one vial Legal Status: Phesgo is a prescription only medicine. **Additional risk minimisation measures:** None	*Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication errors (altered safety and efficacy)	**Routine risk communication:** Section 4.2 of the EU SmPC **Routine risk minimisation activities recommending specific clinical measures to address the risk:** At the beginning of Section 4.2 of the SmPC, there is a statement re-enforcing the need to check the vial labels to ensure that the drug being prepared and administered is Phesgo. Additionally, the fact that Phesgo should be administered via subcutaneous injection only is stated. Outer and inner packaging differentiation: between each strength of Phesgo as well as between HER2 approved products - peel off label - subcutaneous is stated in bold and red on the vial and packaging, in addition to the SmPC. - difference in vial size **Other risk minimisation measures beyond the Product Information:** None **Medicine's legal status:** Legal Status: Phesgo is a prescription only medicine **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None *Other forms of routine pharmacovigilance activities:* Presentation of cumulative data in PSURs **Additional pharmacovigilance activities:** None

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.1 is acceptable.

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 29.06.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group accepts the request for use of minimum particulars on the vial labels, however regarding the complete omission of the pharmaceutical form, the Group asked that at least the short pharmaceutical form (i.e., injection) is displayed on the labels. If the mock-ups assessment concludes that the inclusion of the term is not possible without compromising the readability of the labels, then the omission can eventually be acceptable.

The particulars to be omitted as per the QRD Group decision described above will, however, be included in the Annexes published with the EPAR on EMA website and translated in all languages, but will appear in grey-shaded to show that they will not be included on the printed materials.

2.8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Phesgo is included in the additional monitoring list as it contains a biological product which is not a new active substance and authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant has developed a new product containing pertuzumab and trastuzumab in one fixed-dose combination for SC injection –Phesgo, PH FDC SC– and seeks approval in the same indications as those that pertuzumab (IV) holds in the EU: in combination with trastuzumab and chemotherapy for the treatment of early (neoadjuvant and adjuvant) and metastatic HER2+ breast cancer.

3.1.2. Available therapies and unmet medical need

Trastuzumab and pertuzumab in their IV formulation have been approved and available in the market for a number of years, with a consolidated role in the treatment of HER2+ breast cancer. Trastuzumab SC was developed subsequently and proven non-inferior and as safe as its IV predecessor, receiving approval for marketing in the EU in September 2013.

PH FDC SC, as a fixed non-weight-based dose, is intended for subcutaneous administration, and was developed to offer patients a less invasive and faster administration of pertuzumab and trastuzumab as a single product compared to individual IV infusions. In turn, this should reduce the strain on medical centres with respect to time and resources required to prepare and administer IV therapy.

3.1.3. Main clinical studies

The applicant submitted data from the primary analysis of the FeDeriCa trial, an ongoing Phase III, open-label, multicentre study that investigated the pharmacokinetics, efficacy, and safety of PH FDC SC compared with P+H IV, in combination with chemotherapy, in 500 subjects with HER2-positive early breast cancer in the neoadjuvant/adjuvant settings. The primary objective of the study was to prove the pharmacokinetic non-inferiority of the SC vs. the IV formulation of the drugs. Efficacy and safety were secondary objectives.

3.2. Favourable effects

- The primary endpoint of the study was met, since the geometric mean ratio (GMR) of Cycle 7 (pre-dose Cycle 8) serum pertuzumab C_{trough} SC/C_{trough} IV was 1.22 (90% CI: 1.14, 1.31). The lower limit of the two-sided 90% CI of 1.14 was above the pre-specified non-inferiority margin of 0.8.
- The PH FDC SC yields pre-dose Cycle 8 C_{trough} concentrations of trastuzumab that are non-inferior to the concentrations seen in the IV administration of the two agents. Furthermore, trastuzumab PK was not altered by co-formulation with pertuzumab.
- Key efficacy endpoint: the proportions of locally assessed tpCR in both arms of the FeDeriCa trial are comparable: 59.5% in the P+H IV arm and 59.7% in the PH FDC SC arm, with nearly matching and considerably overlapping 95% confidence intervals. These results are analogous to similar anthracycline regimens with dual HER2 blockade in recent neoadjuvant trials that used akin pCR definitions.

- tpCR rates are similar across most subgroups of both arms, particularly concerning the stratification factors used for randomisation.
- Exploratory analyses, including bpCR, GBG pCR were consistent with the main efficacy results.

3.3. Uncertainties and limitations about favourable effects

- 64 patients (36 patients from the P+H IV arm and 28 from the PH FDC SC arm) were excluded from the PPP population due to at least one predefined PK protocol violation. The exclusion of 14% of patients from PK analysis brings some uncertainty to results from the PK endpoints.
- Long-term efficacy data from FeDeriCa study, from prospective time-to-event endpoints, is expected – final CSR from the trial anticipated in Q4 2023.

3.4. Unfavourable effects

- The overall distribution of AEs, G3/4 AEs, G5 AEs, serious AEs and AEs leading to discontinuation across the neoadjuvant and adjuvant phases is comparable between the IV and SC arms of this open-label trial. Importantly, the proportions of each subcategory of AEs correspond to those seen in similar trials with dual HER2-blockade plus chemotherapy in the neoadjuvant setting of HER2+ EBC.
- Diarrhoea was reported in about 60% of patients from each arm. G3/4 diarrhoea occurred in 13 patients from the IV arm and 18 from the SC arm.
- Cardiac dysfunction events (e.g. peripheral oedema, EF decreased, nocturnal dyspnoea) were predominantly low grade (G1/2) and balanced across arms. Overall, incidence and type of cardiac toxicity events were comparable between arms and as expected for dual HER2-blockade in the neoadjuvant setting, but led to withdrawal of anti-HER2 treatment in 15 patients (10 IV, 5 SC).
- The proportion of patients who suffered SAEs were similar in the IV (20%) and SC (19%) arms of the trial. Most SAEs were of haematological (like attributable to the chemotherapy backbone) or infectious nature.
- Only one patient (IV arm) seems to have died from cardiac failure related to anti-HER2 treatment.
- The frequency and type of reactions related to the administration route of anti-HER2 treatment differed considerably between the IV and SC arms. Systemic reactions (G1-3) were more frequent in the IV arm (11% vs. 0.8% in SC arm), whereas local injection site events occurred more in the SC arm (16% vs. 0.4% in the IV arm). Most of the local site reactions to PH FDC SC were injection site pain or erythema and none led to discontinuation of the drug.
- The incidence and severity of AEs seems balanced between the IV and SC arms of FeDeriCa across categories of age, region and race, though higher risk for diarrhoea was seen in patients ≥65 years.

3.5. Uncertainties and limitations about unfavourable effects

- No studies have been done in patients with hepatic impairment, so no specific dose adjustment is recommended (see SmPC section 4.2).

- The incidence of ADAs and NAbs in both arms of the study is too low to assess their potential impact on efficacy and safety at this point. The applicant has committed to provide more immunogenicity data through an Integrated Summary of Immunogenicity in February 2021 (see RMP).

3.6. Effects Table

Effects Table for PH FDC SC in the neoadjuvant setting of HER2+ breast cancer, data cut-off 4-JUL-2019 for the PK and efficacy endpoints, 10-JUL-2020 for safety results.

Effect	Unit	PD FDC SC (experimental) N=248	P+H IV (control) N=252	Uncertainties / Strength of evidence
Favourable Effects				
*Geometric mean C_{trough} pertuzumab pre-cycle 8 (n=409)	µg/mL	88.7	72.4	GMR C_{trough} SC/C_{trough} IV pertuzumab: 1.22 90% CI: 1.14, 1.31
Geometric mean C_{trough} trastuzumab pre-cycle 8 (n=409)	µg/mL	57.5	43.2	GMR C_{trough} SC/C_{trough} IV trastuzumab: 1.33 90% CI: 1.24, 1.43
tpCR in ITT (n=500)	% (n)	59.7 (148)	59.5 (150)	Difference in tpCR rate: 0.15 §Δ 95% CI: – 8.67, 8.97
Unfavourable Effects (n=500)				
AEs	%	100	99.6	
G3/4/5 AEs	%	53.6	59.1	
Serious AEs	%	19.0	19.8	
G5 AEs	% (n)	0.8 (2)	0.8 (2)	
AEs leading to anti-HER2 treatment discontinuation	% (n)	4.8 (12)	6.0 (15)	
Cardiac dysfunction	%	21.4	26.2	
Diarrhoea	%	61.7	59.1	

* Primary endpoint
§ Not formally tested

3.1. Benefit-risk assessment and discussion

3.1.1. Importance of favourable and unfavourable effects

Upon results from the FeDeriCa trial, the applicant proposes to extrapolate the approved pertuzumab indications –early and metastatic settings of HER2+ breast cancer– to a new fixed dose combination of pertuzumab and trastuzumab for subcutaneous (SC) administration to be marketed as Phesgo.

The new subcutaneous fixed-dose formulation of trastuzumab in combination with pertuzumab is not a new therapeutic innovation and does not change breast cancer treatment protocols except for the convenience of the new route of administration.

The analysis of PK parameters shows that PH FDC SC is overall non-inferior to the same combination administered via the IV route, although the exclusion of 14% of patients from PK analysis brings some uncertainty to results from the PK endpoints.

Efficacy in terms of locally-assessed tpCR after neoadjuvant treatment is also comparable between both SC and IV arms, but the eventual support from prospective time-to-event endpoints –final CSR from the trial anticipated in Q4 2023– is expected.

The structure of the submitted clinical safety data is considered adequate for safety evaluation of PH FDC SC, entailing both the neoadjuvant and adjuvant phases of the trial. Overall, the safety profile of Phesgo across both phases of the trial is considered comparable to its IV counterparts, noticing obvious differences in AEs related to the route of administration. The incidence and severity of cardiac dysfunction events and diarrhoea, the main AEs related to dual-HER2 blockade, was comparable to similar trials in HER2+ EBC.

Because of low incidence, the role of ADAs to any of the components of PH FDC SC is still unclear.

3.1.2. Balance of benefits and risks

Data from the neoadjuvant phase of the FeDeriCa trial indicate that the fixed dose combination of pertuzumab and trastuzumab for SC administration (Phesgo) is pharmacokinetically non-inferior to its IV counterparts. Early efficacy results from both arms are similar and ensure long-term follow-up for time-to-event endpoints. The safety profile of Phesgo across the neoadjuvant and adjuvant phases of FeDeriCa is comparable to pertuzumab + trastuzumab for IV administration.

3.1.3. Additional considerations on the benefit-risk balance

Not applicable.

3.2. Conclusions

The overall B/R of Phesgo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Phesgo is favourable in the following indication:

Early breast cancer (EBC):

Phesgo is indicated for use in combination with chemotherapy in:

• the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence

• the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence

Metastatic breast cancer (MBC):

Phesgo is indicated for use in combination with docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or

chemotherapy for their metastatic disease.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.