EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/17250/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Perjeta

International non-proprietary name: PERTUZUMAB

Procedure No. EMEA/H/C/002547/0000

Note

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

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Executive Summary

Breast cancer is the most common form of malignancy in women, with a global prevalence of more than 1.3 million patients and a mortality rate of approximately 450,000 deaths per year (Ferlay et al, 2010). In Europe, more than 80,000 deaths from breast cancer are expected in 2011 (Malvezzi et al, 2011). Most breast cancers are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Howlader et al, 2011; Sant et al, 2003). At this stage the disease is usually operable and can be treated with curative intent. However, around 20%-45% of patients experience relapse (EBCTCG, 2011a, 2011b) and those with metastatic or unresectable disease are generally incurable. Patients with metastatic disease have a median survival of around 24 months and a 5-year life expectancy of 18%-23% (Howlader et al, 2011; Sant et al, 2003).

In December 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the authorisation of pertuzumab (Perjeta) in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Pertuzumab is subject to restricted medical prescription and therapy should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. Pertuzumab should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation service is immediately available. The recommended initial loading dose of pertuzumab is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes.

The HER2 receptor has emerged as one of the most important targets for the treatment of breast cancer. HER2 is involved in regulating cell growth, survival and differentiation (Sundaresan et al, 1999). HER2 overexpression/amplification ('HER2-positivity') is associated with increased tumor aggressiveness, higher rates of recurrence, and increased mortality (Borg et al, 1990; Ross et al, 1998; Menard et al, 2001; Brown et al, 2008; Curigliano et al, 2009; Ross et al, 2009).

Pertuzumab is a monoclonal antibody that targets HER2. It prevents dimerisation of HER2 with other members of the HER family. These dimers are responsible for signal transduction via critical pathways that are involved in the survival, growth and division of breast cancer cells. Pertuzumab results in a more complete inhibition of the HER2 axis when combined with the monoclonal antibody trastuzumab, which binds to a different epitope. Pertuzumab is also able to induce antibody-dependent cell-mediated cytotoxicity (ADCC).

The demonstration of clinical benefit for pertuzumab was based on a single randomized controlled trial comparing the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated patients with locally advanced or metastatic HER2-positive breast cancer. Patients with clinically important cardiac risk factors or brain metastases were not included in the trial.

Pertuzumab and trastuzumab were given at standard doses in a 3-weekly regimen. Patients were treated with pertuzumab and trastuzumab until disease progression, withdrawal of consent or unmanageable toxicity. Docetaxel was given as an initial dose of 75 mg/m2 as an intravenous infusion every three weeks for at least 6 cycles. The dose of docetaxel could be escalated to 100 mg/m2 at the investigator's discretion if the initial dose was well tolerated.

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

In the primary efficacy analysis, the addition of pertuzumab to trastuzumab+docetaxel resulted in a 38% improvement in PFS compared to placebo (hazard ratio = 0.62; 95% CI: 0.51, 0.75; p < 0.0001). The median PFS was 18.5 months in the pertuzumab group compared to 12.4 months in the placebo group. The result of the primary analysis was supported by the results of secondary endpoints, including overall survival (hazard ratio = 0.66; 95% CI: 0.52, 0.84; p= 0.0008) and objective response rate (80.2% vs. 69.3% for the pertuzumab group vs. placebo group, respectively). The proportion of patients alive at 12, 24 and 36 months, respectively, was 94%, 81% and 66% for the pertuzumab group compared to 89%, 69% and 50% in the placebo group.

The main concern in the assessment of efficacy has been that the patient population of the pivotal trial appeared to have been undertreated compared to the current standard of care in Europe. Only about half of patients in the pivotal study had received prior (neo-) adjuvant therapy, and the vast majority of patients were trastuzumab-naïve. However, exploratory analyses did not reveal any major differences in efficacy according to prior trastuzumab treatment. Thus, the efficacy of pertuzumab was considered established in the overall patient population as well as in patients pre-treated with trastuzumab. The results of two ongoing studies will be submitted as a post-marketing commitment to further confirm the efficacy of pertuzumab in patients pre-treated with trastuzumab.

Common adverse events (incidence >25%) observed in the pivotal trial were alopecia (60.5% in the placebo arm, 60.9% in the pertuzumab arm), diarrhoea (46.3%/66.8%), neutropenia (49.6%/52.8%), nausea (41.6%/42.3%), fatigue (36.8%/37.6%), rash (24.2%/33.7%), asthenia (30.2%/26.0%), decreased appetite (26.4%/29.2%), peripheral oedema (30.0%/23.1%) and mucosal inflammation 19.9%/27.8%). Overall, the toxicity profile was similar between groups except for higher incidence in diarrhoea, rash, mucosal inflammation, dry skin and neutropenia associated with the pertuzumab group. No significant difference in severe or life-threatening toxicity was observed between the placebo and pertuzumab arms (72.0% and 73.5%, respectively) although the proportion of patients with severe or life-threatening febrile neutropenia and diarrhoea was higher in the pertuzumab group compared to the placebo group. Adverse events resulting in death were observed in 2.5% of patients in the placebo arm and in 2.0% of patients in the pertuzumab arm.

In terms of balance of benefits and risks, the totality of data indicated that pertuzumab was associated with clinically and statistically significant benefits in a patient population with limited treatment options. Based on the review of data on quality, safety and efficacy, the risk-benefit balance of pertuzumab, in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease, was considered to be positive.

Product information

Name of the medicinal product:	Perjeta
Applicant:	Roche Registration Ltd. 6 Falcon Way Shire Park Welwyn Garden City, Hertfordshire AL7 1TW United Kingdom
Active substance:	pertuzumab
International Nonproprietary Name/Common Name:	pertuzumab
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agent, monoclonal antibody (L01XC13)
Therapeutic indication(s):	Perjeta is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	420 mg
Route(s) of administration:	Intravenous use
Packaging:	Vial (glass)
Package size(s):	1 vial

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List of abbreviations

ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse event
AIFA	Agenzia Italiana del Farmaco
ATA	Anti-therapeutic antibodies
ATS	Attribute Testing Strategy
ATSR	ATS Robustness
CBR	Clinical benefit response
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CL	Clearance
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CQA-AC	CQA Acceptance Criteria
CQA-TR	CQA Target Range
CR	Complete response
CRC	Cardiac Review Committee
CrCL	Creatinine clearance
CRO	Clinical Research Organization
CTD	Common Technical Document
CYP450	Cytochrome P450
DDI	Drug-drug interactions
DMA	Danish Medicines Agency
EBC	Early breast cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECLA	Electrochemiluminescence assay
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
FACT-TOI-PFB	Functional Assessment of Cancer Therapy – Trial Outcome Index – Physical/Functional/Breast
FEC	Fluorouracil, epirubicin, cyclophosphamide
FISH	Fluorescence in situ hybridization
HCP	Host Cell Protein
HER2	Human epidermal growth factor receptor 2
HMWS	High Molecular Weight Species
HR	Hazard Ratio

HRQoL	Health-related quality of life
IHC	Immunohistochemistry
IRF	Independent Review Facility
IIV	Inter-individual variability
IV	Intravenous
KPI	Key Performance Indicator
LMWS	Low Molecular Weight Species
LVSD	Left ventricular systolic dysfunction
LVEF	Left ventricular ejection fraction
MAR	Multivariate Acceptable Range
MBC	Metastatic breast cancer
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Medicinal Products Agency
MQC	Minimum quantifiable concentration
NCCN	National Comprehensive Cancer Network
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PACMP	Post-Approval Change Management Protocol
PAR	Proven Acceptable Range
pCR	Pathological complete response
PD	Progressive disease
PFS	Progression-free survival
Pla+T+D	Placebo in combination with trastuzumab and docetaxel
popPK	Population pharmacokinetics
PR	Partial response
Ptz+D	Pertuzumab in combination with docetaxel
Ptz+T	Pertuzumab and trastuzumab
Ptz+T+D	Pertuzumab in combination with trastuzumab and docetaxel
PK	Pharmacokinetic
q3w	Every 3 weeks
QbD	Quality by Design
c-QTc	Concentration corrected QT interval
QTcF	QT interval corrected with the Fridericia's formula
QTPP	Quality Target Product Profile
RECIST	Response evaluation criteria in solid tumors
RRF	Risk Ranking and Filtering
SAE	Serious adverse event
SCPS	Summary of Clinical Pharmacology Studies

SE	Standard error
SMQ	Standardized MedDRA query
SUSAR	Serious, unexpected, suspected adverse reaction
T+D	Trastuzumab in combination with docetaxel
TTP	Time to disease progression
$t_{1/2}$	Terminal half-life
V_c	Central compartment volume
V_{ss}	Volume of distribution at steady-state
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Ltd. submitted on 1 December 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Perjeta, 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 30/06/2011.

The applicant applied for the following indication:

Pertuzumab is indicated in combination with Herceptin and docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision *P/345/2010* 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.

New active Substance status

The applicant requested the active substance (pertuzumab) contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on July 2007, December 2009 and October 2010. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the biological active substance

Genentech, Inc.
1000 New Horizons Way
Vacaville, CA 95688-9431
USA

A process- and product-related inspection of this manufacturing site was carried out by the Federal Institute of Vaccines and Biomedicines – Paul Ehrlich Institute and by the Italian Medicines Agency. The findings of the inspection are in compliance with the EU Good Manufacturing Practice requirements.

Manufacturer responsible for batch release

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

1.3. Steps taken for the assessment of the product

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

Rapporteur: **Jens Ersbøll** Co-Rapporteur: **Daniela Melchiorri**

- The application was received by the EMA on 1 December 2011.
- The procedure started on 21 December 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2012 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2012 (Annex 2).
- During the meeting on 19 April 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 April 2012 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 August 2012.
- The report of the inspection carried out at the following site: Genentech, Inc., 1000 New Horizons Way, Vacaville, CA 95688-9431, USA between 25-26 April 2012 was issued on 21 August 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 September 2012 (Annex 4).
- During the CHMP meeting on 18 October 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 12 November 2012.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 6 December 2012 (Annex 6).

- During the meeting on 13 December 2012, 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 Perjeta on 13 December 2012.

2. Scientific discussion

2.1. Introduction

HER2-positive breast cancer (BC)

Breast cancer is the most common form of malignancy in women, with a global prevalence of more than 1.3 million patients and a mortality rate of approximately 450,000 deaths per year (Ferlay et al, 2010). In Europe, more than 80,000 deaths from breast cancer are expected in 2011 (Malvezzi et al, 2011). Most breast cancers in the Western world (around 94%-95% of patients in the US and Europe) are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread (Howlader et al, 2011; Sant et al, 2003). At this stage ('early breast cancer' [EBC]), the disease is usually operable and can be treated with curative intent. However, around 20%-45% of patients experience relapse (EBCTCG, 2011a, 2011b) and those with metastatic or unresectable disease are generally incurable. Patients with metastatic disease have a median survival of around 24 months and a 5-year life expectancy of 18%-23% in the US and Europe (Howlader et al, 2011; Sant et al, 2003).

The HER2 receptor has emerged as one of the most important targets for the treatment of breast cancer. HER2 is involved in regulating cell growth, survival and differentiation (Sundaresan et al, 1999). Amplification and/or overexpression of HER2 occurs in around 15% to 20% of breast cancers (Wolff et al, 2007; Chia et al, 2008; Ross et al, 2009) and is a hallmark of the HER2-positive and luminal-B intrinsic sub-types of breast cancer (Sorlie et al, 2004). HER2 overexpression/amplification ('HER2-positivity') is associated with increased tumor aggressiveness, higher rates of recurrence, and increased mortality (Borg et al, 1990; Ross et al, 1998; Menard et al, 2001; Brown et al, 2008; Curigliano et al, 2009; Ross et al, 2009).

Although improved early detection and advances in systemic therapy for early-stage disease have resulted in a decline in breast cancer mortality in recent years (Levi et al, 2005; Malvezzi et al, 2011), MBC (Metastatic Breast Cancer) (of all sub-types) remains essentially incurable. Despite improvements in progression-free and overall survival with trastuzumab-based and lapatinib-based therapies, some patients with HER2-positive MBC never respond to these targeted agents, and almost all patients with HER2-positive MBC will eventually progress and die of breast cancer. Of the 450,000 global deaths from breast cancer each year (Ferlay et al, 2010), around 15%-20% (60,000~90,000) are likely to be due to HER2-positive disease. This translates to around 12,000-15,000 deaths per annum in Europe and 6,000-8,000 deaths per annum in the US. The median age of patients presenting with HER2-positive breast cancer is in the mid-50s, around five years younger than the general breast cancer population (Neven et al, 2008; Kwan et al, 2009). At a time when the actuarial survival for women is over 80 years of age, the median loss of life-years per patient is around two decades. New active agents are, therefore, urgently required to improve disease control and extend survival in patients with HER2-positive MBC.

About the product

Pertuzumab (Ptz) is a recombinant, humanized, IgG mAb which also targets HER2, but Ptz binds to a different epitope (domain II) than Trastuzumab (T) and prevents dimerisation of HER2 with other members of the HER family (HER1 (=EGFR), HER3 and HER4). These dimers (homodimerisation or heterodimerisation) are responsible for signal transduction via critical pathways (MAP kinase and PI3K)

that are involved in the survival, growth and division of BC cells. Ptz results in a more complete inhibition of the HER2 axis when combined with T (dual HER2 blockade). Ptz is also able to induce antibody-dependent cell-mediated cytotoxicity (ADCC).

Initially, the Applicant claimed pertuzumab was indicated in combination with Herceptin and docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy.

Subsequently, as a result of the evaluation procedure, the approved indication states as follows:

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

Perjeta is subject to restricted medical prescription and therapy should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. Perjeta should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation service is immediately available.

Patients treated with Perjeta must have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of ≥2.0 by in situ hybridisation (ISH) assessed by a validated test.
To ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures. For full instructions on assay performance and interpretation please refer to the package leaflets of validated HER2 testing assays.

The recommended initial loading dose of Perjeta is 840 mg administered as a 60 minute intravenous infusion, followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes.

When administered with Perjeta the recommended initial loading dose of trastuzumab is 8 mg/kg body weight administered as an intravenous infusion followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight.

When administered with Perjeta the recommended initial dose of docetaxel is 75 mg/m^2, administered thereafter on a 3 weekly schedule. The dose of docetaxel may be escalated to 100 mg/m^2 on subsequent cycles if the initial dose is well tolerated.

The medicinal products should be administered sequentially. Perjeta and trastuzumab can be given in any order. When the patient is receiving docetaxel, this should be administered after Perjeta and trastuzumab. An observation period of 30 to 60 minutes is recommended after each Perjeta infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel.

Patients should be treated with Perjeta until disease progression or unmanageable toxicity.

2.2. Quality aspects

2.2.1. Introduction

Pertuzumab is a full-length recombinant humanised IgG1(κ) monoclonal antibody containing an N-linked oligosaccharide.

Pertuzumab is targeted against sub-domain II of the extracellular domain of human epidermal growth factor 2 (HER2), blocking heterodimerisation of HER2 with other members of the receptor family and resultant ligand activated signalling. HER2 is a transmembrane glycoprotein with intrinsic tyrosine kinase activity. It is one of four members of the human EGFR family which also includes EGFR (HER1), HER3 and HER4. HER signalling is known to play roles in neoplastic cell growth, malignant transformation and resistance to chemotherapy. In addition, pertuzumab activates antibody-dependent cell cytotoxicity (ADCC), as does trastuzumab. In contrast, trastuzumab binds to sub-domain IV of the extracellular domain of HER2 and disrupts ligand independent interactions, but is not effective in blocking dimerisation of HER2 with ligand activated family members EGFR, HER3 or HER4. In addition, trastuzumab, by binding to domain IV, blocks a proteolytic cleavage site on the HER2 ectodomain and the resulting generation of phosphorylated p95 and constitutive activation of the intracellular kinase domains. Pertuzumab does not share this activity with trastuzumab.

The Applicant has applied Quality by Design (QbD) principles to develop the process and product controls for the commercial manufacture of Perjeta.

2.2.2. Active Substance

Manufacture

The active substance is manufactured at Genentech Inc., 1000 New Horizons Way, Vacaville, CA 95688-9431, USA. This site is also responsible for batch release testing of the active substance.

The manufacturing process is based on a platform approach applied in relation to other centrally authorised Chinese Hamster Ovary (CHO)-derived monoclonal antibody products manufactured by the Applicant.

The plasmid containing the heavy and light chains was transfected into CHO cells and a pre-bank was established.

Cell banking system
A two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) was developed and maintained in accordance to current Good Manufacturing Practices (cGMP) and ICH guidelines.
Procedures followed for the preparation of the MCB and WCB were described. An extensive range of tests was performed for their characterisation, in accordance to ICH guidelines, including identity, viability, stability, presence of adventitious agents.

Cell culture process
Pertuzumab is produced in a fed-batch process using a suspension-adapted CHO cell line. The source of cell is typically the WCB but can also be the MCB.

The cell culture process involves three stages:
- The seed train,
- The inoculum train,
- The production stage.

Following the production phase, the cell culture fluid containing pertuzumab is separated from the cells by centrifugation and filtered. The resulting cell culture filtrate is then further purified (see below).

Cell culture conditions and in-process controls (IPC) have been sufficiently described and are considered appropriate.

Purification process
The purification process consists of a series of chromatography, viral inactivation and filtration and ultrafiltration/diafiltration steps.
Each step of the purification process has been adequately described, including description of the different buffers used, column regeneration and storage conditions of both columns and product after each step. Suitable IPC controls are in place, with acceptable limits.

Process validation

Development, characterisation, and validation of the pertuzumab process is built upon a comprehensive science- and risk-based approach, which incorporates process and product understanding developed from pertuzumab-specific studies as well as platform knowledge gained from similar molecules and processes.

Manufacturing process development
Changes to the manufacturing process have occurred three times during development.

Characterisation
A) Elucidation of structure and other characteristics:

A1) Physicochemical characterisation:
The molecular weight was determined by electrospray ionisation mass spectrometry (ESI-MS). The mass for deglycosylated non-reduced pertuzumab is approximately 145.2 kDa. Tryptic peptide mapping confirmed the primary structure.

Tryptic digestion of non-reduced vs reduced reference standard followed by reversed phase liquid chromatography mass spectrometry (LC-MS) analysis was used to identify disulfide bond sites.

The N-linked glycosylation site of pertuzumab was confirmed by tryptic peptide mapping. The quantitative glycosylation profile for this site was also determined.

Glycation of lysine residues was assessed. Sites of glycation were identified.

Hydrophobic interaction chromatography analysis of carboxypeptidase B and papain digested active substance was used to assess oxidation.

Deamidation has been examined on stressed material.

Size exclusion high-performance liquid chromatography (SE-HPLC) was performed to analyse the size distribution of the pertuzumab molecule. The detected peaks correspond to the monomer peak (main peak) and high-molecular weight species (HMWS) and low-molecular-weight species (LMWS) of the pertuzumab molecule.

SDS-PAGE was performed under non-reducing and reducing conditions.

A2) Biological characterisation:
- Functional Fab-related assays
Binding of pertuzumab to HER2 was demonstrated by a HER2 ELISA.

An anti-proliferation assay is used as potency assay for characterisation and control of pertuzumab. It is based on the ability of pertuzumab to bind and inhibit the proliferation of a HER2-expressing breast cancer cell line.

- Functional Fc-related assays
As pertuzumab is an IgG1, it was also characterised for effector functions:

Since pertuzumab was shown to be capable *in vitro* (ELISA) of binding C1q, complement-dependent cytotoxicity (CDC) was evaluated.

Binding of pertuzumab to soluble human FcγRI, FcγRIIa R131, FcγRIIa H131, FcγRIIb, FcγRIIIa V158, FcγRIIIa F158 was assessed.

The ability of pertuzumab to induce ADCC (Antibody-dependent cell-mediated cytotoxicity) *in vitro* was confirmed using three target HER2-expressing breast cancer cell lines and two effector cell lines.

The impact of glycosylation on biological activity of pertuzumab was assessed.

- Apoptosis assay
Apoptosis was evaluated by assessing caspase-3 and -7 activity using three HER2-expressing cell lines.

B) Variants and impurities

The impurity profile of pertuzumab active substance was determined by a thorough physicochemical and biological characterisation in combination with comprehensive process validation studies that demonstrated the removal of process-related impurities.

Product-related substances conform to the peaks observed in the applied methods for size distribution, presence of fragments, dimers and higher aggregates and charge properties of pertuzumab in the dissolved state.

Potential process-related impurities include:
- Cell substrate derived impurities: host cell proteins (HCP) and DNA;
- Cell culture derived impurities;
- Downstream-derived impurities such as leached Protein A;
- Other impurities including endotoxin, bioburden.

Specification

The active substance release specifications have been suitably justified and are supported by consistent data from multiple lots. The specifications contain test for pharmacopoeial methods as well as specific methods to ensure sufficient safety and quality with respect to identity, purity, quantity, potency.

Stability

The design of the stability program, including the testing intervals and temperature storage conditions, are in accordance to current guidelines. The tests chosen are a subset of tests from the release specifications selected for stability-indicating properties.
The stability data provided were within the specifications and support a shelf life for the active substance of 36 months when stored at less than -20°C.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Pertuzumab finished product is provided as a clear to slightly opalescent, colourless to pale brown, sterile liquid solution and contains no preservatives. Each single-use 20 mL vial contains 420 mg pertuzumab for intravenous infusion. The finished product is formulated as 30 mg/mL pertuzumab in L-histidine, sucrose and polysorbate 20 at pH 6.0. These excipients are commonly used in formulating protein pharmaceuticals.

Two formulations were used over the course of product development.

Adventitious agents

No animal-derived raw materials are used directly in the pertuzumab manufacturing process. Fetal bovine serum, porcine trypsin and bovine apotransferrin were used in early development of the parental CHO cell line. Animal-derived materials are used to generate raw materials for pertuzumab manufacture. However, based on their derivation, processing and sourcing, they are not considered to be a risk with respect to TSE.

All cell banks and end-of-production cells were shown to be free of detectable microbial contaminants besides the presence of retrovirus-like particles in the cell line. These particles are non-infectious and typical of a CHO cell line. The viral testing of the cell banks is in line with the relevant guidelines.

Viral removal capacity by the pertuzumab purification process was evaluated for X-MuLV, MMV and SV40, which is the standard panel of model viruses from the Applicant for a rodent cell line. Historical platform knowledge related to viral inactivation and removal was considered by the Applicant in the demonstration of viral safety.

Manufacture of the product

The finished product manufacturing process starts with the thawing of the active substance. Multiple bulks may be pooled in a steam-sterilised stainless steel mixing vessel and then filtered. A second sterile filtration is performed in-line within a closed system directly into the filler. The finished product solution is filled into sterilised, depyrogenated Type I borosilicate glass vials. The filled vials are then stoppered, capped and crimped with an aluminium seal fitted with a plastic flip-off cap. Following vial inspection, the final product is labelled and packaged. The finished product is stored at 2°C–8°C.

Product specification

Appropriate specifications have been developed. The specifications contain tests for pharmacopoeial methods as well as specific methods.

Stability of the product

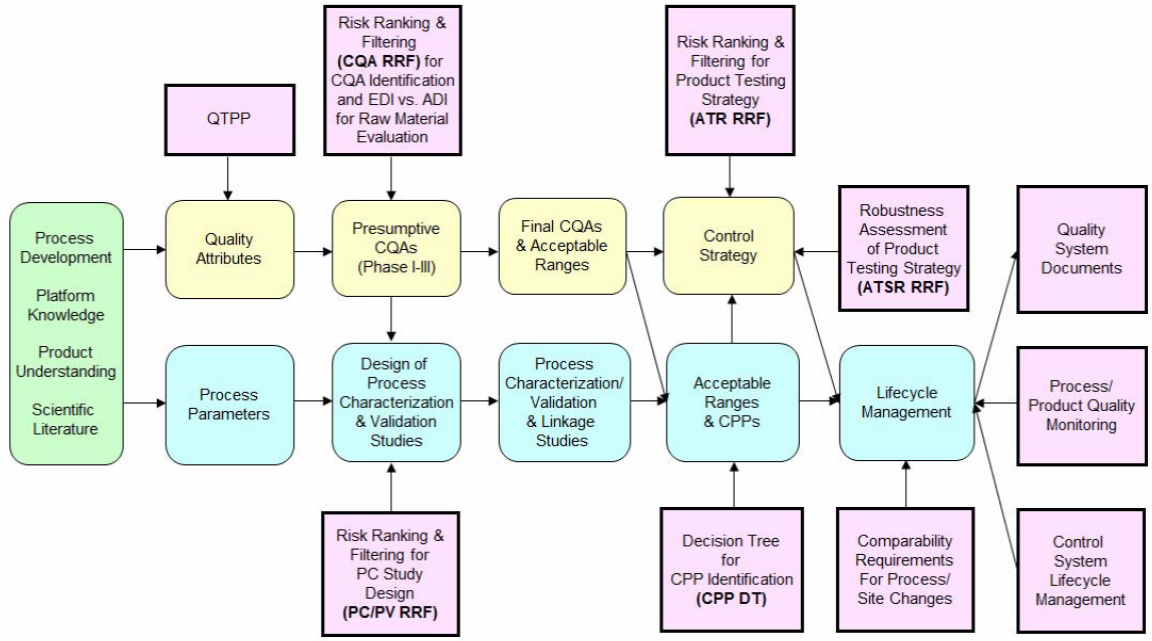
Real-time and accelerated stability studies were initiated in accordance to ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of finished product. On the basis of the data provided, the approvable shelf life for the finished product is 36 months at 2-8°C.

2.2.4. Overview of the Quality by Design approach

The standard elements in Modules 2 and 3 supporting a recombinant antibody filing are present in the pertuzumab dossier. In addition, the use of risk assessments and decision tools is described, providing transparency into the definition of Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), acceptable process parameter ranges, the active substance and finished product control systems and process monitoring. These tools have been developed as part of an integrated risk management system building on concepts expressed in ICH Q8, Q9 and Q10, and key decision criteria were calibrated using information from the Applicant's approved products. This systematic approach to risk assessment is based on an understanding of the connections between the product quality and the manufacturing process and rests strongly on platform knowledge for recombinant antibody products manufactured by the Applicant.

The decision-making framework for identification of pertuzumab CQAs and CPPs, as well as the development of an overall control strategy, are depicted in Figure 1.

Figure 1 – Approach to Implementing Quality by Design



ADI = acceptable daily intake; ATS = attribute testing strategy; ATSR = attribute testing strategy robustness; CPP = critical process parameter; CQA = critical quality attribute; DT = decision tree; EDI = estimated daily intake; PC = process characterization; PV = process validation; QTPP = quality target product profile; RRF = risk ranking and filtering.

Quality Target Product Profile

Pertuzumab is an IgG1 antibody made in a manner typical of the Applicant's platform monoclonal antibody process, using IgG1 frameworks, cell culture production host cells, process conditions, operational strategies, and the number and sequence of downstream unit operations similar to those used for several of the Applicant's licensed antibodies. Knowledge derived from this process and product platform experience, along with other relevant process development knowledge, pertuzumab product understanding (product characterisation based on prior knowledge), and relevant scientific literature, informed the Risk Ranking and Filtering (RRF) assessments that guided the identification of a Quality Target Product Profile (QTTP) and CQAs and the design of process characterisation studies.

Quality Attributes

Quality attributes are divided into the following assessment categories: product variants, process-related impurities, composition and strength, adventitious agents, other obligatory CQAs and raw materials and leachables (Table 1).

Table 1 – Categories of Product Quality Attributes for Pertuzumab

Category of Attribute	Assessment	Rationale for Approach
Product Variants Charge, Size, Glycans, Oxidation, Structure	CQA RRF	Impact to patient safety and product efficacy is specific to variant in question, the product's mechanism of action and route of administration, clinical experience, etc.
Process-Related Impurities Host Cell Protein, Host Cell DNA, Leached Protein A	CQA RRF	With appropriate justification, data from similar products can be used to assess safety in the absence of product-specific clinical experience.
Composition and Strength pH, Excipient Concentrations, Protein Concentration, Osmolality	None required, obligatory CQAs	Potentially high impact to patient safety and product efficacy.
Adventitious Agents Potential Viruses, Bioburden, Mycoplasma, Endotoxin	None required, obligatory CQAs	Potentially high impact to patient safety.
Other Appearance, Particulates	None required, obligatory CQAs	Potentially high impact to patient safety and product efficacy.
Raw Materials and Leachables Cell culture and recovery components (nutrients, trace elements, salts, buffers, etc.) including leachables from contacting materials	Comparison of EDI_0, EDI_{actual}, and ADI	Extensive data are often available from safety and toxicity assessments and can be leveraged.

ADI = acceptable daily intake; CQA = critical quality attribute; EDI_0 = estimated daily intake assuming zero clearance; EDI_{actual} = estimated daily intake with clearance; RRF = risk ranking and filtering.

Product variants

Criticality of product variants and process-related impurities was assessed using an RRF approach and acceptance criteria were established for CQAs as applicable. The CQA RRF approach involved assigning both impact (Table 2) and uncertainty (Table 3) scores to each quality attribute. Impact Scores were assigned based on the magnitude or severity of the effect on four components: bioactivity, pharmacokinetics (PK), immunogenicity, and safety. Uncertainty scores were based on the level of knowledge of the particular quality attribute. Product variants were assessed on a product-specific basis to account for the unique modifications, mechanism of action, route of administration, non clinical and clinical experience, *in vitro* studies and other factors that influence potential risk to patients. Prior knowledge was applied as applicable, in part to assess risk for process-related impurities in products manufactured using this same platform process.

Table 2 – Impact Scale for RRF Tool for Criticality Assessment of Product Variants and Process-Related Impurities

Impact and Rating	Biological Activity[a]	PK[b]	Immunogenicity[c]	Safety
Very High (20)	> 100% change	> 40% change	ATAs detected that may be life threatening	Irreversible or life-threatening AEs and/or life-threatening loss of efficacy
High[d] (16)	40%–100% change	20%–40% change with impact on PD	ATAs detected that may be associated with non-life-threatening loss of efficacy	Reversible AEs and/or loss of efficacy that is not life threatening
Moderate (12)	20%–40% change	20%–40% change with no impact on PD	ATAs detected with effect that can be managed by clinical treatment (i.e., dose titration, medication, etc.)	AEs that can be managed by clinical treatment (i.e., dose titration, medication, etc.)
Low (4)	<20% change	<20% change with no impact on PD	ATAs detected with effect on PK or PD, but no effect on safety or efficacy	Safety or efficacy effect with minimal clinical significance
None (2)	No change	No impact on PK or PD	ATAs not detected or ATAs detected with no effect on PK, PD, safety, or efficacy	No effect on safety or efficacy

AE = adverse event; ATA = anti-therapeutic antibody; PD = pharmacodynamics; PK = pharmacokinetics.

[a] Based on clinically relevant potency assay results of isolated variants relative to reference standard.

[b] Serum exposure (area under the curve) or relevant in vitro clearance receptor binding (FcRn and mannose receptor). PD considered if information is available.

[c] Effect observed in clinical studies. Prior to clinical experience, product variants known to be present on plasma-derived antibodies are given a score of 2.

[d] Attributes for which no information is available must be ranked as High (16) until further data are collected.

Table 3 - Uncertainty Scale for RRF Tool for Criticality Assessment of Product Variants and Process-Related Impurities

Rank	Uncertainty	Description (Product Variants and Host Cell–Derived Impurities)
7	Very High	No information (new variant).
5	High	Published external literature on variant in related molecule.
3	Moderate	Nonclinical or in vitro data on this molecule. Data (nonclinical, in vitro, or clinical) on a similar class of molecule.
2	Low	Variant has been present in material used in clinical studies.[a]
1	Very Low	Impact of specific variant established in clinical studies with this molecule.

[a] Applies to assigning impact for immunogenicity and safety; typically does not apply to pharmacokinetics or biological activity.

Risk score for product variants and process related impurities is obtained by multiplying impact rating with uncertainty (Table 4).

Table 4 - Risk Scoring for Product Variants and Process-Related Impurities

Uncertainty[a] / Impact[b]	1 (Very Low)	2 (Low)	3 (Moderate)	5 (High)	7 (Very High)
20 (Very High)	20	40	60	100	
16 (High)	16	32	48	80	112
12 (Moderate)	12[c]	24	36	60	
4 (Low)	4	8	12	20	
2 (None)	2	4	6	10	

Note: Light green indicates low-risk attributes (non-CQAs); light red indicates high-risk attributes (CQAs). Boxes blacked out indicate Impact and Uncertainty combinations that are disallowed because Very High Uncertainty attributes are assigned a default impact of 17.
a Uncertainty scales are defined in Table 18.
b Risk scales are defined in Table 17.
c The combination of Uncertainty of 1 and Impact of 12 is categorised as CQA.

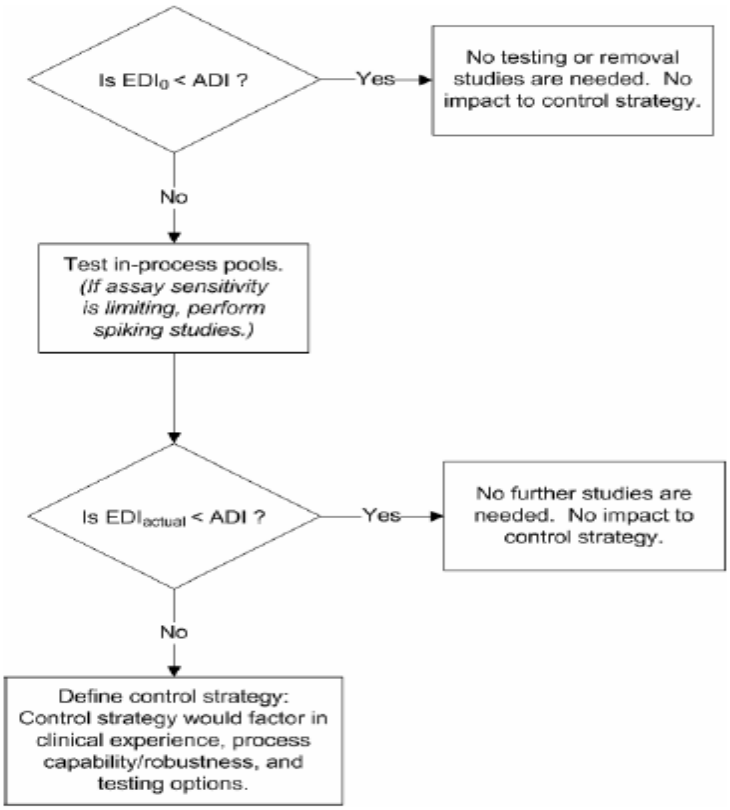
Obligatory CQA

Regulatory requirements specify that certain attributes in the composition/strength and adventitious agent categories must always be controlled. Therefore, these attributes were classified as obligatory CQAs and were not subject to further evaluation. For these attributes, appropriate process and analytical controls were implemented.

Raw materials

Raw materials were evaluated for potential toxicity by considering an Estimated Daily Intake, assuming no clearance in the process or with clearance, compared to the Acceptable Daily Intake (Figure 2). This approach was taken as a means to evaluate and express theoretical risk to patients related to the presence of these materials. In practice, these materials are consistently removed by the process. In many cases, raw materials are common to the Applicant's platform CHO antibody process.

Figure 2 – Approach to Assessing Risk Associated with Pertuzumab Raw Materials



ADI = acceptable daily intake; EDI_0 = estimated daily intake assuming zero clearance; EDI_{actual} = estimated daily intake with clearance.

Leachables

The approach for identification of specific leachable as CQAs is dependent on whether a specific compound can be detected. If a specific leachable is shown to exceed acceptable and safe levels, that compound may be designated as a CQA.

Establishing Acceptance Criteria for CQAs (CQA-AC)

CQA-ACs are generally based on information that links quality attribute to product safety and/or efficacy. These acceptance criteria are used to design cell culture, purification, and finished product process characterisation studies to identify CPPs. Degradation of the active substance and finished product during processing and storage is considered in order to ensure consistent delivery of product that conforms to specifications throughout its shelf life.

The general approach to setting acceptance criteria for CQAs is shown in Table 5.

Table 5 – Approach to Setting Acceptance Criteria for Pertuzumab CQAs

Category of Attribute	Basis for Setting CQA Acceptable Ranges	Rationale for Approach
Product Variants Charge, Size, Glycans, Oxidation, Structure	Product-specific and platform knowledge	Dependent on impact variant has on safety and efficacy. Levels of the same variant found in similar products[a] may be used to support establishing safe ranges to supplement product-specific clinical experience.
Process-Related Impurities Host Cell Protein, DNA, Leached Protein A	Product-specific and platform knowledge	Levels of the same impurity found in similar products may be used to support establishing safe ranges to supplement product-specific clinical experience.
Obligatory Requirements pH, Excipient Concentrations, Protein Concentration, Appearance, Particulates, Osmolality	Align with Health Authority and Sponsor expectations	Potentially high impact to safety and product efficacy.
Adventitious Agents Potential Viruses, Bioburden, Mycoplasma, Endotoxin	Align with Health Authority and Sponsor expectations	Potentially high impact to safety.
Raw Materials and Leachables Cell culture and recovery components (nutrients, trace elements, salts, buffers, etc.) including leachables from contacting materials	Prior knowledge and safety assessments used to establish Acceptable Daily Intake	Data from similar products and extensive studies of raw materials and leachables from product-contacting materials can be used to establish safe ranges.

CQA = critical quality attribute.

[a] Requires justification including patient population, indication, dose, treatment duration, route of administration, and potential mechanisms of action.

For attributes of high criticality due to safety or immunogenicity concerns, CQA-ACs are based closely on product-specific clinical experience, augmented by applicable knowledge gained from similar products and processes.

For attributes critical because of potential impacts on potency or PK, data collected from clinical and non-clinical experience with pertuzumab as well as similar products were considered when appropriate to justify wider acceptance criteria. The cumulative impact of attributes on potency or PK is not allowed to exceed ± 20% (potency) or –20% to + 25% (PK). Specific acceptance criteria for attributes related to potency and PK are ultimately set considering process performance data, with the objective of ensuring robust parametric control of each attribute, minimising the need to test directly during Quality batch release or stability testing. A proportionality factor was applied that takes into account the relative potency of the attribute determined from an *in vitro* biological assay or the relative area under the curve for a particular attribute determined from PK studies compared to the control.

Process characterisation and validation

The complete process characterisation and validation project includes studies conducted using a combination of scale-down models and full-scale equipment. Site- and scale-independent characterisation studies to support identification of CPPs were conducted using scale-down models of the manufacturing-scale unit operations. These studies were designed by integrating process understanding developed during process and product development, platform knowledge and scientific and engineering principles.

- **Scale-down model qualification**

The pertuzumab scale-down model was qualified based primarily on the comparison of small scale and manufacturing scale averages for each KPI (Key Performance Indicator), non-CQA and CQA relevant to the unit operation.

- **Risk assessment of each unit operation**

After identification of pertuzumab CQAs, and following collection of sufficient process knowledge during early development, a risk assessment of each unit operation in the pertuzumab manufacturing process (RRF) was performed to identify parameters that may potentially have critical impact to the quality of pertuzumab (CQAs) or to process performance through impact to KPIs. By this process, parameters are ranked based on the estimated severity of the parameter's direct effect on a product quality attribute or KPI, or its potential effect through interactions with other parameters. The rankings for impact to CQAs are scaled more steeply than for non-CQAs and for KPIs (Table 6).

The parameters considered for each unit operation were based on the function and operating principles of the unit operation and required outputs (for example cell mass generation, product generation, host cell impurity clearance, aggregate removal, etc). The output of the RRF procedure is a recommendation on the minimum level of complexity with which parameters should be characterised.

Table 6 – Impact Description and Corresponding Ranking for Pertuzumab Process Characterisation / Process Validation RRF

Impact Description	Rank	
	Critical Quality Attribute (CQA)	Noncritical Product Quality Attribute or KPI
No Impact	1	1
Minor Impact	4	2
Major Impact	8	4

Note: Effect is considered for variation of parameter across a proposed characterization range.

KPI = key performance indicator.

Definitions for the relative impact descriptions are provided in Table 7.

Table 7 – Impact Descriptions and Definitions for Pertuzumab Process Characterisation / Process Validation RRF

Impact Description	Definition
No Impact	Effect causes variation in process output that is not expected to be detectable (e.g., no effect or within assay variability)
Minor Impact	Effect causes variation in process output that is expected to be within acceptable range
Major Impact	Effect causes variation in process output that is expected to be outside acceptable range

Note: Effect is considered for variation of parameter across a proposed characterisation range.

Main effect and interaction effect impact ranks are multiplied to generate an overall Severity Score. The minimum level of experimental complexity for characterising the parameter is determined based on the Severity Score as summarised in Table 8.

Table 8 – Severity Scoring for Pertuzumab Process Characterisation / Process Validation RRF

Main Effect Ranking	Severity Score			
8	8	16	32	64
4	4	8	16	32
2	2	4	8	16
1	1	2	4	8
	1	2	4	8
	Interaction Effect Ranking			

Three potential experimental design strategies are available for characterising a parameter: inclusion in a multivariate study, in an univariate study, or no further study needed (Table 9). The highest score assigned to a process parameter between impact to CQA, non-CQA and KPI is used to determine how this process parameter should be characterised.

Table 9 – Experimental Design Strategies Based on Severity Score for Pertuzumab Process Characterisation

Severity Score	Experimental Strategy
≥ 32	Multivariate study
8–16	Multivariate study, or univariate with justification
4	Univariate study acceptable
≤ 2	No additional study required

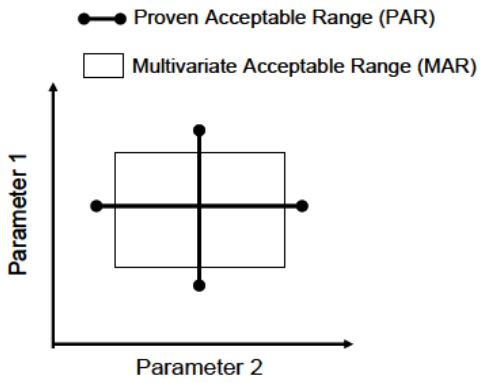
- **Univariate and multivariate studies**

The Process Characterisation/Process Validation RRF outcomes provide a systematic recommendation for the design of univariate studies and for multivariate Design of Experiments (DoE) required to characterise product variability in response to variation in process conditions. These studies provide the basis for identification of CPPs. These studies also allow identification of worst-case conditions for CPPs for each unit operation, enabling the performance of worst-case linkage studies that challenge overall process robustness.

To provide an additional degree of assurance that the manufacturing process will deliver product that consistently meets CQA-ACs, the results of process characterisation studies are compared to a more conservative CQA target range (CQA-TR). The CQA-TR is derived by narrowing the CQA-AC and is intended to account for some of the uncertainties associated with the use of scale-down systems and statistical modeling.

Two different types of acceptable ranges are defined for a process parameter: proven acceptable range (PAR) and multivariate acceptable range (MAR). As defined in ICH Q8, a PAR is the characterised range of a process parameter for which operation within this range, while keeping other parameters at target, will result in a product meeting relevant quality criteria. PARs can be used to resolve manufacturing deviations (single-parameter excursions). A MAR is defined by the Applicant as the range of a parameter that results in acceptable product quality when all parameters tested are varied across their acceptable ranges. PARs are usually wider than MARs for the same parameter (as illustrated in Figure 3) and may be established from univariate experiments, but may also be derived from multivariate data where this is most efficient. MARs are typically established from multivariate experiments, but may be derived from univariate data where it is known that the parameter does not interact with other parameters. MARs and PARs are established for all process parameters included in process characterisation and validation studies, whether or not they are eventually classified as critical. It is expected that an excursion of a process parameter from its MAR will result in an investigation. PARs will be used only to evaluate the impact of a deviation from the MAR.

Figure 3 – Acceptable Parameter Ranges



Identification of CPPs

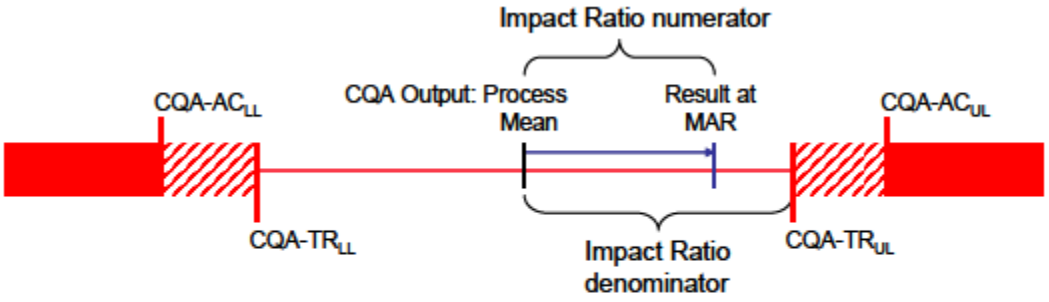
Impact Ratio

A parameter is identified by the Applicant as a CPP when its variation has a practically significant impact on a CQA. Practical significance is expressed as a quantitative metric, the Impact Ratio:

$$\text{Impact Ratio} = \frac{\left|\text{Process Mean} - \text{MAR Result}\right|}{\left|\text{Process Mean} - \text{CQA-TR}\right|}$$

The process mean term represents the mean CQA response when the process is operated at target and the MAR result is the expected value of the CQA response when the parameter is set to its MAR limit. The Impact Ratio numerator is the effect on a CQA due to moving the process parameter from its target value to its MAR limit. It is derived from the Estimate (β) of a linear regression analysis. The denominator is the absolute difference between the mean CQA response and the closest CQA-TR limit, when the process is run under target conditions. Conceptually, the numerator represents how much a CQA may vary when a process parameter is moved to the edge of its MAR, while the denominator represents how much CQA variability is allowed before the CQA approaches its CQA-TR. A graphical representation of this concept is shown Figure 4.

Figure 4 – Graphical Conceptualisation of Impact Ratio Terms for Pertuzumab CPP Identification



CQA-AC$_{LL}$ = lower limit of CQA-AC; CQA-AC$_{UL}$ = upper limit of CQA-AC;
CQA-TR$_{LL}$ = lower limit of CQA-TR; CQA-TR$_{UL}$ = upper limit of CQA-TR.

Impact Ratios are also calculated for interactions, where the quantity in the numerator represents the *additional* variation in a CQA response due to operation of two process parameters at the limit of their MARs *beyond* the variation due to each process parameter individually.

CQA-TRs are calculated for the final step of a process, either bulk active substance or finished product. CQA-TRs are translated to upstream steps to assess outcomes of studies on those unit operations. In some cases a CQA-TR cannot be translated upstream, for example when a high degree of change occurs across the process, and a CQA-TR cannot be determined for CQA results in those unit operations. This is the case for some impurities that have substantial clearance across the purification steps (e.g. HCP in upstream pools due to significance clearance during further purification). When a CQA-TR cannot be defined, the allowable variation is expressed as a function of the process mean, i.e. a degree of variation away from the process mean, as defined by the impact ratio threshold. This is also applicable to the impact ratio calculation of quality attributes which are not CQAs.

$$\frac{|Effect\ (\beta)|}{|Process\ Mean|}$$

A scale offset was applied or not to take into account an observed difference in means between results from manufacturing scale and small scale for a given process attribute. It was applied as needed for outputs classified as “Not Equivalent” or “Probable Non-Equivalence” in order to provide a more predictive scale-down model for interpreting process characterisation and worst-case linkage results:

$$\frac{|Effect\ (\beta)|}{|(Process\ Mean + Scale\ Offset) - CQA.TR|}$$

Based on process characterisation study results for individual unit operations, an initial assessment is performed using the Impact Ratio to classify parameters as high-impact, low-impact, or non-impact with the following criteria:

- Impact Ratio > 0.33: high-impact
- 0.33 ≥ Impact Ratio ≥ 0.10: low-impact
- 0.10 > Impact Ratio: non-impact

Selection of the cut-off values of 0.33 and 0.10 are based on likelihood of multiple process parameters simultaneously operating at their worst-case conditions.

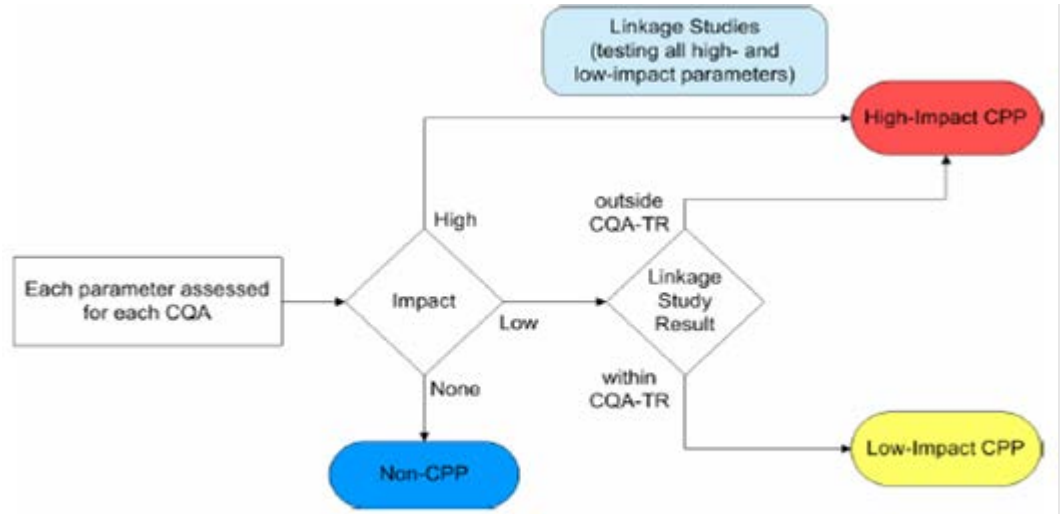
Worst case linkage studies

Linkage studies spanning the manufacturing process are performed. For each CQA, the study includes at minimum, worst-case conditions for all parameters meeting the criteria for high- and low-impact. Based on the results of this study, parameters initially categorised as low impact either remain low-impact based on the acceptable outcome of the linkage study (i.e. the CQA result is within the CQA-TR), or they are reclassified as high-impact CPPs. Parameters initially categorised as high impact remain identified as high-impact regardless of linkage study results. For pertuzumab, there were no linkage studies that resulted in CQA results outside the CQA-TRs.

Designation of CPP / non-CPP

The cumulative data collected during process characterisation and validation were considered in identifying CPPs. Process parameters are ultimately categorised by the Applicant as high-impact CPPs, low-impact CPPs, or non-CPPs by a decision tree (Figure 5).

Figure 5 – Overall Decision Tree for Pertuzumab CPP Identification



CPP = critical process parameter; CQA = critical quality attribute; CQA-TR = critical quality attribute target range.

Control strategy

The pertuzumab overall control strategy comprises:

- Raw material control
- Robust process control via procedural and process parameter control
- In-process, batch release, and stability testing
- Testing done as part of process monitoring
- Testing to demonstrate comparability.

These measures assure all pertuzumab CQAs remain within acceptable ranges.

RRF assessment for Attribute Testing Strategy

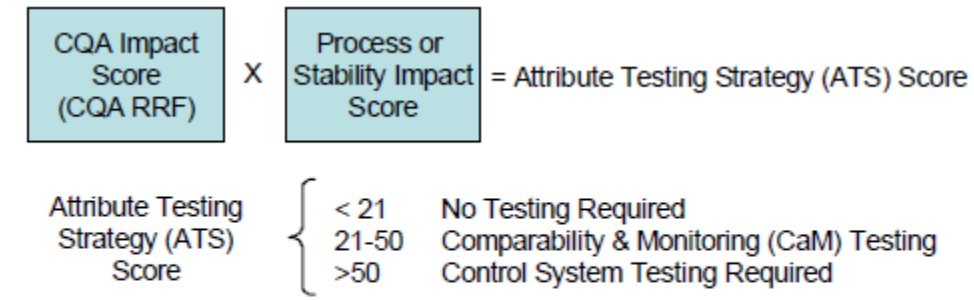
The RRF tool for determining the Attribute Testing Strategy (ATS RRF) is shown in Figure 6. The tool multiplies the score for impact of a quality attribute (Table 2) with a score representing either the impact from the manufacturing process (Figure 7) or the attribute stability during storage of active substance and finished product (Figure 8).

In addition to determining the testing strategy for the product and process-related variants by this tool, the assessment was also performed for attributes considered to be obligatory due to statutory testing

requirements and for formulation components. For obligatory CQAs such as protein concentration, the CQA Impact Score is assigned as 20 for the purposes of this assessment.

The evaluation is performed identically for the active substance and finished product manufacturing processes.

Figure 6 – Attribute Testing Strategy Ranking Filter (ATS RRF)

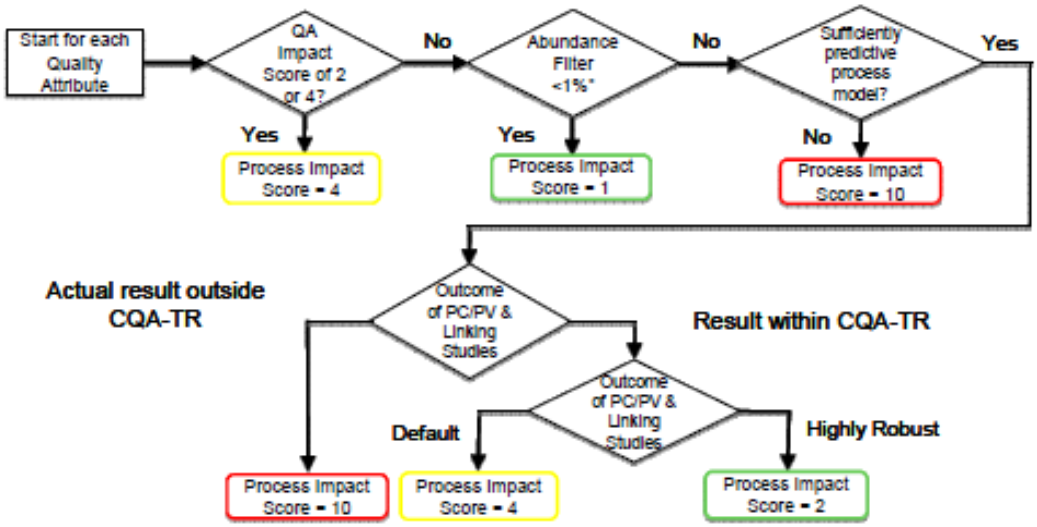


CQA = critical quality attribute.

Note: The highest Impact Score is used for each CQA.

The Process Impact score represents an estimation of the residual risk that a CQA could exceed its CQA-TR when the process is operated within the acceptable ranges (Figure 7).

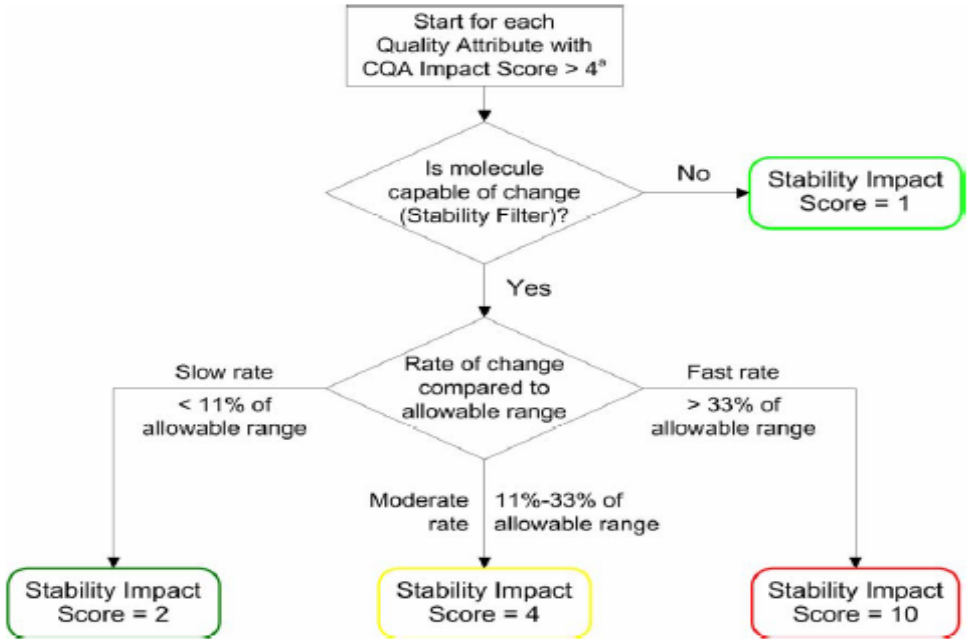
Figure 7 – Decision Tree for Assigning the Process Impact Score



* Applies to product-related variants only. Abundance threshold for aggregates is < 0.1%; threshold for some sequence variants is < 0.2%.

The Stability Impact score represents the residual risk that an attribute will exceed its CQA-AC during active substance and finished product storage at the recommended conditions. It is used in combination with the CQA Impact score to generate an ATS score for the active substance and finished product that assesses whether or not testing of an attribute should be performed as part of the stability program (Figure 8).

Figure 8 – Decision Tree for Assigning the Stability Impact Score



CQA = critical quality attribute.
[a] For attributes with CQA Impact Score of 2 or 4, Stability Impact Score is assigned as 4.

Three outcomes of the ATS RRF assessment are possible:

- Control System testing is required (in-process, batch release, and/or stability testing)
- Testing is required as part of process monitoring or to support comparability: attributes in this category are tested as part of process monitoring under a process validation protocol and/or evaluated during change assessments.
- No testing is required.

Testing Strategy Robustness

The final testing strategy for each attribute was assessed for its robustness using the Attribute Testing Strategy Robustness (ATSR) RRF tool to determine the risk to the overall program that a quality attribute is missed by the defined control strategy (Figure 9, Tables 10 and 11). The type of measurement (i.e. direct versus indirect measurement) as well as its sensitivity and robustness were considered. For the proposed pertuzumab control strategies for the active substance and finished product, each CQA was judged to be adequately controlled.

Figure 9 – RRF for Assessment of the Robustness of the proposed Testing Strategy for Quality Attributes

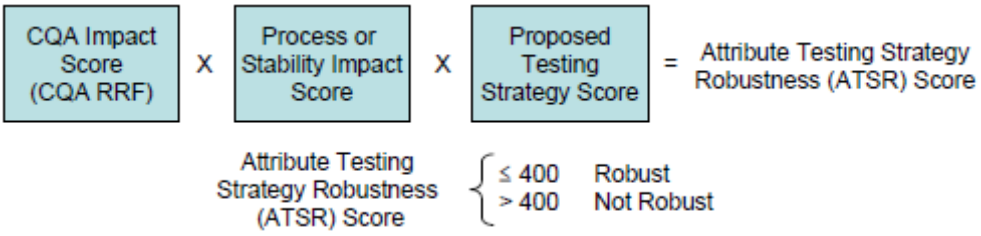


Table 10 – Proposed Testing Strategy Scoring for ATSR RRF

Testing Strategy Score	Description
2	Attribute is measured directly with a highly sensitive and precise assay (IP, BR, or S).
4	The impact of an attribute is measured in a surrogate assay, is measured collectively, or is measured directly with a relatively insensitive assay (IP, BR, or S).
6	The attribute is monitored directly, collectively, or via a surrogate assay *only* during CaM testing.
10	No testing is required.

ATSR = attribute testing strategy robustness; CaM = Comparability and Monitoring; IP = in-process; BR = batch release; RRF = risk ranking and filtering; S = stability.

Table 11 – ATSR Scoring Matrix

ATS Score / Testing Strategy Score	8	16	24	32	40	48	64	80	120	160	200
2							128	160	240	320	400
4							256	320	480	640	800
6			144	192	240	288					
10	80	160									

ATSR Scoring	
≤ 400	Robust Testing Strategy
> 400	Non-Robust Testing Strategy

Regardless of whether the attribute is tested through the Applicant's in-process, batch release or stability testing, or is monitored as a part of ongoing process monitoring, the management of the attribute during the post-approval lifecycle of the commercial pertuzumab process is defined in a process monitoring protocol required by the Applicant's Pharmaceutical Quality System.

Comparability testing
Testing to support comparability assessments includes tests that are performed as part of batch release, stability and in-process testing as well as additional testing of selected attributes. For stability studies performed as part of comparability exercises, the assays selected will include those assays performed as part of the normal stability program as well as additional assays to measure selected attributes, if appropriate.

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

A) Aspects related to Quality by Design

Consistent manufacture of a medicinal product of acceptable quality was demonstrated. The thorough work to develop a manufacturing process by use of QbD concepts was acknowledged. Whilst Major Objections were raised during the evaluation, some QbD principles and elements, for example the use of platform knowledge, the extension of CQA-AC beyond clinical experience, the use of Risk Ranking and Filtering (RRF) tool to assign criticality to quality attributes, were endorsed and the Major Objections were appropriately addressed by the Applicant.

Quality Attribute Criticality
Pertuzumab variants and process-related impurities were thoroughly characterised.
The principle of applying a RRF tool, based on impact to biological activity, pharmacokinetics, immunogenicity and safety and on the uncertainty of that impact, in order to define quality attribute criticality was endorsed. A conservative approach was taken for CQA designation.

ADCC in the mode of action of pertuzumab was unclear but could not be totally dismissed according to the data presented (characterisation and non clinical). Assessment of the fucosylation pattern, which can impact ADCC activity, was initially not taken into consideration as part of the control strategy. This was considered as a Major Objection.

In their response, the Applicant provided a justification to support their view that ADCC activity does not add to the efficacy of pertuzumab. However, the Applicant acknowledged that residual risk from ADCC impacting variants cannot be totally excluded.

The Applicant evaluated various attributes in relation to a possible increased or decreased impact on ADCC. Studies clearly demonstrated that afucosylation increases *in vitro* ADCC and the predominant afucosylated form, G0-F, gives a strong correlation with ADCC. G0-F was added to the list of CQAs. The Attribute Testing Strategy (ATS) RRF tool was applied to G0-F to determine the suitable testing strategy and it was concluded that this attribute needs to be tested as part of the active substance Control System testing. Currently, and until the method is finally validated, the test is part of the process validation protocol. The Applicant will have to apply for a variation to add %G0-F to the active substance release specifications.

The CQA-ACs and specifications initially proposed by the Applicant for selected attributes, taking into consideration the experience with other monoclonal antibody products licensed by the Applicant, were not considered acceptable. In their Day 180 responses, the Applicant tightened the proposed limits to be more in line with levels found in clinical batches. The revised limits were considered acceptable.

The principle applied for the assessment of raw materials in relation to Acceptable Daily Intake (ADI) and removal was acknowledged. Impact of raw material variability on the process was also discussed. The Applicant claimed both product-specific and platform knowledge with regard to raw material variability. The Applicant considered that variability of raw materials discussed and its impact on the process are not significant and that the current raw material specifications provide sufficient control. The justification and supportive data provided were considered acceptable.

There was also discussion on the setting of the CQA Target Range (CQA-TR) from the corresponding CQA-AC and discussion on the setting of CQA-ACs for certain CQAs.

Design Space

A “process-wide” Design Space for the active substance manufacturing process was initially applied including unit operations, process parameters with their associated Multivariate Acceptable Ranges that define the limits of the Design Space and raw materials.

The principles used to define the proposed Design Space were endorsed. However, there were several issues which, taken together, led to a Major Objection at Day 120 and Day 180 of the procedure that precluded the approval of the Design Space.
As a consequence, the claimed Design Space was withdrawn. CHMP acknowledged the efforts made by the Applicant on the development of a Design Space. There is the possibility to reapply for a Design Space post-approval.

Process Parameter Criticality

The strategy to conduct a risk assessment of each unit operation in order to estimate the impact of process parameters on CQAs, non-CQAs and KPIs, with the subsequent determination of a severity score to determine the conduct of univariate and multivariate studies, was endorsed.

It was acknowledged that the concept of Impact Ratio is an objective measure of process parameter criticality. However, a Major Objection was raised. It was considered that the calculation of this Impact Ratio could be affected by potential sources of bias related to:
- The adequacy of the statistical multivariate models which could then affect the effect estimates;
- The offset introduction which could lead to inaccurate predictions for scale differences.

Justification was provided for the different possible calculations of an Impact Ratio and the choice of the cut-off values of 0.10 and 0.33.

Following narrowing of the CQA-AC for selected attributes at Day 180, with consequential narrowing of the respective CQA-TR, the process characterisation was reviewed and validation data associated with these CQAs and determined that for use in a traditional process description without a Design Space

claim, no further narrowing of the process parameter ranges is required and no additional parameters were elevated to CPPs.

Post-Approval Lifecycle Management (PALM) plan

A PALM plan was initially proposed to describe how the Applicant would:
- Perform real-time and/or retrospective monitoring of process and product attributes (CPP and KPI excursions, quality attributes in the Control System testing and those classified as CaM attributes);
- Manage changes in attribute criticality;
- Manage changes to CPPs and non-CPPs;
- Update the Control System as necessary based on additional process and product knowledge gained;
- Manage the PALM plan in the Pharmaceutical Quality System.

The principle of implementing such a PALM plan was fully endorsed as part of the QbD approach developed by the Applicant. Following the withdrawal of the Design Space, the PALM plan was removed from the dossier.

B) Other Quality aspects

Active substance

The description of the manufacturing process is satisfactory.

The cell culture process and purification process were carefully characterised.

The few “other concerns” identified in relation to process validation/evaluation were satisfactorily addressed.

The characterisation data presented support the conclusion that pertuzumab has the structure expected for a recombinant humanised monoclonal antibody expressed in CHO cells. Product variants and process-related impurities were quantified and were consistent with those described for several other monoclonal antibody products. Biological and immunological characterisation demonstrated that pertuzumab inhibits cell proliferation by blocking the association of HER2 with other members of the HER receptor family.

The analytical methods used to control the active substance were adequately described and validated.

The setting of the active substance and finished product specifications for potency by bioassay are considered acceptable.

On the basis of the primary stability data on registration batches, the representative stability data on Phase 3 batches and the comparability established between them, a shelf life of 36 months at -20°C was considered acceptable.

Finished product

The manufacturing process of the finished product was adequately described and process validation was considered satisfactory.

Data to support pharmaceutical development of pertuzumab finished product were satisfactory.

The analytical methods used to control the finished product were adequately described and validated.

The release and shelf life specifications for the finished product were adequately justified.

The proposed shelf life of 36 months at 2°C–8°C for pertuzumab finished product is considered acceptable.

Adventitious agents safety evaluation

Data provided to demonstrate adventitious agents safety were considered satisfactory.

Cell growth issue

During the Q1/Q2 2012 active substance manufacturing campaign, issues were experienced with the thaw and subsequent propagation of cells from the Working Cell Bank. The Applicant has provided updates on the issues and has worked with Health Authorities to ensure a consistent manufacturing process.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of pertuzumab is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The cell culture and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.
The overall Quality of Perjeta is considered acceptable.

2.2.7. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended a couple of points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development program comprises of pharmacology, pharmacokinetic and toxicology studies. As required, the pivotal toxicity studies were conducted in accordance with Good Laboratory Practice (GLP). Supportive non-GLP studies were claimed to apply to good scientific practice.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Pertuzumab binds to a region of HER2 involved in receptor dimerisation with a binding affinity of 0.8 nM. Pertuzumab sterically interferes with HER2 dimerisation and thus signaling. It was demonstrated *in vitro* that, in contrast to trastuzumab, pertuzumab is able to inhibit the association of HER2 with EGFR/HER1 and HER3 receptors. Similarly, it was shown *in vitro* that pertuzumab but not trastuzumab inhibited HER2 signalling following HER3 activation. This was evidenced via an absence of HER2 and HER3 phosphorylation as well the lack of activation of the MAPK and PI3K signalling pathways following pertuzumab treatment.

Combination treatment of BT474 breast cancer cells with trastuzumab and pertuzumab for 24 hours caused a dose-dependent downregulation of total and phosphorylated HER2 expression levels to a greater extent than either single agent. The combination of trastuzumab and pertuzumab reduced levels of active phospho-Akt (PI3K pathway) to a greater degree *versus* either agent alone. In contrast, signalling from the MAPK cascade was not inhibited.

In vitro experiments in which HER2-positive human tumour cells KPL-4 and Calu-3 were used as target cells and human peripheral blood mononuclear cells were used as effector cells showed that pertuzumab activates antibody-dependent cellular cytotoxicity (ADCC) with identical potency as trastuzumab. This is to be expected since pertuzumab and trastuzumab have identical Fc regions. No decrease in potency was observed when both agents were used in combination at the same individual concentration as applied during monotherapy testing. While it was found that pertuzumab had the ability to bind complement C1q, pertuzumab treatment was not associated with complement-dependent cytotoxicity (CDC) in neither of the tested breast cancer cell lines (MDA-MB-175-VII and BT474). The lack of CDC activity *in vitro* was ascribed the presence of complement inhibitory proteins in breast cancer tumour cells which protect these cells from complement-mediated lysis. While

pertuzumab was able to induce apoptosis in MDA-MB-175-VII cells which have a low to moderate HER2 expression it did not induce apoptosis in breast cancer cell lines with a high HER2 expression (BT474 cells and SKBR3 cells). Considering that pertuzumab is indicated in patients with tumour expressing high levels of HER2, this finding questions to what extent pertuzumab-mediated tumour cell apoptosis occurs in the *in vivo* setting.

Pertuzumab inhibited the heregulin (HER3 and HER4 ligand) stimulated growth of three cell lines expressing low/normal levels of HER2, namely the breast cancer cell lines MCF7 and T47D and the ovarian cancer cell line Caov3. Furthermore, pertuzumab inhibited EGF-induced growth induction in various breast cancer cell lines. While the individual drugs did not alter cell survival, the 1:1 combination of trastuzumab and pertuzumab synergistically inhibited the growth of the HER2 overexpressing breast cancer cell line BT474.

Weekly IV/IP administrations of pertuzumab demonstrated anti-tumour efficacy in various tumour xenografts models based on breast cancer, prostate, non-small cell lung cancer and ovarian cell lines expressing either low or high levels of HER2. Treatment efficacy was monitored using tumour volume. Based on pharmacodynamic/pharmacokinetic analysis, more than 80% tumour growth inhibition was observed at trough pertuzumab serum concentrations ranging from 5 to 25 µg/mL. However, in a xenograft model based on a trastuzumab-resistant cell line (Founder 2-134R) only around 50% tumour growth inhibition was observed at trough pertuzumab serum concentrations of ≥ 50 µg/mL.

While both pertuzumab and trastuzumab as single agents exhibited anti-tumour activity against HER2 overexpressing Calu-3 NSCLC xenografts (85% and 82% TGI), the combination of the two was superior compared with monotherapy, resulting in tumour regression and, in some cases, complete remission. Moreover, although not statistically significant, combined treatment with pertuzumab and trastuzumab appeared to result in a higher tumour growth inhibition in the breast cancer cell line MDA-MB-175 xenograft model than the individual drugs alone.

The anti-tumour activity of pertuzumab (100 mg/kg IP once or twice weekly) was evaluated in nude mice implanted with patient-derived tumours representing breast cancer, ovarian cancer and NSCLC. Pertuzumab exhibited 13-45% tumour growth inhibition in 1 of 6 tested breast tumour, 1 of 4 ovarian cancer tumour and 4 out of 18 NSCLC tumour xenograft models. The other tested xenografts were refractory to pertuzumab single-treatment. The Applicant has clarified that the lack of activity in the in patient-derived breast tumour xenografts could be ascribed to the finding that the patient-derived tumours were HER2 negative.

Secondary pharmacodynamic studies

In a study of pertuzumab cross-reactivity with normal human tissues, pertuzumab binding was demonstrated in a membranous pattern with normal human tonsil, parathyroid gland, mammary gland, haired skin, ureter, urinary bladder, placenta, and kidney tissues. In a Cynomolgus monkey tissue panel, pertuzumab binding was demonstrated in a membranous pattern with sweat and sebaceous glands, mammary gland, placenta, kidney, ureter, urinary bladder, and prostate gland. Overall, the immunohistochemical cross-reactivity profile of pertuzumab was in general agreement with the literature on the HER2/neu expression and data from the cross-reactivity study conducted with trastuzumab.

Safety pharmacology programme

No dedicated safety pharmacology studies were submitted. However, an evaluation of the risk for effects on the respiratory and cardiovascular system was performed.

Safety pharmacology end points were incorporated into the 7-week IV repeat-dose toxicology study in Cynomolgus monkeys where no effect on rectal body temperature, respiration rate, blood pressure, heart rate, or electrocardiographic (ECG) parameters were seen at doses up to 150 mg/kg/week. Moreover, in the 26-week repeat-dose toxicity study, no ECG, respiratory or blood pressure findings were made in Cynomolgus monkeys dosed up to 150 mg/kg/week.

Cardiotoxicity has been reported to occur with trastuzumab when administered alone or in combination with antineoplastic agents, particularly anthracyclines. Pertuzumab was not associated with cardiotoxicity in the 7- and 26-week repeat-dose toxicity studies since treatment-related findings were neither made in the troponin T analysis nor in the microscopic examination on the heart. Despite targeting the same HER2 receptor pathway as trastuzumab, pertuzumab appears to add no significant cardiac toxicity in the clinic when given with trastuzumab. Regarding the potential for inducing CNS effects, no effects on the general behaviour of the animals were apparent in the 7- and 26-week toxicity studies. Moreover, it is unlikely that pertuzumab will enter the central nervous system to a significant extent unless the blood-brain barrier is compromised.

hERG and Purkinje fibre assays were not performed and are not required for biotech products.

Pharmacodynamic drug interactions

The anti-tumour efficacy of pertuzumab was investigated in combination with other anti-cancer agents (cisplatin, gemcitabine, capecitabine, erlotinib, paclitaxel and bevacizumab) in several xenograft models for non-small cell lung carcinoma, colon carcinoma, mammary tumour, and ovarian carcinoma. Generally, combination therapy was superior to the corresponding monotherapies. Responses were in some cases dependent on tumour type.

2.3.3. Pharmacokinetics

Method of analysis

A sandwich enzyme-linked immunosorbent assay (ELISA) was validated to quantify pertuzumab in CD1 mouse, Nude mouse, and Sprague-Dawley rat serum. A second sandwich ELISA was validated to quantify pertuzumab in Cynomolgus monkey serum. The following parameters were tested for both assays: limit of detection, limit of quantification, accuracy and linearity, specificity, precision, robustness, ruggedness, and stability. Because the method in Cynomolgus monkeys was later retired, a third sandwich ELISA was also validated to quantitate pertuzumab in human serum, Cynomolgus monkey adult serum, Cynomolgus monkey foetal serum, and Cynomolgus monkey amniotic fluid.

An antibody bridging ELISA was validated to detect antibodies (Anti-therapeutic antibodies – ATA) to pertuzumab in Cynomolgus monkey serum. The following parameters were tested: cut-point determination, relative sensitivity, precision, cross-reactivity, interference, robustness, ruggedness, and stability.

ELISA methods were validated and used to support the pharmacokinetic and toxicity studies. The methods were validated under non-GLP conditions, however, as they were performed and reported to good scientific standard this is acceptable. Overall, the methods of analysis are considered sufficiently validated.

Absorption

Pertuzumab serum exposure was evaluated in mice (IV and IP), rats (IV and SC) and Cynomolgus monkeys (IV and SC). After a single IV bolus dose in Cynomolgus monkeys of pertuzumab a linear relationship between dose and clearance was observed. The clearance (CL) was 4.98, 5.23 and 5.24

ml/day/kg for doses of 15, 50 and 150 mg/kg, respectively. Volume of distribution in central compartments (Vc) approximated the serum volume, ranging from 30.9-37.4 ml/kg. Mean values for volume of distribution at steady state (Vss) ranged from 68.1-72.7 ml/kg. These volumes did not vary with dose. The mean terminal half-life ranged from 9.89-10.4 days. It is not clear from the applicant's summary, if gender differences exist in PK parameters; however, reviewing the individual parameters in the PK reports, it seems that no such gender difference exists.

After multiple IV dosing (7 weeks) in monkeys clearance ranged from 5.09-7.42 ml/day/kg, the volume of distribution of central compartments ranged from 35.6-40.5 ml/kg and the mean terminal half-life ranged from 8.13-10.6 days. The maximum serum concentration (Cmax-obs) was estimated to be approximately 5.7 mg/mL for the 150 mg/kg/dose group. Following repeated IV dosing, the exposure to pertuzumab appeared to demonstrate a non-linear relationship to dose. This effect may be related to the approximately 30% increase in clearance observed when increasing the dose from 50 to 150 mg/kg/week. According to the applicant, the pharmacokinetics of pertuzumab is consistent with trastuzumab and other IgG1 monoclonal antibodies that share the same Fc region. This is seen as a distribution phase of less than 1 day, a terminal half-life of app. 10 days and a volume of distribution of the central compartment – approximating the serum volume (of 30-50 ml/kg). Finally, no ATAs against pertuzumab were detected after repeat dose administration in monkeys. Based on the popPK model (population pharmacokinetic analysis of pertuzumab in cancer patients) developed using all 12 clinical studies, pertuzumab clearance (CL) was 0.239 L/day (3.4 ml/kg/day) and the central compartment volume (Vc) was 3.07 L (43.86 ml/kg). The median terminal elimination half-life was 17.2 days (95% CI range: 7.8-32 days).

The pharmacokinetic studies in mice and rats were performed under non-GLP conditions, however, as they were performed and reported to good scientific standard this is acceptable. More importantly the toxicokinetic studies, used to support the pivotal safety toxicity studies in monkeys, were performed under GLP conditions.

Distribution

Dedicated studies investigating the distribution of pertuzumab were not performed. Tissue concentrations, when using radio labelled proteins, may be difficult to interpret due to the rapid *in vivo* metabolism or unstable radiolabel linkage. Hence, the lack of a tissue distribution study is considered acceptable.

No studies evaluating milk transfer have been performed. It is well-established, that antibodies (IgG) are known to be excreted in human breast milk, and as such the lack of a milk excretion study is considered acceptable. Moreover, an adequate warning has been provided in section 4.6 of the SmPC.

The extent of placental transfer of pertuzumab after IV administration to pregnant monkeys was investigated. Both foetal and maternal exposure was confirmed at the time of caesarean section (GD100) with pertuzumab serum exposures in foetuses constituting approximately 1/3 of the maternal exposure, and thus indicating placental transfer of pertuzumab. The transfer of antibodies from mother to foetus occurs primarily in the second and third trimester in humans and in nonhuman primates. In Cynomolgus monkeys an exponential increase in IgG transfer from mother to foetus seems to start around GD84 and by the time of birth (GD165) antibody levels in the neonates are similar to that of the mothers. Therefore it is expected to see only a fraction (around 25%) of the maternal levels in the foetuses around the time of caesarean section (GD100).

Metabolism

No studies on metabolism have been performed. The expected consequence of pertuzumab metabolism is degradation to small peptides and amino acids. Hence, in accordance with ICH S6 (R1) guideline, it is acceptable that the metabolism of pertuzumab has not been studied.

Excretion

No studies on elimination have been performed. Following degradation of pertuzumab metabolism into small peptides and amino acids, the latter may be incorporated into new proteins or excreted renally. It is acceptable that no dedicated studies on elimination of pertuzumab have been studied.

Pharmacokinetics drug interactions

The potential for pharmacokinetic drug interactions between pertuzumab and bevacizumab (humanized monoclonal antibody against VEGF) were investigated in a single-dose pharmacokinetic study in SD rats. No substantial differences, and therefore no PK interactions, were apparent between the PK parameters of the rats given a single agent and those of the rats given combination treatment.

Other pharmacokinetic studies

The mean clearance of pertuzumab in serum was higher in tumour-bearing mice than in non tumour-bearing mice. Additionally the terminal half-life was considerably shorter in the tumour-bearing mice than in the non tumour-bearing mice. The applicant's explanation for this difference in clearance is pertuzumab binding to HER2 expressed on the human tumour cells and to circulating shed extracellular domain or an acute metabolic response caused by the implanted tumour.

Changes have been introduced in the manufacturing process of pertuzumab during development to support up-scaling processes and a change in cell line. Hence, as part of the comprehensive comparability strategy, three (non-GLP) pharmacokinetic studies in male rats were designed and performed to show biocomparability of different lots of pertuzumab. Generally the studies showed that the different lots of pertuzumab had comparable pharmacokinetic parameters in rats.

2.3.4. Toxicology

A complete toxicology assessment was conducted in accordance with the relevant guidelines for biologics and anti-cancer products; ICH S6 (R1) guideline, part 1 and 2 and ICH S9. Studies included IV repeat-dose toxicity of up to 6 month duration, embryo-foetal development toxicity, and other toxicity studies. These studies were conducted, except for one (4-week toxicity study in monkeys), in compliance with GLP. The intended human route is IV.

The Cynomolgus monkey was the preferred toxicity species based on the comparable *in vitro* human and monkey binding affinity and due to lack of binding to the rodent (mouse) ortholog, *neu.*

Single dose toxicity

No dedicated single dose toxicity studies have been performed in accordance with the current recommendations from EMA (CHMP/SWP/302413/08 and EMA/CHMP/SWP/81714/2010).

Repeat dose toxicity

In the repeat dose toxicity studies performed, no treatment related effects were seen on body temperature, respiration rates, blood pressure, electrocardiography and opthalmoscopy or on haematology, urinalysis, organ weights, gross pathology or histopathology. Moreover analyses were made on antibodies to pertuzumab (ATAs), troponin T, creatinine kinase, sperm, testosterone, and showed no treatment related effects either. Occasionally decreases in food consumption and body weight were noted, which was primarily considered secondary to the high incidence of diarrhoea seen

in the studies. In the 7-week toxicity study two males and two females/group where telemetry instrumented in the control and high dose group (150 mg/kg), respectively and no treatment related findings were seen on the cardiovascular parameters. Additionally, in the 26-week study no ECG and blood pressure findings were seen on non-instrumented Cynomolgus monkeys dosed up to 150 mg/kg/dose.

No clinical signs were seen in the 4-weeks IV and subcutaneously dosed studies, whereas major treatment related findings were seen on clinical observations in the 7- and 26-weeks toxicity studies, displayed as diarrhoea, liquid and non-formed faeces.

In the 7-week toxicity study clinical observations revealed liquid or non-formed faeces at a higher incidence and in a dose dependent manner in all dosed groups compared to the control group. Three males and two females in the high dose were so affected that they were carefully examined by veterinary staff and had intensive supportive care. Hence, the No Observed Adverse Effect Level (NOAEL) was considered to be 50 mg/kg. In the treatment free period a partly recovery of the faeces consistency was apparent as well as stable body weight and normal food consumption.

Throughout the 26-week toxicity study a higher incidence of liquid, non-formed faeces was seen in treated monkeys vs. controls (not in a dose dependent manner). The diarrhoea was so severe in one female animal dosed 50 mg/kg/dose, that it was euthanized *in extremis* on Day 126 of treatment. Three days in advance the female had been hunched and hypoactive, had no food consumption, and exhibited diarrhoea. In addition to this, a significantly low body temperature was measured (34.6ºC). In two other monkeys (one male dosed 15 mg/kg/dose and one female dosed 150 mg/kg/dose) similar adverse findings were seen during the study, displayed as hunched posture, lethargy, weight loss, diarrhoea and low body temperature (in one animal). However, due to the supportive care given throughout the study it was not necessary to euthanize these animals. Due to the severe diarrhoea and increased urea nitrogen values at all dose levels, a No Observed Adverse Effect Level (NOAEL) could not be determined. After an 8-week treatment free period no clear recovery was apparent for the abnormal faeces or for the increased urea nitrogen.

For both the 7-week and 26-week toxicity study, the toxicokinetics showed exposure to pertuzumab and increased with increasing dose.

As highlighted, the major non-clinical findings were diarrhoea, liquid and non-formed faeces. This is in line with the clinical studies in which the main adverse events reported with pertuzumab were diarrhoea, fatigue and nausea. In combination with trastuzumab and docetaxel it has in the clinic, according to the applicant, added only little toxicity to the adverse event profile. Also in the clinic, it is concluded that the diarrhoea is generally manageable and had no major impact on patients' ability to continue study treatment. According to the literature, diarrhoea is a common side effect of agents which inhibits the EGFR/HER1 receptor. The diarrhoea seen non-clinically was without histopathological changes. As explained by the applicant, although the mechanism relating to the diarrhoea is not fully understood, it is thought to be caused by disruption of the intestinal chloride balance following inhibition of HER1/HER2 and HER2/HER3 heterodimer formation.

In the 26-week repeat-dose toxicity study, increased blood urea nitrogen values were observed in almost all pertuzumab treated animals and the finding persisted following a 8-week recovery period. However, this finding was not accompanied by histopathological findings in the kidney and clinical safety data do not indicate that pertuzumab-treatment is associated with adverse effects on kidney function.

Genotoxicity

No genotoxicity studies have been submitted, in accordance with ICH S6 (R1) guideline. It is not expected that peptides/proteins would interact directly with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity studies have been submitted According to ICH S6 (R1) guideline standard carcinogenicity bioassays are generally not appropriate for biotechnology derived pharmaceuticals and according to ICH S9 carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with late stage or advanced cancer.

Reproduction Toxicity

Fertility and early embryonic development

According to the ICH S9 guidance, fertility studies are not required for medicinal products indicated for late stage cancer. In such cases, information on the risk of effects on fertility can be obtained from the examination of reproductive organs in repeat-dose toxicity studies.

No information could be obtained on the potential effect of pertuzumab on the male reproductive organs. The large majority of male Cynomolgus monkeys used in the repeat-dose toxicity studies were sexually immature hence only a single male undergoing high-dose (150 mg/kg) pertuzumab treatment was sexually mature. However, evidence of menses was noted for 12 out of 14 female monkeys treated with pertuzumab hence the large majority of the female monkeys were sexually mature during the treatment period.

No effects on the female reproductive organs were seen in the repeat-dose toxicity studies performed with pertuzumab.

Embryo-foetal development

In the embryo-foetal development study, pregnant monkeys were weekly IV dosed with pertuzumab during the period of foetal organogenesis (gestation days (GD) 19 to 50). Maternal and foetal toxicity was observed in all pertuzumab treated groups hence the NOAEL was below 30/10 mg/kg/week (loading/maintenance dose). Findings consisted of low amniotic fluid volume, high foetal lethality, retarded development, and external (paw hyperextension, paw hyperflexion and microtia), visceral (small lungs, thin ventricular wall and ventricular septum defect, hypoplasia of the collecting glomeruli, renal tubules, collecting tubules and pelvis) and skeletal abnormalities (reduced length of ossified bones).

Generally, for monoclonal antibodies, there is very low likelihood of teratogenic effects occurring due to the low direct embryonic exposure during organogenesis (Cavagnaro, JA, 2008). Hence, the observed external, visceral and skeletal abnormalities were considered secondary to intrauterine restriction resulting from the oligohydramnios (low amniotic fluid volume). Indeed, in humans oligohydramnios may be associated with marked deformation of the foetus due to intrauterine constraint. Moreover, oligohydramnios adversely affects foetal lung development resulting in pulmonary hypoplasia. Cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin® (trastuzumab). It that respect, it is noteworthy that no maternal toxicity, embryotoxicity or teratogenicity was observed in a Cynomolgus monkey embryo-foetal development study conducted with trastuzumab (EPAR).

Because the amniotic fluid is primarily foetal urine in the latter half of the pregnancy, the absence of foetal urine production or blockage in the foetus' urinary tract can result in oligohydramnios. Histopathologically, kidney hypoplasia was observed in all treated foetuses which were associated with a dose-dependent increase in severity. Tumor growth factor-alpha and EGF, both ligands of HER1, are expressed in normal human kidney tissue and serve to enhance renal cell proliferation, migration, differentiation, and morphogenesis. EGFR and HER2 are also expressed in renal tissue. Consistent with this expression, pertuzumab bound to monkey and human kidney tissues in the *in vitro* cross-reactivity studies. Thus, HER-family members play an important role in the regulation of growth, differentiation and morphogenesis of renal tissue and the interaction of these receptors may be perturbed by inhibition of HER2 dimerisation by pertuzumab.

It has been reported that HER2 plays an essential role in both the developing and adult heart. Hence, embryos that lack the HER2 receptor die due to improper formation of the ventricular trabeculae and ventricular enlargement has been observed in adult mice deficient of ventricular HER2 (Hynes and Hale, 2005). On this basis, it cannot be excluded that the ventricular abnormalities in the foetuses are the result of a direct treatment-related effect.

As expected, toxicokinetic data demonstrated exposure to pertuzumab both in maternal and foetal serum. At GD100, the ratios of foetal to maternal pertuzumab levels were comparable among all dose groups. It is not possible to calculate AUC based animal:human exposure margins as no full profile of toxicokinetic samples have been collected (serum samples were only collected pre-dose and 30 minutes post-dose on GD19, 36, 50 and on the day of caesarean sectioning). However, as no NOAEL for foetal toxicity was established in this study, it cannot be excluded that the observed foetal toxicity may occur at therapeutic pertuzumab concentrations in human. Hence, as with trastuzumab, pertuzumab should be avoided during pregnancy.

Prenatal and postnatal development, including maternal function

No segment III studies (pre- and postnatal development) were submitted in accordance with ICH S6 (R1) and ICH S9 guidelines.

Toxicokinetic data

Toxicokinetic studies were conducted in monkeys.

In the 7- and 26-week toxicity study measurable levels of pertuzumab were found occasionally in individual samples from control groups at concentration levels above the lower limit of quantification.

In the 7-week toxicity study, pertuzumab concentrations exceeded the LLOQ in 17 out of 21 samples from one monkey (concentration range of 0.28 to 0.68 µg/mL). Moreover, the pertuzumab concentration in 6 out of a total of 199 of the remaining control samples was above the LLOQ (0.29-0.96 µg/mL). In the pivotal 26-week toxicity study concentrations exceeded the LLOQ in 2 out of 12 animals on two occasions (Day 8, predose and Day 113 +1 hour post dose with pertuzumab concentrations of 0.251 and 0.546 µg/mL, respectively).

Representative clinical serum exposure levels can be obtained from the clinical study BO16934. Due to the loading dose, the 840 mg/420 mg dosing regimen reached approximate steady-state concentrations following the first maintenance dose. AUC and C_{max} values in this study was 3598 µg*day/ml and 289 µg/ml, respectively. The table below shows the exposure levels obtained in the repeat-dose toxicity studies, and gives the calculated animal:human exposure margins. The number given in bold corresponds to exposure margin at the NOAEL.

Table 36. Selected non-compartmental PK parameters for Cynomolgus monkeys (7-week and 26-week toxicity study) are listed in the below table.

Study ID	Species Study length Route	Dose (mg/kg)	Cmax-obs (µg/ml)	Tmax-obs (day)	AUC day0-7 (day* µg/ml)	AUC day0-48 (day* µg/ml)	AUC day0-182 (day* µg/ml)	Animal:Human Exposure Multiple (AUC)
00-377-1821	Monkey 7-week IV	15	713	35	1310	19500	NA	5
		50	2210	42	3800	57100	NA	16
		150	5690	35	10700	149000	NA	**41**
01-458-1821	Monkey 26-week IV	15	862	119	1270	NA	97100	27*
		50	2820	135	3990	NA	282000	78
		150	7310	118	11000	NA	723000	201

*AUC = area under the curve, Cmax = maximum concentration, Tmax = time of maximum concentration, NA = not applicable. * A NOAEL could not be established in this study due to diarrhoea and increased urea nitrogen at all dose levels.*

Local Tolerance

No dedicated local tolerance studies were submitted. The intended clinical route of administration is IV. No pertuzumab-related clinical observations (IV and SC) or histopathologic (IV) findings were noted at the injection sites when pertuzumab was administered by IV or SC injection in the repeat-dose toxicity studies in monkeys.

Other toxicity studies

No antibodies to pertuzumab were detected in the 7- and 26-week toxicity studies. Despite possible interference in the ELISA assays, it appears that pertuzumab was not immunogenic in Cynomolgus monkeys.

Pertuzumab and pertuzumab vehicle did not cause haemolysis of human or monkey erythrocytes and were compatible with Cynomolgus monkey and human serum and plasma.

2.3.5. Ecotoxicity/environmental risk assessment

No environmental risk assessment was submitted for pertuzumab in accordance with the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA, 2006). Peptides are exempted from the need to provide an environmental risk assessment, because they are unlikely to result in significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

Based on *in vitro* and *in vivo* pharmacodynamic data, there is a clear rationale for the inclusion of pertuzumab in a drug combination regimen in the treatment of breast cancer. No effects on safety pharmacology end points (respiratory and cardiovascular) were noted in the repeat-dose toxicity studies.

The major finding made in the Cynomolgus repeat-dose toxicity studies was severe diarrhoea which led to the need for intensive supportive care and in one case it was necessary to euthanize the animal. In line with ICH S6 and S9 guidance, no studies on genotoxicity and carcinogenicity have been performed.

According to the ICH S9 guidance, fertility studies are not required for medicinal products indicated for late stage cancer. In such cases, information on the risk of effects on fertility can be obtained from the

examination of reproductive organs in repeat-dose toxicity studies. In the present application, the large majority of male Cynomolgus monkeys used in the repeat-dose toxicity studies were sexually immature hence only a single male undergoing high-dose (150 mg/kg) pertuzumab treatment was sexually mature. As a result, no information could be obtained on the potential effect of pertuzumab on the male reproductive organs. However, evidence of menses was noted for 12 out of 14 female monkeys treated with pertuzumab hence the large majority of the female monkeys were sexually mature during the treatment period. No effects on the female reproductive organs were seen in the repeat-dose toxicity studies performed with pertuzumab.

Findings made in the Cynomolgus monkeys embryo-fetal development study, consisted of low amniotic fluid volume, high fetal lethality, retarded development, and external (paw hyperextension, paw hyperflexion and microtia), visceral (small lungs, thin ventricular wall and ventricular septum defect, hypoplasia of the collecting glomeruli, renal tubules, collecting tubules and pelvis) and skeletal abnormalities (reduced length of ossified bones). The observed external, visceral and skeletal abnormalities were considered secondary to intrauterine restriction resulting from the oligohydramnios (low amniotic fluid volume). Indeed, in humans oligohydramnios may be associated with marked deformation and growth restriction of the fetus due to intrauterine constraint. Moreover, oligohydramnios adversely affects fetal lung development resulting in pulmonary hypoplasia. Histopathologically, kidney hypoplasia was observed in all treated fetuses and this was associated with a dose-dependent increase in severity. HER-family members play an important role in the regulation of growth, differentiation and morphogenesis of renal tissue and the interaction of these receptors may be perturbed by inhibition of HER2 dimerisation by pertuzumab. Moreover, it is likely that the ventricular abnormalities in the fetuses were the result of a direct treatment-related effect. As no NOAEL for fetal toxicity was established in this study, it cannot be excluded that the observed fetal toxicity may occur at therapeutic pertuzumab concentrations in humans.

2.3.7. Conclusion on the non-clinical aspects

In line with ICH S6 and S9 guidance, no studies on genotoxicity and carcinogenicity have been performed.

No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. No definitive conclusion on adverse effects can be drawn on the male reproductive organs in cynomolgus monkey repeated dose toxicity study.

Reproductive toxicology studies have been conducted in pregnant cynomolgus monkeys (Gestational Day (GD) 19 through to GD 50) at initial doses of 30 to 150 mg/kg followed by bi-weekly doses of 10 to 100 mg/kg. These dose levels resulted in clinically relevant exposures of 2.5 to 20-fold greater than the recommended human dose, based on C_{max}. Intravenous administration of pertuzumab from GD19 through GD50 (period of organogenesis) was embryotoxic, with dose-dependent increases in embryo-foetal death between GD25 to GD70. The incidences of embryo-foetal loss were 33, 50, and 85% for pregnant female monkeys treated with bi-weekly pertuzumab doses of 10, 30, and 100 mg/kg, respectively (2.5 to 20-fold greater than the recommended human dose, based on C_{max}). At Caesarean section on GD100, oligohydramnios, decreased relative lung and kidney weights and microscopic evidence of renal hypoplasia consistent with delayed renal development were identified in all pertuzumab dose groups. In addition, consistent with foetal growth restrictions, secondary to oligohydramnios, lung hypoplasia (1 of 6 in 30 mg/kg and 1 of 2 in100 mg/kg groups), ventricular septal defects (1 of 6 in 30 mg/kg group), thin ventricular wall (1 of 2 in 100 mg/kg group) and minor skeletal defects (external - 3 of 6 in 30 mg/kg group) were also noted. Pertuzumab exposure was

reported in offspring from all treated groups, at levels of 29% to 40% of maternal serum levels at GD100.

In cynomolgus monkeys, weekly intravenous administration of pertuzumab at doses up to 150 mg/kg/dose was generally well tolerated. With doses of 15 mg/kg and higher, intermittent mild treatment-associated diarrhoea was noted. In a subset of monkeys, chronic dosing (7 to 26 weekly doses) resulted in episodes of severe secretory diarrhoea. The diarrhoea was managed (with the exception of euthanasia of one animal, 50 mg/kg/dose) with supportive care including intravenous fluid replacement therapy.
These main non-clinical findings are appropriately reflected in section 5.3 of the SmPC.

Based on the review of the data on non clinical aspect the following statements to address the potential risk of pertuzumab in pregnant women have been included in section 4.6 of the SmPC:

- Women of childbearing potential and male patients with female partners of childbearing potential, must use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta.

- There is limited amount of data from the use of pertuzumab in pregnant women. Studies in animals have shown reproductive toxicity. Perjeta is not recommended during pregnancy and in women of childbearing potential not using contraception.

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

- No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. Only very limited data are available from repeat-dose toxicity studies with respect to the risk for adverse effects on the male reproductive system. No adverse effects were observed in sexually mature female cynomolgus monkeys exposed to pertuzumab.

2.4. Clinical aspects

2.4.1. Introduction

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 37: Tabular Overview of Clinical Studies

Study	Phase	Indication	Dose [a]/Regimens	Patients Treated	Status [b]
Single-agent studies					

Phase I, dose escalation					
TOC2297g	Ia	Advanced solid tumors	0.5, 2.0, 5.0, 10.0, and 15.0 mg/kg qw3k	21	Completed
JO17076 [c,]	I	Advanced solid tumors	5.0, 10.0, 15.0, 20.0 and 25.0 mg/kg q3wk	18	Completed
Phase II					
TOC2689g	II	Advanced ovarian cancer	Cohort 1: 420 mg qw3k[a] Cohort 2: 1050 mg qw3k [a]	61 62	Completed
BO16934	II	MBC with low HER2 expression	Arm A: 420 mg qw3k [a] Arm B: 1050 mg qw3k	41 37	Completed
BO17004	II	HRPC, chemotherapy naive	Cohort 1: 420 mg qw3k [a] Cohort 2: 1050 mg qw3k [a]	35 33	Completed
TOC2682g	II	CRPC pretreated with docetaxel	420 mg qw3k [a]	41	Completed
TOC2572g	II	Advanced, recurrent NSCLC	420 mg qw3k [a]	43	Completed
Combination Therapy Studies					
Phase I studies					
BO17003	Ib	Advanced solid tumors	Cohort 1: pertuzumab: 1050 mg q3wk capecitabine: 825, 1000, 1250 mg/m^2	18	Completed
BO17021	Ib	Advanced solid tumors	pertuzumab: 1050 mg docetaxel: 60,75 mg/m2 or pertuzumab: 420 mg (840 mg loading dose) Docetaxel 75, 100 mg/m2 q3w	19	Completed
WO20024	Ib	Advanced NSCLC	pertuzumab: 420 mg q3wk Cohort 1:erlotinib: 100 mg/day Cohort 2: erlotinib 150 mg/day	15	Completed
Phase II/III randomized studies					
TOC3258g	II	Platinum-resistant ovarian, peritoneal, or fallopian tube cancer	gemcitabine: 800 mg/m2 ± pertuzumab: 420 mg q3wk	Gemcitabine + Pertuzumab: 65 Gemcitabine: 65	Completed

WO20697 (NEOSPHERE)	II	HER2+, locally advanced, inflammatory or early stage breast cancer (EBC)	Pertuzumab: 840 mg loading dose IV, then 420 mg IV every 3 weeks for 4 cycles. Trastuzumab: 8 mg/kg loading dose IV, then 6 mg/kg every 3 weeks for 4 neoadjuvant cycles and up to 1 year total post-surgery. Docetaxel: 75 mg/m2 escalating, if tolerated, to 100 mg/m2 IV every 3 weeks for 4 cycles. T+D (Regimen A), PtZ+T+D (Regimen B), Ptz+T (Regimen C) Ptz+D (Regimen D).	417	Completed
BO17929	II	HER2-positive MBC	Pertuzumab: loading dose of 840 mg given i.v. over 60± 10 minutes, followed by a maintenance dose of 420 mg given i.v. over 30± 10 minutes if well tolerated. Cohort 1 (Ptz+T) Cohort 2 (Ptz +T) Cohort 3 (Ptz)	24 42 29	Completed
Pivotal Phase III, randomized study					
WO20698/TOC4129g (CLEOPATRA)	III	HER2-positive MBC (first-line treatment)	Placebo + docetaxel + trastuzumab Pertuzumab + docetaxel + trastuzumab pertuzumab: 420 mg q3w (840 mg loading dose) trastuzumab: 6 mg/kg q3w (8 mg/kg loading dose) docetaxel: 75 mg/m2 escalating to 100 mg/m2 q3w	402[d] 402	Completed

2.4.2. Pharmacokinetics

Methods

Quantitation of Pertuzumab and Trastuzumab

A validated enzyme-linked immunosorbent assay (ELISA) was used to measure pertuzumab concentrations in serum samples from patients in studies BO16934, BO17003, BO17004, BO17021, JO17076, TOC2297g, TOC2572g, TOC2682g, TOC2689g, TOC3258g, and WO20024 (all studies in which pertuzumab was administered without concurrent trastuzumab). The minimum quantifiable concentration (MQC) in human serum was 400ng/mL.

A subsequent validated ELISA was used to measure pertuzumab in the presence of trastuzumab in serum samples from patients in study WO20698/TOC4129g. The MQC in human serum was 150 ng/mL.

A third ELISA was used to measure trastuzumab in the presence of pertuzumab in serum samples from patients in study WO20698/TOC4129g. The MQC in human serum was 200 ng/mL.

Pharmacokinetic data analysis

Pertuzumab PK parameter values were derived from pertuzumab concentration-time data from studies where pertuzumab was administered as a single agent or in combination with a range of therapeutic agents in a variety of oncology indications. Characterization of the PK of pertuzumab was estimated by compartmental and non-compartmental methods, population pharmacokinetic (popPK) and covariate analyses.

In the PopPK analysis pertuzumab serum concentration data consisting of 4525 samples obtained from 481 cancer patients across twelve Phase I/II/III studies were analyzed by nonlinear mixed effects modeling using the software package NONMEM 7, version 7.1.2 with the firstorder conditional estimation (FOCE) method.

Absorption

Bioequivalence

During the development of pertuzumab, biocomparability of different generations of drug substance and drug product was established using a comprehensive strategy comprising in vitro binding characterization, antiproliferative activity and nonclinical PK studies. Once biocomparability was demonstrated, no additional clinical biocomparability studies were conducted.

Distribution

Following intravenous infusion, the estimated mean values for volume of distribution at steady state (Vss) were 3.53-7.05 L. The large range is the result of the different sampling times in various studies. In general the parameters are very similar across studies and represent values expected for an IgG1 monoclonal antibody.

In the final PopPK analysis model, elimination clearance (CL) was 0.239 L/day (2.1% SE), and the central compartment volume (V_c) was 3.07 L (1.2% SE). Inter-individual variability in CL and V_c expressed as CV% were 34.5% and 19.3% respectively. Distribution clearance (Q) was 0.558 L/day (8.4% SE), and peripheral volume (V_p) was 2.36 L (3.5% SE). The median distribution and terminal elimination half-lives were 1.5 days (95% range: 0.9-2.24 days) and 17.2 days (95% range: 7.8-32 days) respectively.

In the PopPK analysis albumin was identified as a statistically significant covariate on pertuzumab PK. Clearance decreased in patients with higher albumin concentration. After inclusion of albumin and lean body weight in the final popPK model, the inter-individual variance in CL decreased by 21.7%, explaining app. 1/5 of the inter-individual variance in CL.

Although these covariates were statistically significant, the magnitude of their effects on pertuzumab exposure (AUC and C_{max}) was assessed to be minimal compared to the inter-individual variability of the population such that dose adjustment for the identified covariates would not be expected to result in a meaningful change in pertuzumab exposure variability.

Elimination

Excretion

Large molecule monocloncal antibodies are known to be cleared primarily by target mediated clearance as well as simple non-target specific IgG clearance mechanisms. Clearance across studies ranged from 0.232 – 0.329 L/day and T½ ranged from 11.1 – 22.3 days. Pertuzumab is not cleared via the kidney nor is it eliminated via cytochrome P450 (CYP450) isoenzymes.

Dose proportionality and time dependencies

Single dosing in single-agent studies

Results from the two dose escalating studies TOC2297g and JO17076 showed that Cmax after single dose adminstration increased in a proportional manner with increasing doses of pertuzumab:

Table 38 Study TOC2297g: Selected Pertuzumab Pharmacokinetic Parameter Estimates following IV Infusion (Mean± SD)

Dose Group (mg/kg)	CL (mL/day/kg)	V_c (mL/kg)	V_{ss} [a] (mL/kg)	$t_{1/2}$ initial [a] (days)	$t_{1/2}$ terminal (days)
0.5 (n = 3)	13.1 ± 5.5	43.6 ± 4.6	NA	NA	2.6 ± 0.9
2.0 (n = 3)	3.74 ± 1.28	35.5 ± 3.5	69.5 ± 13.7	0.96 ± 0.99	14.9 ± 1.1
5.0 (n = 4)	3.52 ± 0.85	39.7 ± 6.2	74.1 ± 30.4	1.09 ± 0.74	17.2 ± 10.3
10.0 (n = 3)	2.69 ± 0.92	38.4 ± 5.3	73.4 ± 13.6	1.23 ± 0.90	22.3 ± 9.9
15.0 (n = 8)	3.68 ± 1.47	42.8 ± 7.9	85.3 ± 36.7	1.50 ± 1.17	18.6 ± 8.8

CL=systemic clearance; NA = not applicable; $t_{1/2}$ initial = initial distribution half-life; $t_{1/2}$ terminal =terminal half-life; V_c =volume of central compartment; V_{ss}= steady-state volume of distribution.

[a] Available for dose groups in which only a two-compartment model was used.

Note: A one-compartment model was used for the 0.5 mg/kg dose group, and a two-compartment model was used for the 2.0–15.0 mg/kg dose groups.

Table 39 Cmax values from the Study TOC2297g

Study	**TOC 2297g**
Dose (mg/kg)	Cmax (µg/ml)
0.5	11.5
2	55
5	126
10	257
15	358

Table 40 Study JO17076: Selected Pertuzumab Pharmacokinetic Parameter Estimates following IV Infusion (Mean ± SD)

Dose Group (mg/kg)	CL (mL/day/kg)	V_{ss} (mL/kg)	$t_{1/2}$ (days)	AUC_{last} (day • µg/mL)	AUC_{inf} (day • µg/mL)	C_{max} (µg/mL)
5.0 (n = 3)	5.62 ± 0.8	90.2 ± 12.8	11.1 ± 0.5	608 ± 112	902 ± 121	105 ± 32.4
10.0 (n = 3)	4.82 ± 1.5	93.7 ± 18.7	14.4 ± 2.7	1400 ± 447	2230 ± 773	181 ± 32.6
15.0 (n = 3)	4.25 ± 1.7	94.1 ± 40.9	16.8 ± 3.96	2350 ± 852	3970 ± 1740	320 ± 73.2
20.0 (n = 3)	4.87 ± 0.6	99.6 ± 10.8	15.0 ± 2.6	2640 ± 193	4150 ± 507	340 ± 51.3
25.0 (n = 6)	4.54 ± 1.7	94.7 ± 12.3	16.3 ± 5.9	3730 ± 893	6060 ± 1900	498 ± 108

PK parameters generated by non-compartmental analysis

PK parameter values after cycle 1 from the two single agent studies BO16934 and BO17004 investigating the two fixed doses of pertuzumab 840 mg as loading dose followed by 420 mg as maintenance dose and 1050 mg q3w are shown below:

Table 41 Study BO16934: Pharmacokinetic Parameters of Pertuzumab Following IV Infusions of 840 and 1050 mg Doses in Cycle 1 (Mean (CV%))

Parameters	n	840 mg	n	1050 mg
$t_{1/2}$ (day)	38	12.2 (31)	36	11.4 (36)
C_{max} (µg/mL)	40	289 (37)	37	409 (39)
AUC_{last} (µg.day/mL)	40	2517 (36)	37	3465 (30)
AUC_{∞} (µg.day/mL)	38	3598 (39)	36	4750 (32)
CL (mL/day)	38	270 (42)	36	247 (36)
V_{ss} (mL)	38	4122 (40)	36	3527 (39)

PK parameters generated by non-compartmental analysis

Table 42. Study BO17004: Pharmacokinetic Parameters of Pertuzumab Following IV Infusion of 840 or 1050 mg Doses Following Cycle 1 (Mean(CV%))

Parameters	n	840 mg	n	1050 mg
$t_{1/2}$ (day)	35	13.7 (39)	31	19.3 (69)
C_{max} (µg/mL)	35	255 (23)	33	294 (24)
AUC_{last} (µg•day/mL)	35	2305 (22)	33	2626 (28)
AUC_{∞} (µg•day/mL)	35	3488 (44)	31	5097 (71)
CL (mL/day)	35	270 (29)	31	253 (35)
V_{ss} (mL)	35	4452 (26)	31	5227 (24)

PK parameters generated by non-compartmental analysis

Combination Therapy studies:

Below are PK data from the combination therapy study BO17003 investigating the higher fixed dose of 1050 mg q3w:

Table 43. Study BO17003: Mean (±SD) Pharmacokinetic Parameters of Pertuzumab after 1 cycle

Dose	$t_{½}$ (day)	C_{max} (µg/mL)	AUC_{last} (µg • day/mL)	AUC_{inf} (µg • day /mL)	CL (mL/day)	V_{ss} (mL)
1050 mg (n=18)	14.6 ±4.1	355 ±59	2740 ±744	4010 ± 1280	283 ± 98	5202 ± 1007

Table 44. Summary of selected pertuzumab pharmacokinetic parameters estimates following iv infusion (mean+-SD).

Study	Dose[a] Group (Cycle; No. of PK-Evaluable Patients)	CL (L/day)	V_{ss} (L)	$t_{1/2}$ (days)
Single-agent studies				
Phase I, dose-escalation				
TOC2297g[b, c] (advanced solid tumors)	0.5 mg/kg (1; n = 3)	0.917 ± 0.385	3.05 [d] ± 0.32	2.6 ± 0.9
	2.0 mg/kg (1; n = 3)	0.299 ± 0.102	5.56 ± 1.10	14.9 ± 1.1
	5.0 mg/kg (1; n = 4)	0.275 ± 0.070	5.78 ± 2.37	17.2 ± 10.3
	10.0 mg/kg (1; n = 3)	0.258 ± 0.088	7.05 ± 1.31	22.3 ± 9.9
	15.0 mg/kg (1; n = 8)	0.232 ± 0.093	5.37 ± 2.31	18.6 ± 8.8
JO17076[c] (advanced solid tumors)	5.0 mg/kg (1; n = 3)	0.308 ± 0.094	4.89 ± 1.21	11.1 ± 0.5
	10.0 mg/kg (1; n = 3)	0.269 ± 0.105	5.31 ± 2.14	14.4 ± 2.7
	15.0 mg/kg (1; n = 3)	0.245 ± 0.066	5.35 ± 1.18	16.8 ± 4.0
	20.0 mg/kg (1; n = 3)	0.270 ± 0.012	5.56 ± 0.76	15.0 ± 2.6
	25.0 mg/kg (1; n = 6]	0.254 ± 0.072	5.42 ± 0.77	16.3 ± 5.9
Phase II				
TOC2689g[e] (ovarian cancer)	420 mg (n = 56)	NA	NA	NA
	1050 mg (n = 55)	NA	NA	NA
BO16934 (MBC)	420 mg (1; n = 38)	0.270 ± 0.113	4.12 ± 1.65	12.2 ± 3.8
	1050 mg (1; n = 36)	0.247 ± 0.088	3.53 ± 1.38	11.4 ± 4.1
BO17004 (HRCP, chemo naïve)	420 mg (1; n = 35)	0.270 ± 0.078	4.45 ± 1.16	13.7 ± 5.3
	1050 mg (1; n = 33)	0.253 ± 0.089	5.23 ± 1.25	19.3 ± 13.0
TOC2682g[e] (CRPC, pretreated with docetaxel)	420 mg (n = 40)	NA	NA	NA
TOC2572g[e] (NSCLC)	420 mg (n = 43)	NA	NA	NA
Combination therapy studies				
Phase I				

BO17003 (+ capecitabine) (advanced solid tumors)	1050 mg (1; n = 18)	0.283 ± 0.098	5.20 ± 1.01	14.6 ± 4.1
BO17021 (+ docetaxel) (advanced solid tumors)	420 mg (1; n = 11)	0.329 ± 0.097	5.36 [f] ± 1.68	12.1 ± 5.4
	1050 mg (1; n = 8)	0.282 ± 0.083	5.21 [f] ± 1.39	13.4 ± 4.2
WO20024 (+ erlotinib) (advanced NSCLC)	420 mg (2; n = 8)	0.240 ± 0.050	4.90 ± 1.3	17.9 ± 2.2
Phase II, randomized				
TOC3258g [e] (+ gemcitabine) (platinum-resistant ovarian, peritoneal, or fallopian tube cancer)	420 mg (n = 21)	NA	NA	NA
Pivotal Phase III, randomized				
WO20698/TOC4129g (CLEOPATRA) [e] (+ trastuzumab + docetaxel)	420 mg (n = 20)	NA	NA	NA

CL = systemic clearance; CRPC = castration-resistant prostate cancer; HRPC = hormone-resistant prostate cancer; IV = intravenous; MBC = metastatic breast cancer; NA = not analyzed; NSCLC = non–small cell lung cancer; PK = pharmacokinetic; $t_{1/2}$ = terminal half-life Vc = volume of the central compartment; V_{ss} = steady-state volume of distribution; Vz = volume of distribution in the terminal phase.
[a]Pertuzumab given q3wk – the 420 mg dose is given after an initial 840-mg loading dose,
[b]PK parameters estimated by two-compartment model except for the 0.5 mg/kg dose group for which a one-compartment model was used.
[c]CL and V_{ss} adjusted due to dosing per kg using median body weight of 70, 80, 78, 96, and 63 kg for dose groups 0.5, 2, 5, 10, and 15 mg/kg, respectively for Study TOC2297g, and using individual body weights in all dose levels for Study JO17076.
[d]V_c reported.
[e]PK parameters were not calculated for Studies TOC2689g, TOC2682g, TOC2572g, TOC3258g, and WO20698/TOC4129g as only peak and trough samples were collected.
[f]V_z reported.

Dose proportionality after multiple-dose (steady-state)

Four clinical phase 1 and 2 studies compared the two fixed dosing regimens: 840 mg loading dose followed by 420 mg q3w as maintenance dose and 1050 mg q3w. In studies TOC2689g, BO16934 and BO17004 pertuzumab was administered alone and in study BO17021 pertuzumab was administered in combination with other anti-cancer drugs.

Pertuzumab appeared to show dose proportionality at steady state (Figures 13-16, Table 45).

Single-agent studies

Table45 Study TOC2689g: Cohort 1 Mean (± SD) Serum Pertuzumab Concentrations (µg/mL) for the First Three Treatment Cycles

Treatment Cycle	Dose (mg)	Sampling Event (Study Day)	N	Serum Pertuzumab (µg/mL)
		Day 1: predose	48	LTR
1	840	Day 1: postdose	52	332.4 ± 60.1
		Day 22: predose	44	64.6 ± 20.9
2	420	Day 22: postdose	43	231.7 ± 50.6
3	420	Day 43: predose	36	66.5 ± 38.0

	Day 43: postdose	27	237.6 ± 55.0

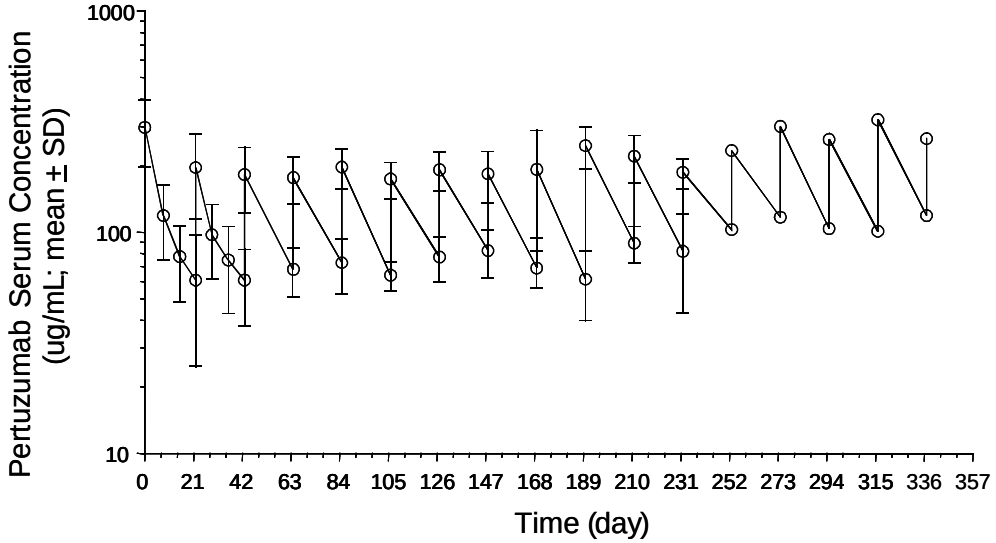
LTR = less than reportable; MQC = minimum quantifiable concentration. Note: LTR ≤ MQC (0.25–0.40 mg/mL of serum pertuzumab).

Table 46 Study TOC2689g: Cohort 2 Mean (± SD) Serum Pertuzumab Concentrations (µg/mL) for the First Three Treatment Cycles

Treatment Cycle	Dose (mg)	Sampling Event (Study Day)	N	Serum Pertuzumab (µg/mL)
		Day 1: predose	54	LTR
1	1050	Day 1: postdose	55	354.2 ± 96.0
		Day 22: predose	48	90.1 ± 68.1
2	1050	Day 22: postdose	41	390.9 ± 114.7
		Day 43: predose	28	94.7 ± 47.3
3	1050	Day 43: postdose	17	357.2 ± 112.4

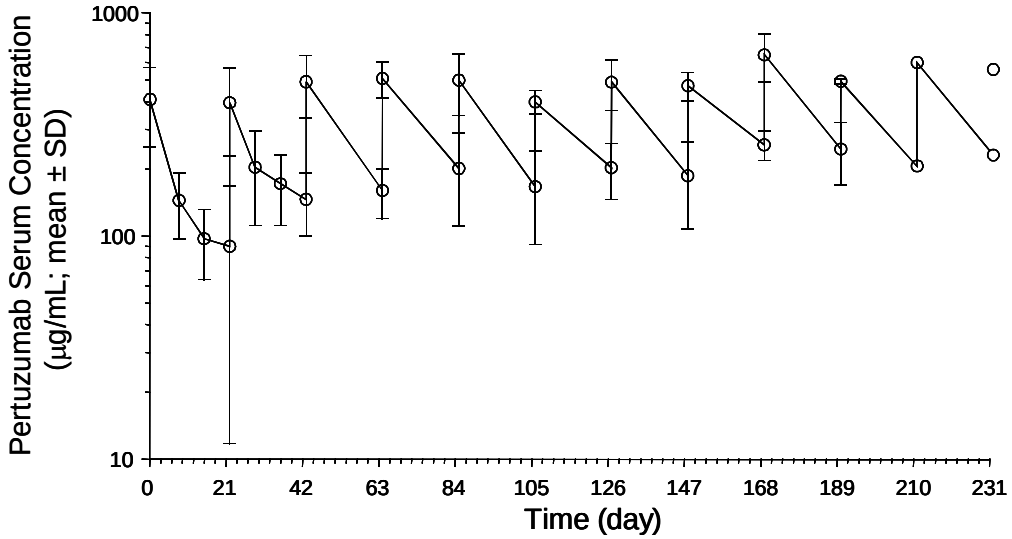
LTR = less than reportable; MQC = minimum quantifiable concentration. Note: LTR ≤ MQC (0.25–0.40 mg/mL of serum pertuzumab).

Figure 13 Study BO16934: Serum Concentration-Time Plots of Pertuzumab Following IV Infusion of 420 mg After a Loading Dose of 840 mg



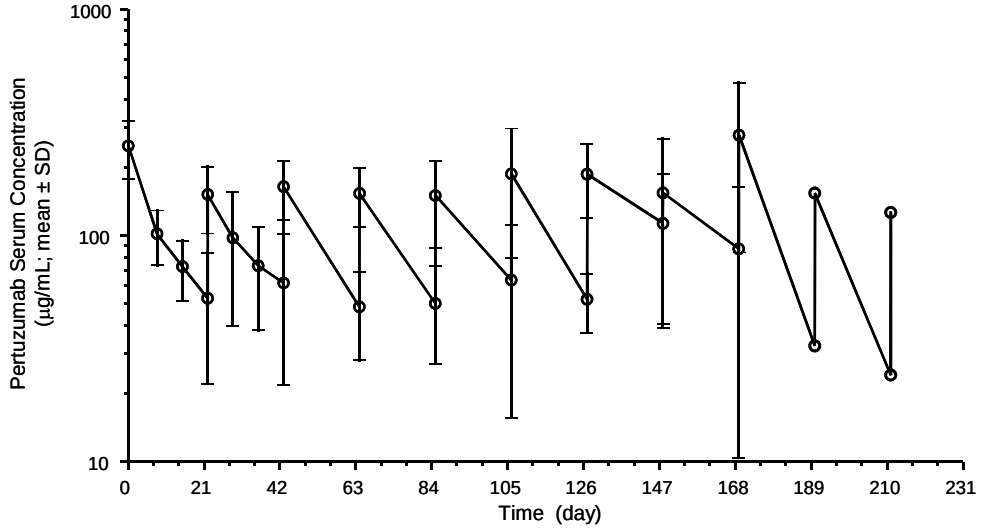
Serum samples were taken at baseline, before and within 15 min of the end of pertuzumab infusion for all cycles, and once on days 8 and 15 for Cycles 1 and 2.

Figure 14 Study BO16934: Serum Concentration-Time Plots of Pertuzumab Following IV Infusion of 1050 mg



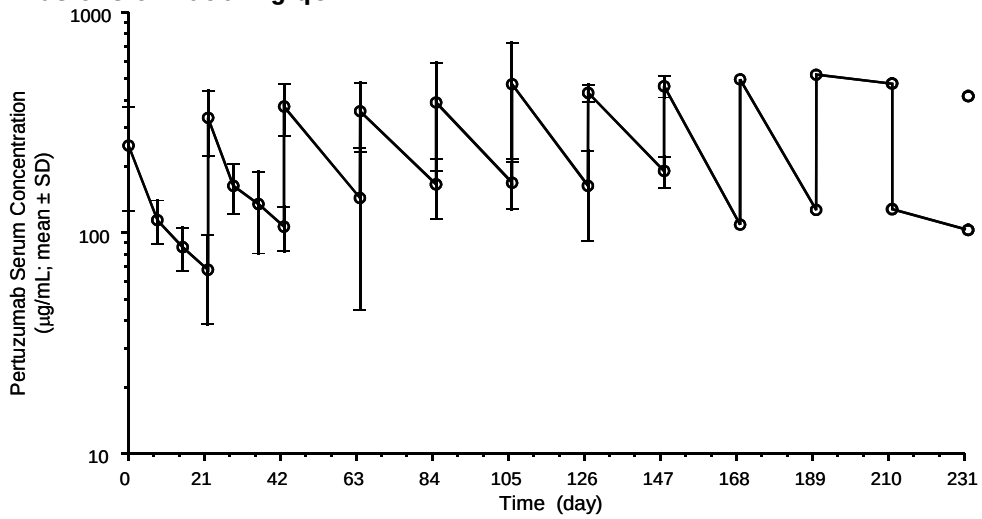
Serum samples were taken at baseline, before and within 15 min of the end of pertuzumab infusion for all cycles, and once on days 8 and 15 for Cycles 1 and 2.

Figure 15 Study BO17004: Serum Concentration-Time Plots of Pertuzumab Following a Loading Dose (IV infusion) of 840 mg Followed by a Maintenance Dose of 420 mg q3wk



Serum samples were taken at baseline, before and within 15 min of the end of pertuzumab infusion for all cycles, and once on Days 8 and 15 for Cycles 1 and 2.

Figure 16 Study BO17004: Serum Concentration-Time Plots of Pertuzumab following IV Infusions of 1050 mg q3wk



Serum samples were taken at baseline, before and within 15 min of the end of pertuzumab infusion for all cycles, and once on Days 8 and 15 for Cycles 1 and 2.

Combination Therapy Studies:

Table 47 Study BO17021: Summary of Pharmacokinetic Parameters for Pertuzumab in Combination with Docetaxel

Dose (mg)	Cycle		$t_{1/2}$ (day)	C_{max} (µg/mL)	AUC_{0-last} (µg.day/mL)	$AUC_{0-\infty}$ (µg.day/mL)	V_z (mL)	Cl (mL/day)
1050	1	n	8	8	8	8	8	8
		Mean	13.36	301	2390	3951	5214	282
		SD	4.18	93	584	919	1386	83
1050	2	n	7	7	7	7	7	7
		Mean	22.08	368	3500	6856	4672	167
		SD	12.89	79	551	2335	1221	49
840	1	n	11	11	11	11	11	11
		Mean	12.13	255	1749	2796	5355	329
		SD	5.40	84	543	967	1680	97
420	2	n	10	10	10	10	10	10
		Mean	19.10	150	1491	2762	4233	169
		SD	9.49	43	472	892	1555	60

Time dependency

In the pivotal study WO20698/4129g, with a loading dose of 840 mg followed by 420 mg as maintenance dose every three weeks, the mean trough concentrations (Cmin) serum pertuzumab concentrations and mean peak (Cmax) serum pertuzumab concentrations were increased from Cycles 3 to 15. The mean and CV% for these two PK parameters for Cycle 1 and 3 are presented in Table 46.

Figure 17 displays pertuzumab concentration data (Cmax and Cmin) from the pivotal study WO20698/TOC4129g:

Figure 17

Mean (±SD) Serum C_{min} (Trough Concentrations) and C_{max} (Peak Concentrations) of Pertuzumab (in the Presence of Trastuzumab and Docetaxel) at Cycles 1, 3, 6, 9, 12 and 15

C_{min} (Trough Concentrations) of Pertuzumab (Collected Pre-Infusion)

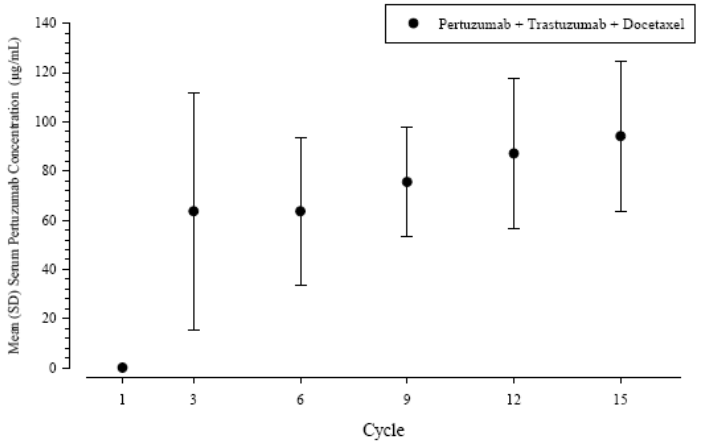
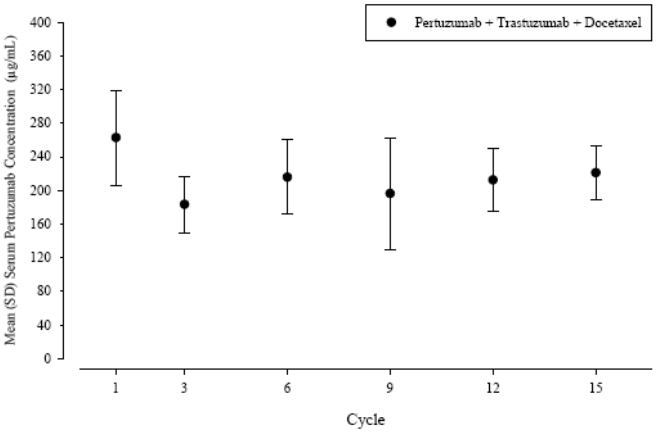


Figure 18

Mean (±SD) Serum C_{min} (Trough Concentrations) and C_{max} (Peak Concentrations) of Pertuzumab (in the Presence of Trastuzumab and Docetaxel) at Cycles 1, 3, 6, 9, 12 and 15 (continued)

C_{max} (Peak Concentrations) of Pertuzumab (Collected at the End of Infusion)



Following a loading dose of 840 mg on Day 1 of Cycle 1 and a dose of 420 mg on Day 2 of Cycle 1 and then 420 mg every three weeks, mean trough concentrations (Cmin) serum pertuzumab concentrations and mean peak (Cmax) serum pertuzumab concentrations increased from Cycles 3 to 15. The mean and CV% for these two PK parameters for Cycle 1 and 3 are presented in table 48.

Table 48

Descriptive Statistics of Serum PK Parameters of Pertuzumab – Cycles 1 and 3

Parameter	Unit	Mean (CV%)	
		Cycle 1 (N=18)	Cycle 3 (N=18)
C_{min}	(µg/mL)	N/A	63.6 (75.6)
C_{max}	(µg/mL)	263 (21.5)	183 (18.3)

Cycle 1 - Day 1- Pertuzumab 840 mg IV; Cycle 1, Day 2 and all subsequent Cycles- Pertuzumab 420 mg IV
Cycle 3 - Pertuzumab 420 mg IV
Patient 9961 was excluded. This patient received 6 mg/kg trastuzumab IV on Day 1 of Cycle 1, instead of 8 mg/kg trastuzumab IV.
N/A = Not applicable
Source: Table 15.1.4.1 and Table 15.1.4.2

Intra- and inter-individual variability

Inter-individual variability (IIV) was 34.5% for Cl and 19.3%for Vc. Inter-individual variability was assessed in the population PK analysis.

Pharmacokinetics in target population

The Phase III study WO20698/TOC4129g investigated the combination of pertuzumab with trastuzumab and docetaxel in patients with HER2 positive first line locally recurrent unresectable or metastatic breast cancer patients (MBC). Sparse sampling of pertuzumab did not allow for the estimation of CL, V_{ss} or $t_{1/2}$, but the trough and peak concentrations (table 19) for pertuzumab were not different from those seen in the other clinical studies. Values of Cmin and Cmax were comparable, but no formal comparison between MBC patients and other patients were presented in the dossier.

Population PK results showed that the median clearance of the patients in the pivotal study WO20698/TOC4129g was lower than the estimated value for all studies (0.191 L/day versus 0.239 L/day). This might be due to the fact that patients from study WO20698/TOC4129g had a lower LBW (46 kg versus 48 kg in all studies) and higher albumin (4.3 g/dL versus 3.9 g/dL in all studies). The PK in these patients was found to be within the range of predictions of the popPK model, after adjusting for albumin and LBW, which suggests that pertuzumab PK in combination with trastuzumab and docetaxel in untreated HER2+ MBC is similar to that in patients receiving pertuzumab in other Phase I/II studies, in which pertuzumab was administered as a single monoclonal antibody-based treatment (Figure 13).

Figure 19 Observed and PopPK Model Predicted Serum Concentrations of Pertuzumab

Semi-log plot

Special populations

Impaired renal function

Safety and efficacy of pertuzumab have not been studied in patients with renal impairment.

Impaired hepatic function

Safety and efficacy of pertuzumab have not been studied in patients with hepatic impairment.

Gender

Overall in the clinical studies, 147 of 444 patients were male gender, which was evaluated as covariate in the Population PK analysis. Gender did not influence pertuzumab PK.

Race

Study JO17076 was performed in Japanese patients with solid tumors. No difference in PK parameters compared to the other clinical studies was observed.

Weight

Based on population PK modelling, weight appeared to impact the trough level of pertuzumab as shown in the table below.

Table 49 Baseline Body Weight and Percentage of Patients with Predicted Trough Concentrations Below 20 µg/mL at Steady State

Sensitivity Result	Baseline Body Weight (kg)			
	36+ thru 61	61+ thru 71	71+ thru 84	84+ thru 151
Number of patients	111	110	109	110
Median $C_{min,ss}$ (µg/mL)	58.4	47.7	52.7	40.8
Number of patient < 20 (µg/mL)	4	9	10	13
% patients < 20 (µg/mL) within each quartile	3.6	8.2	9.2	11.8

Elderly

Age as a covariate in the Population PK analysis did not influence pertuzumab PK.

Children

There were no PK data of pertuzumab in children and adolescents below 18 years of age.

Population PK analysis

A popPK analysis was conducted using pertuzumab concentration data (n=3890) from 444 cancer patients across twelve Phase I/II/III studies to estimate typical values and inter-patient variability of PK parameters. However; concentration data (n=635) from 37 patients were inadvertently excluded and a new PopPK analysis was conducted with concentration data (n=4525) in 481 patients. The amendment of the additional concentration data in the updated PopPK analysis did not change the conclusions made from the first PopPK analysis.

The objectives of the popPK analysis were to:

- Describe the PK of pertuzumab in cancer patients using popPK modeling. Quantify typical PK parameter values and associated inter-individual variability.
- Determine the effects of demographic, disease, target-related and pathophysiological covariates on pertuzumab PK parameters.
- Confirm the selection of fixed, non-weight-based doses for routine clinical use.
- Compare pertuzumab PK between the Phase III (WO20698/TOC4129g) population and the other Phase I/II populations.

The data were analyzed by nonlinear mixed effects modeling using the software package NONMEM 7, version 7.1.2 with the first-order conditional estimation (FOCE) method.

The population PK model development screened for a number of clinically relevant covariates to determine if they contributed to inter-individual variability in PK parameter estimates.

The covariate selection was based on potential biological and clinical rationale and/or previous experience with similar IgG1 monoclonal antibodies and included demographic variables (age, LBW, sex, race), laboratory variables indicating hepatic functions (ALT, AST, TBIL, ALBU) and ALK, serum creatinine (as a marker of renal function) and disease variables (ECOG/KPS, presence/absence MBC, number of metastatic sites, liver metastases and concomitant chemotherapy.

The results of this analysis showed that inter-patient variability was modest, across a large number of patient demographic and laboratory variables. Only serum albumin and lean body weight were found to significantly influence the PK behavior of pertuzumab. However sensitivity analyses performed at the recommended dose and schedule of pertuzumab showed that at the extreme values of these two covariates, there was no significant impact on the ability to achieve target steady-state concentrations identified in preclinical tumor xenograft models. Overall, the population PK analysis supported the use of the recommended pertuzumab dosing regimen of a 840 mg loading dose followed by a 420 mg maintenance dose administered on an every three week schedule.

Pharmacokinetic interaction studies

In vivo

No dedicated drug-drug interaction (DDI) studies were performed and a sub-study from the pivotal study WO20698/TOC4129g served as the in vivo interaction study.

2.4.3. Pharmacodynamics

No clinical pharmacodynamic studies were submitted.

Mechanism of action

Nonclinical studies have shown that the modes of action of trastuzumab and pertuzumab are complementary. In vivo studies in tumour-bearing mice using Near Infrared Fluorescence optical imaging techniques, have demonstrated that binding of each drug when given in combination is not impaired. These data thus suggest there is no negative drug-interaction at the receptor-binding level. In nonclinical studies the combination of pertuzumab and trastuzumab was shown to synergistically inhibit the growth of tumor xenografts derived from HER2-overexpressing non-small cell lung cancer (NSCLC) Calu-3 cells and from KPL-4 breast cancer cells in immune deficient mouse models. In addition to blocking signal transduction, both pertuzumab and trastuzumab are capable of inducing antibody-dependent cell-mediated cytotoxicity (ADCC). However, the combination of the two monoclonal antibodies using in vitro models with human peripheral blood mononuclear cells, does not result in ADCC activity greater than that observed with each drug given individually.

Almost all supporting studies in the development programme for pertuzumab recruited patients unselected for HER2 status and HER2-negative MBC patients. Overall the efficacy of pertuzumab in montherapy in these studies was low and pertuzumab did not appear to improve the efficacy of standard chemotherapy.

Primary and Secondary pharmacology

Primary pharmacology

No clinical dose-finding studies were performed. The target dose has been determined by non-clinical considerations.

The pivotal Phase III trial (WO20698/TOC4129g) used the fixed (non-weight based) dosing regimen of 840 mg loading dose followed by a 420 mg maintenance dose administered q3wk in combination with trastuzumab and docetaxel.

Secondary pharmacology

No formal QTc study was performed.

A sub-study was conducted to investigate the potential of pertuzumab to prolong the QTc interval and other ECG parameters within the Phase III Study WO20698/TOC4129g. The sub-study was designed to enroll a total of 50 ECG-evaluable patients and at least 40 PK-evaluable patients. There were two analysis components: 1) a statistical analysis of ECG data, and 2) a concentration–QTC (C-QTc) analysis.

Based on C-QTc modeling and statistical analysis of ECG parameters, results from this sub-study indicate that pertuzumab does not have a clinically relevant effect on QTcF and other ECG parameters in patients with HER2 positive metastatic breast cancer.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of pertuzumab has been sufficiently investigated, based on non-clinical dose-response studies from which the target concentration was determined. The current dose proposal has been adequately discussed. Population PK analysis showed that for lower doses than the proposed of pertuzumab (840/420 mg) unacceptable large percentages of patients would not achieve the target concentration of 20 µg/ml.

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

Perjeta is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

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

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

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

Perjeta displayed linear pharmacokinetics within the recommended dose range.

Based on the population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of Perjeta between patients < 65 years (n=306) and patients ≥ 65 years (n=175). No dose adjustment is necessary in the elderly population ⩾ 65 years of age. Very limited data are available in patients > 75 years of age. This is appropriately reflected in the SmPC.

No dedicated renal impairment trial for Perjeta has been conducted. Based on the results of the population pharmacokinetic analysis, Perjeta exposure in patients with mild (creatinine clearance [CLcr] 60 to 90 ml/min, N=200) and moderate renal impairment (CLcr 30 to 60 ml/min, N=71) was similar to that in patients with normal renal function (CLcr greater than 90 ml/min, N=200). No relationship between CLcr and Perjeta exposure was observed over the range of CLcr (27 to 244 ml/min). As indicated in the SmPC, dose adjustments of Perjeta are not needed in patients with mild or moderate renal impairment. No dose recommendations can be made for patients with severe renal impairment because of the limited pharmacokinetic data available.

The safety and efficacy of Perjeta have not been studied in patients with hepatic impairment. No specific dose recommendations can be made. This is appropriately reflected in the SmPC.

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

No pharmacokinetic (PK) interactions were observed between Perjeta and trastuzumab, or between Perjeta and docetaxel in a sub-study of 37 patients in the randomised, pivotal trial CLEOPATRA. In addition, in the population PK analysis, no evidence of a drug-drug interaction has been shown between Perjeta and trastuzumab and between Perjeta and docetaxel.

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

This interaction information is included in the SmPC.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology programme of Perjeta was considered acceptable.

2.5. Clinical efficacy

The clinical efficacy submission is based on one pivotal phase III study (CLEOPATRA) with pertuzumab (420mg concentrate for solution for infusion) in patients with locally advanced/metastatic HER2 positive breast cancer and is supported by 2 phase II studies: 1) study WO20697 (NEOSPHERE) in HER2+ patients in the neoadjuvant setting of EBC and 2) study BO17929 in pre-treated patients with

metastatic HER2+ disease who had progressed during treatment with trastuzumab and who had received ≤ 3 lines of therapy.

2.5.1. Dose response studies

Two of the Phase I studies were ascending dose studies in which pertuzumab was administered as a single agent to patients with advanced solid tumors, in doses of 0.5 up to 25 mg/kg administered as an intravenous (IV) infusion every three weeks (q3w). One study (TOC2297g) was conducted in Caucasian patients in the West and the other (JO17076) in Japanese patients.

Pertuzumab was subsequently tested in Phase Ib and II studies as a single agent (Studies TOC2689g, TOC2682g, TOC2572g, BO17004, BO16934, and TOC2664g) or in combination with cytotoxic and other anti-cancer agents, including gemcitabine (Study TOC3258g), capecitabine (Study BO17003), erlotinib (Study WO20024), docetaxel (Study BO17021) and carboplatin-based chemotherapy (BO17931).

In early clinical development, two fixed (non-weight-based) pertuzumab regimens were tested:

- 840 mg loading IV dose followed by 420 mg IV doses q3w
- 1050 mg IV dose q3w (with no initial loading dose).

Population PK analysis based on the data from Phase Ib/II studies with single-agent pertuzumab predicted that >90% of patients receiving the fixed, non-weight-based dosing regimen (840 mg loading dose with a 420 mg maintenance dose) would achieve steady-state trough serum concentrations that were higher than the target serum concentration (> 20 µg/mL, the target for efficacy predicted from nonclinical models). Since the target concentrations were achieved by this dosing regimen, the higher dose of 1050 mg was not selected.

2.5.2. Main study

WO20698C/TOC4129g (CLEOPATRA) – A Phase III, Randomized, Double Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER-2 Positive Metastatic Breast Cancer.

Methods

Study Participants

Inclusion Criteria

Patients had to fulfil all of the following criteria for inclusion in the study:

Disease-specific inclusion criteria:

• Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease, and candidate for chemotherapy. Patients with measurable and/or non-measurable disease were eligible. Patients with bone only metastases were eligible provided they had some bone metastases that had not been previously irradiated and had tumor tissue samples from the primary tumor available for central HER2 testing and subsequent biomarkers analysis. Locally recurrent disease

must not be amenable to resection with curative intent. Patients with de-novo Stage IV disease were eligible.

• HER2-positive (defined as 3+ IHC or FISH amplification ratio ≥ 2.0) MBC confirmed by a Sponsor-designated central laboratory. It was strongly recommended that a formalin-fixed paraffin-embedded (FFPE) tissue block from the primary tumor (or metastatic if the primary was not available) be submitted for central laboratory confirmation of HER2 eligibility; however, if that was not possible, 25 unstained and freshly cut slides were to be submitted. The tissue was used subsequently used for assessment of biomarkers.

General inclusion criteria:

• Age ≥ 18 years.

• LVEF ≥ 50% at baseline (within 42 days of randomization) as determined by either ECHO or MUGA (ECHO being the preferred method. If the patient was randomized to the study, the same method of LVEF assessment, ECHO or MUGA, was to be used throughout the study, and to the extent possible, be obtained at the same institution). All available historic LVEF values during and post-trastuzumab adjuvant treatment for patients who received such adjuvant therapy prior to enrollment into the study were collected.

• Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

• For women of childbearing potential and men with partners of childbearing potential, agreement to use a highly effective, non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner. Contraception use was to continue for the duration of study treatment and for at least 6 months after the last dose of study treatment. Male patients whose partners were pregnant should use condoms for the duration of the pregnancy.

• Signed, written informed consent (approved by the Institutional Review Board or Independent Ethics Committee) obtained prior to any study procedure

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

Cancer-related exclusion criteria:

• History of anti-cancer therapy for MBC (with the exception of one prior hormonal regimen for MBC, which had to be stopped prior to randomization). Anti-cancer therapy for MBC included any EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or more than one prior hormonal regimen for MBC. One prior hormonal 'regimen' for MBC could have included more than one hormonal therapy. If a patient switched therapy due to toxicity or local standard practice, and not due to PD, this was counted as one 'regimen'. If a patient received hormonal therapy for MBC and switched to a different hormonal therapy due to PD, this was counted as two 'regimens' and the patient was not eligible.

• History of approved or investigative tyrosine kinase/HER inhibitors for breast cancer in any treatment setting, except trastuzumab used in the neoadjuvant or adjuvant setting.

History of systemic breast cancer treatment in the neoadjuvant or adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding hormonal therapy) to metastatic diagnosis of < 12 months.

• History of persistent NCI-CTCAE, Version 3.0 Grade ≥ 2 hematologic toxicity resulting from previous adjuvant therapy.

• Current peripheral neuropathy of Grade ≥ 3 at randomization.

• History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin that was previously treated with curative intent.

• Current clinical or radiographic evidence of central nervous system (CNS) metastases. CT or MRI scan of the brain was mandatory (within 28 days of randomization) in cases of clinical suspicion of brain metastases.

• History of exposure to the following cumulative doses of anthracyclines:
- doxorubicin or liposomal doxorubicin > 360 mg/m2
- epirubicin > 720 mg/m2
- mitoxantrone > 120 mg/m2 and idarubicin > 90 mg/m2
- other (ie liposomal doxorubicin or other anthracycline > the equivalent of 360 mg/m2 of doxorubicin)
- if more than one anthracycline was used, then the cumulative dose must not exceed the equivalent of 360 mg/m2 of doxorubicin.

Exclusion criteria related to hematological, biochemical, and organ function parameters:

• Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) or unstable angina.
• History of congestive heart failure (CHF) of any New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (exception: atrial fibrillation, paroxysmal supraventricular tachycardia).
• History of myocardial infarction within 6 months of randomization.
• History of LVEF decline to below 50% during or after prior trastuzumab neoadjuvant or adjuvant therapy.
• Current dyspnea at rest due to complications of advanced malignancy, or other diseases requiring continuous oxygen therapy.

General exclusion criteria:

• Inadequate organ function, evidenced by the following laboratory results within 28 days of randomization:
- Absolute neutrophil count (ANC) < 1,500 cells/mm3
- Platelet count < 100,000 cells/mm3
- Hemoglobin < 9 g/dL
- Total bilirubin > upper limit of normal (ULN) (unless the patient had documented Gilbert's syndrome)
- AST (SGOT) or ALT (SGPT) > 2.5 × ULN
- AST (SGOT) or ALT (SGPT) > 1.5 × ULN with concurrent serum alkaline phosphatase > 2.5 × ULN. Serum alkaline phosphatase may have been 2.5 × ULN only if bone metastases were present and AST (SGOT) and ALT (SGPT) < 1.5 × ULN
- Serum creatinine > 2.0 mg/dL or 177µmol/L
- International normalized ratio (INR) and activated partial thromboplastin time or partial thromboplastin time (aPTT or PTT) > 1.5 × ULN (unless on therapeutic coagulation).

• Current severe, uncontrolled systemic disease (eg, clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures).
• Major surgical procedure or significant traumatic injury within 28 days of study treatment start or anticipation of the need for major surgery during the course of study treatment.
• Pregnant or lactating women.
• History of receiving any investigational treatment within 28 days of randomization.
• Current known infection with HIV, HBV, or HCV.
• Receipt of IV antibiotics for infection within 14 days of randomization.
• Current chronic daily treatment with corticosteroids (dose of > 10 mg/day methylprednisolone equivalent) (excluding inhaled steroids).
• Known hypersensitivity to any of the study drugs.
• Assessed by the investigator as unable or unwilling to comply with the requirements of the protocol.
• Participation in concurrent interventional or non-interventional studies was not permitted

Treatments

Patients with HER2-positive metastatic breast cancer were randomized in a 1:1 ratio to one of two treatment arms to receive:

Arm A : Placebo in combination with trastuzumab and docetaxel (Pla+T+D).

- Placebo: IV infusion every 3 weeks (q3w)
- Trastuzumab: loading dose of 8 mg/kg IV, followed by 6 mg/kg IV q3w
- Docetaxel dose of 75 mg/m2 IV q3w for at least six cycles

Arm B: Pertuzumab in combination with trastuzumab and docetaxel (Ptz+T+D).

- Pertuzumab: loading dose of 840 mg/kg IV, followed by 420 mg/kg IV q3w
- Trastuzumab: loading dose of 8 mg/kg IV, followed by 6 mg/kg IV q3w
- Docetaxel dose of 75 mg/m2 IV q3w for at least six cycles

At the investigator's discretion, the docetaxel dose could be increased to 100 mg/m2 for patients who tolerated at least one cycle without significant toxicities. After Cycle 6, continuation of docetaxel treatment is at the discretion of the patient and treating physician.

Treatment was given until investigator-assessed radiographic or clinical progressive disease (PD), unacceptable toxicity or withdrawal of patient consent. If pertuzumab/placebo and/or trastuzumab had to be permanently discontinued or withheld for more than two cycles, the patient was taken off the study treatment. However, if docetaxel had to be permanently discontinued for reasons related to toxicity, the patient could continue with pertuzumab/placebo and trastuzumab.

Objectives

The primary objective was to compare progression-free survival (PFS), based on tumor assessments by an independent review facility (IRF), between patients in the two treatment arms.

The secondary objectives of this study were to:

- Compare overall survival (OS) between the two treatment arms.
- Compare PFS between the two treatment arms based on investigator assessment of progression.
- Compare the overall objective response rate (ORR) between the two treatment arms.
- Compare the duration of objective response between the two treatment arms.
- Compare the safety profile between the two treatment arms.
- Compare the time to symptom progression between the two treatment arms, as assessed by the FACT Trial Outcome Index—Physical/Functional/Breast (TOI-PFB).
- Evaluate if biomarkers from tumor tissues or blood samples (eg, HER3 expression, Fcγ-Receptor, and serum ECD/HER2 and/or HER ligand concentrations) correlate with clinical outcomes.

Outcomes/endpoints

Primary Endpoint:

- IRF-assessed PFS

Secondary Endpoints:

- Overall survival (OS),
- investigator-assessed PFS,
- objective response rate (ORR),
- duration of response,
- time to symptom progression,
- biomarker analyses.

Sample size

The primary analysis of PFS was planned for when approximately 381 IRF-assessed PFS events had occurred. It was estimated that a total of 381 IRF-assessed PFS events would provide approximately 80% power to detect a 33% improvement in median PFS (hazard ratio [HR] of 0.75 with a two-sided significance level of 5%).
In designing the study, median PFS for the control group was assumed to be 10.5 months, improving to 14 months with the addition of pertuzumab, assuming that PFS is exponentially distributed.

An interim analysis of OS was performed at the time of the primary analysis of PFS. To account for this interim analysis of OS, a Lan−deMets α-spending function with the O'Brien−Fleming stopping boundary was applied to the OS analyses. The protocol estimated that approximately 50% of the total 385 required deaths (193 deaths) would have occurred at the time of the primary analysis of PFS (under this assumption the alpha level for the first OS analysis would be 0.0031).
The final analysis of OS was planned to take place after 385 deaths have occurred, which wouldl provide 80% power to detect a 33% improvement in OS (median OS for the control group is assumed to be 36 months).

Randomisation

Eligible subjects were to be randomized in a 1:1 ratio.

An Interactive Voice Response System (IVRS) was used to collect patient screening information and to randomize eligible patients to one of the two treatment arms. A complete block randomization scheme was applied to achieve balance in treatment assignment within each of the eight strata, as defined by prior treatment status (de novo vs prior adjuvant or neoadjuvant therapy) and region (Europe, North America, South America and Asia).

Blinding (masking)

The study was double-blind.

Statistical methods

Primary endpoint analysis

The population for the primary analysis was the Intent-to-Treat Population: All randomized patients were included in the intent-to-treat (ITT) population

The difference in primary endpoint, IRF-assessed progression-free survival, between the two treatment arms was compared using a two-sided log-rank test at 5% significance level, stratified by prior treatment status (de novo and prior adjuvant or neo-adjuvant therapy) and region (Europe, North America, South America, and Asia).

The following fixed-sequence testing hierarchy was used at the time of the primary PFS analysis to adjust for multiple statistical testing of IRF-assessed PFS, OS and ORR for the purposes of confirmatory statistical testing:

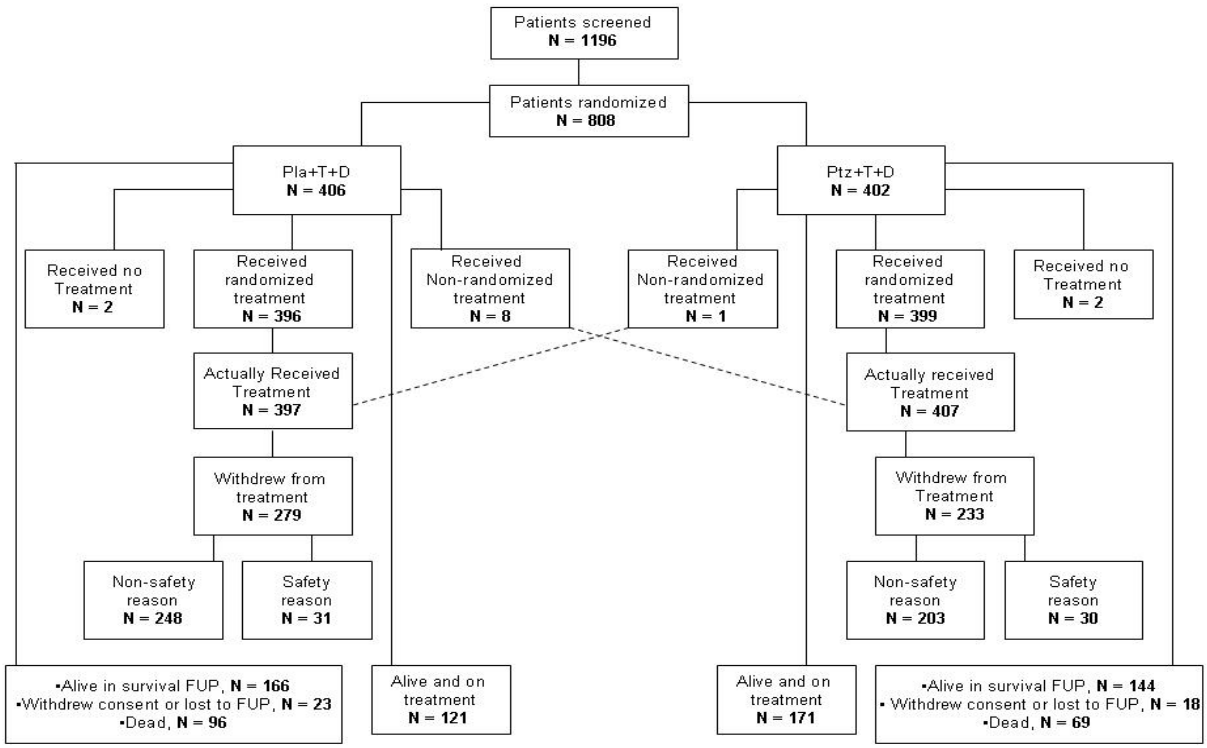
1. Test the primary endpoint, IRF-assessed PFS, at a two-sided 5% significance level. If positive, continue to Step 2; otherwise, stop.
2. Test OS at an overall two-sided 5% significance level. If positive, continue to Step 3; otherwise, stop.
3. Test ORR at a two-sided 5% significance level.

Results

Participant flow

The first patient was enrolled in the pivotal CLEOPATRA study on 12 February 2008. The date for data cut-off for the primary PFS analysis was on 13 May 2011. In total 1196 patients were screened and 808 patients (N) were enrolled and randomized to one of two treatment arms: Pla+T+D (n=406 patients) or Ptz+T+D (n= 402 patients). Overall, patients were enrolled from 204 centres in 25 countries. Two patients in each treatment arm did not receive any study treatment due to elevated liver transaminase levels (3) or a withdrawn consent (1).

Figure 20



Patients withdrawn prematurely from treatment

At the time of data cut-off, 279 patients (70%) had been withdrawn from treatment in the Placebo arm (227 due to progressive disease / 31 for safety reasons) compared to 233 (57%) in the Ptz arm (180 due to progressive disease /30 for safety reasons). 121 patients (29.8%) were still on treatment in the Placebo arm compared to 171 patients (42.5%) in the Ptz arm. 96 patients in the Placebo arm vs. 69

patients in the Ptz arm had died. Overall, these figures seem to be in favour of the Ptz-containing arm. A similar number of patients withdrew consent or were lost to follow-up across treatment arms (23 vs. 18).

A number of protocol violations have been identified. Most of these violations were considered minor in nature, they were equally distributed across treatment arms and they are not considered to have had an impact on the outcome of the pivotal study.

Recruitment

The study was conducted between 12 February 2008 and 13 May 2011, in 25 countries (Brazil, Canada, China, Costa Rica, Croatia, Ecuador, France, Finland, Germany, Great Britain, Guatemala, Italy, Japan, Latvia, Macedonia, Mexico, Poland, Republic of Argentina, Republic of Korea, Republic of the Philippines, Russia, Singapore, Spain, Thailand, USA).

Conduct of the study

Protocol violations were reported in relation to inclusion/exclusion criteria, and on-study procedures and assessments. None of the violations relating to inclusion/exclusion criteria were granted prospectively; all were identified after the patient had been enrolled in the study. The great majority of the protocol violations were due to an assessment being out of the study-defined time window for that assessment, ie, they were minor deviations from the protocol of no clinical significance. None led to exclusion of a patient from the efficacy or safety analysis populations. Approximately 60% of patients in each treatment arm had at least one protocol violation reported (246 patients in each treatment arm).

Violations of Inclusion Criteria

Approximately 1% of patients in each arm violated one of the inclusion criteria defined for the study. However, approximately 12% of patients in each treatment arm overall were categorized as having violated an inclusion criterion because baseline tumor assessments were outside the 28-day screening window. In addition, four patients were randomized despite violations of the entry criteria but never received study medication.

Violations of Exclusion Criteria

Violation of an exclusion criterion occurred for 98 patients (24.1%) in the Pla+T+D arm and 81 patients (20.1%) in the Ptz+T+D arm. These violations mainly related to exclusion criterion number 14 (149 patients overall; 78 in the Pla+T+D arm and 71 in the Ptz+T+D arm). This exclusion criterion defines minimum laboratory test requirements for bone marrow, liver and renal function. Approximately 50% (86/149) of violations within this category were due to missing INR and aPTT (or PTT) results at screening (48/78 in the Pla+T+D arm and 38/71 in the Ptz+T+D arm). This arose from a common misunderstanding amongst investigators. Many thought that baseline assessments of INR/aPTT were only required for patients receiving anti-coagulant therapy. In fact, these tests were intended to provide additional information on liver function in all patients, since patients with hepatic impairment are known to be more susceptible to docetaxel toxicity. However, since docetaxel is routinely given in clinical practice without assessment of INR/aPPT, omission of this baseline test was not considered a concern for patient safety. Of the remaining violations of exclusion criterion no.14, 14/78 in the Pla+T+D arm and 14/71 in the Ptz+T+D arm were for results obtained before the first dose but after randomization. In each of these cases, none of the patients had a value that was outside of the ranges required by the protocol. The remaining 16/78 violations in the Pla+T+D arm and

19/71 violations in the Ptz+T+D arm were either for missing test results or results outside of the requirements of the protocol.

Violations of On-Study Procedures

On-study violations were reported for 193 patients (47.5%) in the Pla+T+D arm and 201 patients (50.0%) in the Ptz+T+D arm. The most common (approximately 40% in each arm) on-study violations were related to ECHO/MUGA scans or tumor assessments being performed outside the protocol-defined window of 9 weeks ± 7 days. Although the overall number of protocol violations appears high, the majority of violations was minor in nature (see listing of protocol violations), and did not affect individual patient safety. In cases where the study team was made aware of a patient being randomized despite violating an inclusion or exclusion criterion, permission was only granted for the patient to continue to receive study treatment if this raised no safety concerns.

Early Withdrawals due to Protocol Violations

Only three patients, one in the Pla+T+D arm and two in the Ptz+T+D arm, withdrew from study treatment due to protocol violations (1 patient with no treatment-free interval between adjuvant systemic therapy and diagnosis of metastatic disease, 1 patient had brain lesions on her baseline tumor assessment, 1 patient had experienced an LVEF reduction to 38% whilst on previous trastuzumab therapy).

A total of 15 investigator sites were audited for the pivotal study WO20698/TOC4129g, as well as the Clinical Research Organization (CRO), Quintiles, responsible for organizing the review of cardiac data by the Cardiac Review Committee (CRC). Major and critical finding(s) involving non-compliance with GCP were observed at investigator sites and also at the CRO, Quintiles. However, appropriate corrective and preventive actions were undertaken and these findings are not considered to have had any impact on the integrity of the data.

Baseline data

A summary of demography characteristics at baseline in the ITT analysis set is shown in the table below.

Table 52

Summary of Baseline Characteristics by Trial Treatment

Taken from t_dm11_i Summary of Demographic Data by Trial Treatment
Protocol(s): WO20698
Analysis: ITT (BY TREATMENT RANDOMIZED) Center: ALL CENTERS
Snapshot Date: 06JUL2011 Clinical Cut-Off Date: 13MAY2011

	Total N = 808	Placebo + Trastuzumab + Docetaxel N = 406	Pertuzumab + Trastuzumab + Docetaxel N = 402
Smoking Status			
CURRENT SMOKER	75 (9.3%)	41 (10.1%)	34 (8.5%)
NEVER SMOKED	629 (77.8%)	315 (77.6%)	314 (78.1%)
PAST SMOKER	104 (12.9%)	50 (12.3%)	54 (13.4%)
n	808	406	402
Baseline ECOG Status			
0	522 (64.6%)	248 (61.1%)	274 (68.2%)
1	282 (34.9%)	157 (38.7%)	125 (31.1%)
2	3 (0.4%)	-	3 (0.7%)
3	1 (0.1%)	1 (0.2%)	-
n	808	406	402
Baseline LVEF (%)			
Mean	65.2	65.5	64.9
SD	6.62	6.53	6.71
SEM	0.23	0.33	0.34
Median	65.0	65.0	65.0
Min-Max	50 - 88	50 - 88	50 - 88
n	803	403	400
Baseline Chest X-Ray Abnormal			
NO	476 (62.8%)	237 (62.4%)	239 (63.2%)
YES	282 (37.2%)	143 (37.6%)	139 (36.8%)
n	758	380	378
Region			
ASIA	253 (31.3%)	128 (31.5%)	125 (31.1%)
EUROPE	306 (37.9%)	152 (37.4%)	154 (38.3%)
NORTH AMERICA	135 (16.7%)	68 (16.7%)	67 (16.7%)
SOUTH AMERICA	114 (14.1%)	58 (14.3%)	56 (13.9%)
n	808	406	402
Prior Treatment Status			
ADJUVANT OR NEO-ADJUVANT THERAPY	376 (46.5%)	192 (47.3%)	184 (45.8%)
DE NOVO	432 (53.5%)	214 (52.7%)	218 (54.2%)
n	808	406	402
Disease Type at Screening			
NON-VISCERAL DISEASE	178 (22.0%)	90 (22.2%)	88 (21.9%)
VISCERAL DISEASE	630 (78.0%)	316 (77.8%)	314 (78.1%)
n	808	406	402
IRF-Determined Disease Status at Screening			
MEASURABLE DISEASE	679 (88.6%)	336 (88.7%)	343 (88.6%)
NON-MEASURABLE DISEASE	87 (11.4%)	43 (11.3%)	44 (11.4%)
n	766	379	387
Investigator-Determ Disease Status Screening			
MEASURABLE DISEASE	738 (91.3%)	371 (91.4%)	367 (91.3%)
NON-MEASURABLE DISEASE	70 (8.7%)	35 (8.6%)	35 (8.7%)
n	808	406	402

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
^ Does the patient agree to use an effective method of contraception? (applicable to male patients consenting to Protocol C only)
DM11 18JUL2011:15:51:33 PDRD (2 of 2)

As expected for patients with advanced HER2+ BC, the study population was mainly represented by women (only 2 men were enrolled in the Placebo arm), with a median age of 54 years (only 15.7% of patients were ≥ 65 years of age), and therefore the majority were post-menopausal (63.5%). The majority of patients were White (59.4%). The second-largest race was Asians (32.3%). Approximately, one third of patients were enrolled in Europe (37.9%), one third in Asia (31.3%) and the rest in North (16.7%) – and South (14.1%) – America.

Only about a half of patients (46.5%) had received prior (neo-) adjuvant therapy whereas the rest of patients were untreated patients with advanced disease at the time of diagnosis. Among patients who received prior (neo-)adjuvant therapy, only 10% had received trastuzumab (47 patients in the pertuzumab arm and 41 patients in the placebo arm). The vast majority of the studied population was therefore trastuzumab naïve. However, less than 10% of patients usually present with metastatic disease at the time of diagnosis in Western countries. The majority of patients had measurable disease (IRF-determined: 88.6%) and visceral involvement at screening (78%) which is also indicative of a relatively advanced disease stage.

In general, baseline characteristics were well-balanced between treatment arms apart from the ECOG PS status where a slightly higher percentage of patients with PS 0 was found in the Ptz arm (68.2%) compared to the Placebo arm (61.1%).

One third of tumors were moderately differentiated adenocarcinomas of the breast, one third was poorly differentiated and in one third the histological tumour grade was unknown. About 90% of tumours were HER2+ by IHC staining and > 99% of tumours was HER2+ by FISH. For the majority of patients (> 90%) the HER2 status was only tested in the primary tumour specimen. About half of tumours were ER/PgR positive which is in line with previous findings in HER2+ BC populations. The median disease-free interval was similar between treatment arms (29.0 months in the Placebo arm vs. 31.0 months in the Ptz arm). The number of patients with locally recurrent disease was very low in both treatment arms (19 patients in total).

Numbers analysed

The following analysis populations were defined:

Intent-to-Treat Population: All randomized patients were included in the intent-to-treat (ITT) population. The ITT population comprised all 808 randomized patients (406 Pla+T+D, 402 Ptz+T+D).

Other Analysis Populations: For objective response and time to response, only patients with measurable disease at baseline were included in the analysis. For duration of response, only responders were included in the analysis. For time to symptom progression based on the FACT-B questionnaire, only female patients were included in the analysis, since a number of the questions were applicable to female patients only.

Safety Analysis Population (SAP); Patients who received any amount of any component of study treatment were included in the safety analysis population. The SAP comprised of 804 patients, with two patients in each treatment arm receiving no study medication after randomization. Eight of the patients randomized to receive placebo actually received at least one dose of pertuzumab during the study. For the purposes of the safety analysis, these patients were included in the Ptz+T+D arm. In addition, one patient randomized to receive pertuzumab received placebo at every cycle, and is therefore included in the Pla+T+D arm for all safety analyses. Thus, overall, the SAP comprised 397 patients in the Pla+T+D arm and 407 patients in the Ptz+T+D arm.

Outcomes and estimation

Primary Endpoint: PFS in ITT population

Table 53. Study WO20698/TOC4129g: Summary of IRF-Assessed Progression-Free Survival months) (ITT Population)

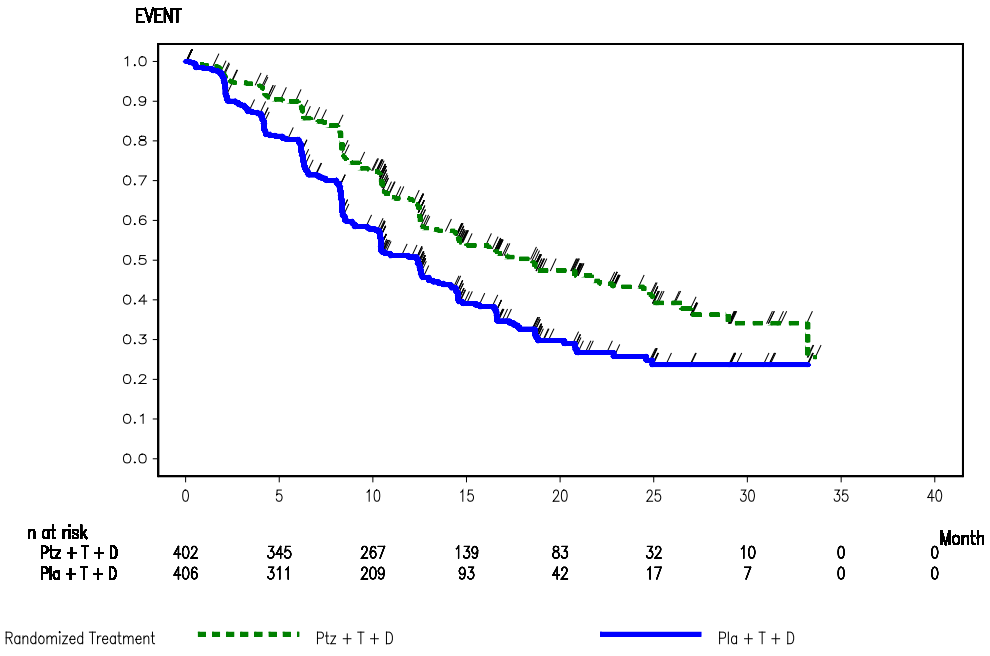
Analysis: ITT (By Treatment Randomized) Snapshot Date: 06JUL2011 Clinical Cut-Off Date: 13MAY2011

	Placebo + Trastuzumab + Docetaxel (N=406)		Pertuzumab + Trastuzumab + Docetaxel (N=402)
Patients included in analysis[1]	406 (100.0 %)		402 (100.0 %)
Patients with event	242 (59.6 %)		191 (47.5 %)
Patients without event*	164 (40.4 %)		211 (52.5 %)
Time to event(Months)			
Median#	12.4		18.5
95% CI for Median#	[10;13]		[15;23]
25% and 75%-ile#	6;25		9;.
Range##	0 to 33		0 to 34
p-value (Log-Rank test, stratified**)		<.0001	
Hazard Ratio (stratified**)		0.62	
95% CI		[0.51;0.75]	
P-value		<.0001	
1 year duration			
Patients remaining at risk	161		211
Event Free Rate#	0.51		0.65
95% CI for Rate#	[0.46;0.56]		[0.60;0.70]

[1] Number of patients in the respective treatment arms who are actually included in the analysis (patients for which records in the event data set are available, time-to-event is non-negative and non-missing and censoring variable is non-missing). *censored. Event = IRF-assessed PFS. # Kaplan-Meier estimates. ## including censored observations. ** Stratified by prior treatment status and region Program : $PROD/cdp11450/wo20698/t_ttev.sas. Output : $PROD/cdp11450/j20698b/reports/t_ttev_irf_str_pfs_i.out. 08JUL2011 13:13 t_ttev_irf_str_pfs_i

Figure 21. Study WO20698/TOC4129g: Kaplan-Meier Plot of IRF-Assessed Progression-Free Survival (ITT Population)

f_ttev1_irf_pfs_i Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival Time (months) by Trial Treatment
Protocol: WO20698
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 06JUL2011 Clinical Cut-Off Date: 13MAY2011



Sensitivity analyses

Six pre-specified sensitivity analyses were performed that took account of the earliest PD data (IRF or investigator assessment), censored for use of next-line therapies, IRF-assessed PFS during treatment or treatment withdrawals due to toxicity or investigated the impact of missing assessments or included all early deaths as events. HRs in all of these analyses were very consistent with the primary analysis (HR from 0.58 to 0.66) thereby confirming the robustness of the primary result.

Table 54

Overview of Sensitivity Analysis Results for IRF-Assessed PFS (ITT Population)

	Pla+T+D N=406	Ptz+T+D N=402
Sensitivity Analysis 1: PD date is earliest of IRF- or Investigator-assessed PD		
IRF-assessed PFS, median (months)*	10.4	14.6
Hazard ratio (95% CI)	0.66 (0.55; 0.79)	
Log-rank test p-value	< 0.0001	
Sensitivity Analysis 2: Next line anti-cancer therapy (NACT)		
IRF-assessed PFS, median (months)*	12.3	18.7
Hazard ratio (95% CI)	0.58 (0.48; 0.71)	
Log-rank test p-value	< 0.0001	
Sensitivity Analysis 3: Censoring for IRF-assessed PFS during treatment		
IRF-assessed PFS, median (months)*	12.4	20.8
Hazard ratio (95% CI)	0.58 (0.47; 0.71)	
Log-rank test p-value	< 0.0001	
Sensitivity Analysis 4: Correcting for potential bias as a result of a missing assessments		
IRF-assessed PFS, median (months)*	12.3	18.5
Hazard ratio (95% CI)	0.62 (0.51; 0.75)	
Log-rank test p-value	< 0.0001	
Sensitivity Analysis 5: Including all deaths as an event		
IRF-assessed PFS, median (months)*	12.4	17.2
Hazard ratio (95% CI)	0.63 (0.52; 0.76)	
Log-rank test p-value	< 0.0001	
Sensitivity Analysis 6: Controlling for treatment withdrawals due to toxicity		
IRF-assessed PFS, median (months)*	12.3	18.5
Hazard ratio (95% CI)	0.61 (0.50; 0.74)	
Log-rank test p-value	< 0.0001	

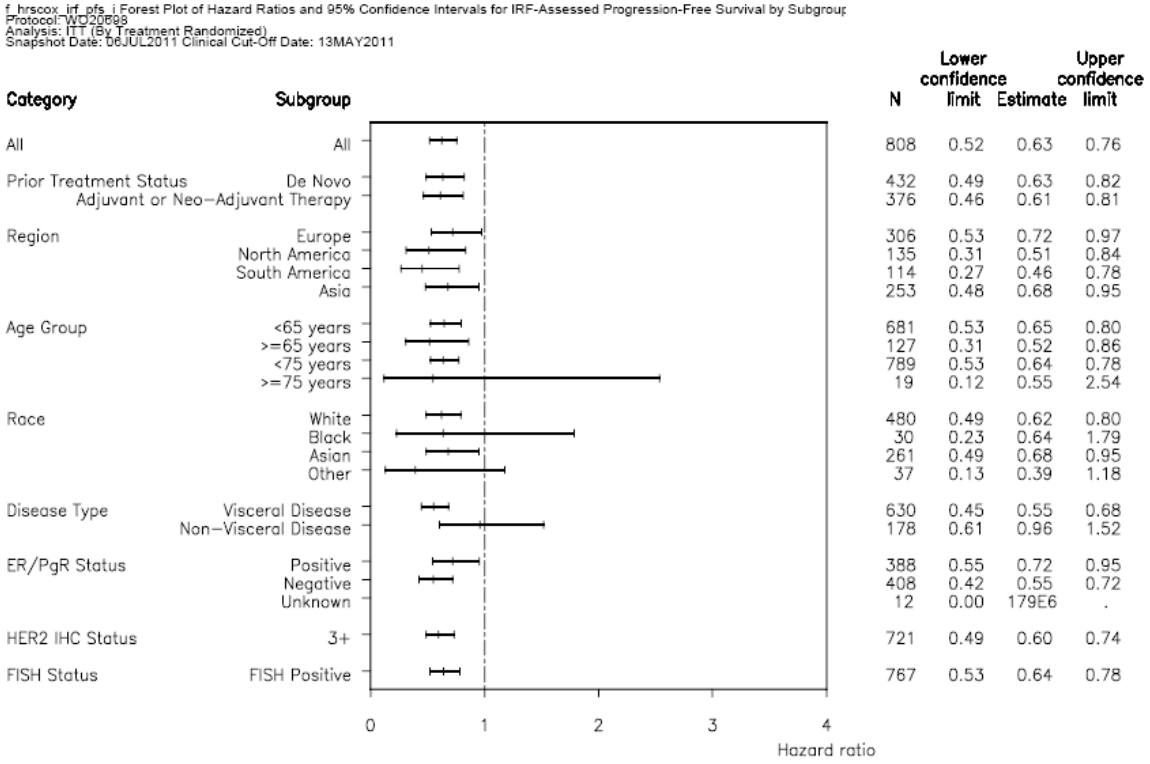
The robustness of the primary result was also tested by taking account of different prognostic factors in exploratory univariate and multivariate Cox regression analyses. None of the tested covariates had an impact on the treatment effect when adjusted for these covariates. Similarly, although ECOG status was found to be significantly associated with PFS, it did not have an influence on the adjusted treatment effect in the model.

Subgroup analyses for PFS

The pre-specified subgroup analyses demonstrated very consistent benefits in most subgroups.

Table 55

Forest Plot Hazard Ratios and 95% Confidence Intervals for IRF-Assessed Progression-Free Survival by Subgroup



Race - other includes patients in the following eCRF race categories: 'American Indian or Alaska Native', 'Native Hawaiian or other Pacific Islander', 'Other'
Non-visceral disease defined as tumors located in the breast, bone, bone marrow, lymph nodes, skin or soft tissue
ER/PgR positive is defined as ER positive and/or PgR positive; ER/PgR negative is defined as ER negative and PgR negative

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Visceral disease status

Results of univariate analysis underlined a covariate effect for visceral disease status versus non-visceral status, showing a non adjusted HR on IRF-PFS of 0.63. Moreover, in the multivariate Cox regression analysis for IRF-PFS using a stepwise approach visceral disease status was still significant after adjustment (visceral disease status vs. non-visceral HR=0.61). An exploratory analysis defined post-database lock was performed and a significant treatment by covariate interaction was observed only for visceral disease status (p = 0.0332). Interaction effect is supported by the results coming from a subgroup analysis showing a different treatment effect when patients were stratified according to visceral disease status (HR = 0.55 [0.45, 0.68] in visceral disease subgroup versus HR= 0.96 [0.61, 1.52] in the non-visceral disease subgroup).

Table 56. Summary of IRF-Assessed Progression-free Survival by Visceral/Non-Visceral disease status

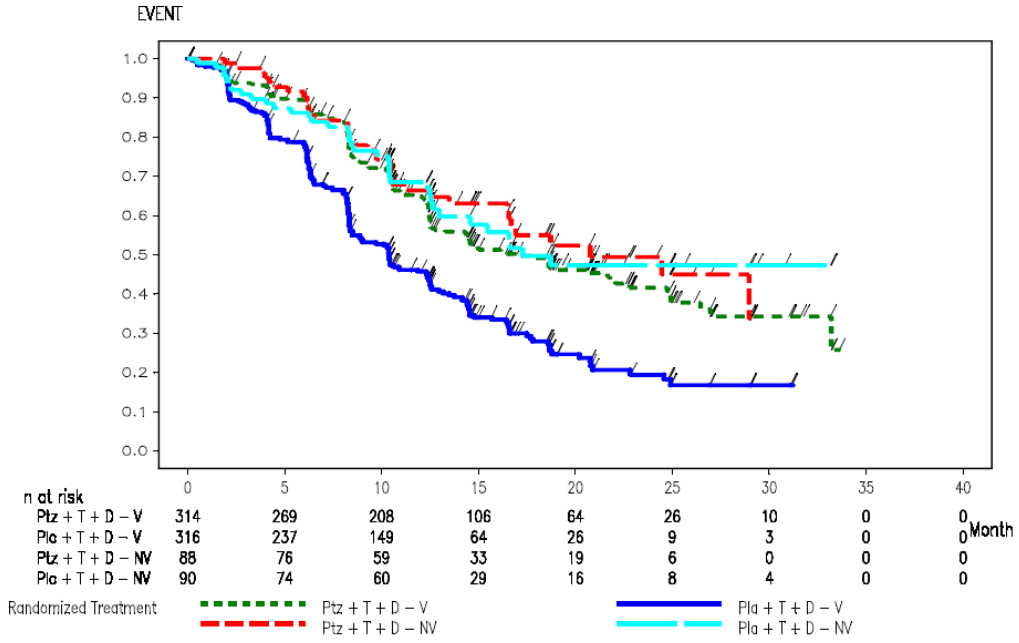
	Pla+T+D	Ptz+T+D
Overall		
Patients included in the analysis	406	402
Patients with an event	242 (59.6)	191 (47.5)
Median Time to event (months)	12.4	18.5
p-value (Log-Rank test)	<0.0001	
Hazard Ratio	0.62 [0.51; 0.75]	
Visceral		

Patients included in the analysis	316	314
Patients with an event	205 (64.9)	155 (49.4)
Median Time to event (months)	10.4	17.2
Hazard Ratio	0.55 [0.45; 0.68]	
Non-Visceral		
Patients included in the analysis	90	88
Patients with an event	37 (41.1)	36 (40.9)
Median Time to event (months)	17.3	20.8
Hazard Ratio	0.96 [0.61; 1.52]	

Derived from t_ttev_str_irf_pfs_i and t_ttev_irf_vnd_pfs_i.(in the WO20698/TOC4129g CSR)

The Figure below shows Kaplan Meier curves of the two treatment arms stratified by visceral disease status.

Figure 22



Ancillary analyses

The applicant submitted a number of post-hoc exploratory investigations in order to further address the potential importance of the ECOG status, the HER2 IHC status, docetaxel dose escalations, and of whether patients had previously been exposed to trastuzumab or not.

Patients with HER2 IHC 2+ disease

Patients with HER2 IHC 2+ disease (n=79) seemed to have a smaller benefit (HR = 0.90 [0.53, 1.54]), but the group was small (n=79) and the broad confidence intervals are noted. 78 of these 79 patients were FISH positive.

Patients with prior exposure to trastuzumab in the (neo-) adjuvant setting:

Only 88 patients had previously received trastuzumab. Nevertheless, a similar benefit in favor of adding Ptz to T+D was also observed in this small sub-group (HR= 0.62 (95 CI: 0.35; 1.07). The observed result in the Placebo arm is also considered representative.

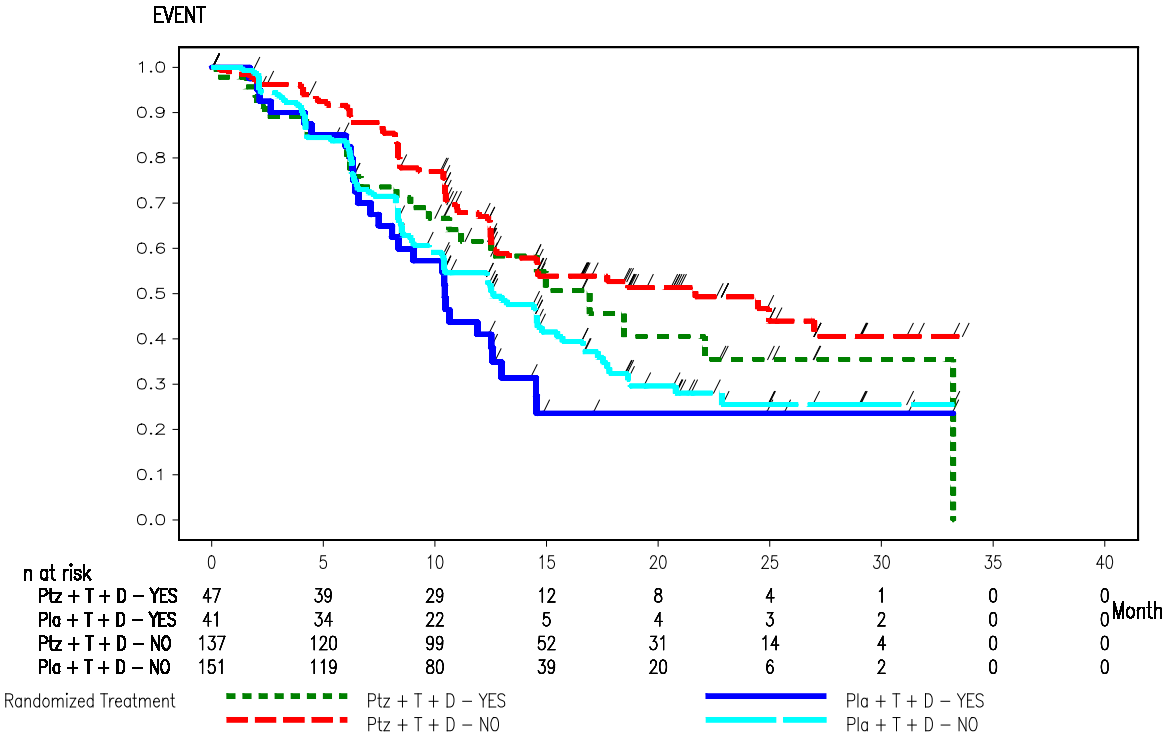
Table 57. Summary of Efficacy in Patients with Prior Trastuzumab Exposure Compared with the Whole WO20698/TOC4129g Study Population

	Sub-population - previously exposed to trastuzumab		Overall patient population	
	Pla+T+D n=41	Ptz+T+D n=47	Pla+T+D n=406	Ptz+T+D n=402
IRF-assessed PFS				
no. pts with event	28 (68.3%)	24 (51.1%)	242 (59.6%)	191 (47.5%)
median time to event (months)	10.4	16.9	12.4	18.5
p value (Log Rank test, stratified)	0.08**		<0.0001	
HR*	0.62		0.62	
95% CI for HR	0.35, 1.07		0.51;0.75	

From t_ttev_irf_adjn_pfs_i, Section 3.2.2 and 3.2.3.1 of the WO20698/TOC4129g CSR. *HR for the overall analysis is stratified, HR for the sub-pop is unstratified (as with all subgroup analyses). ** post hoc exploratory test

Figure 23 IRF-assessed PFS by Prior Trastuzumab Therapy in the Sub-group of Patients who Received Prior (Neo)adjuvant Therapy

Protocol: WO20698
Analysis: ITT (by treatment randomized)
Snapshot date: 06JUL2011 Clinical cut-off Date: 13MAY2011



Ptz+T+D – Yes = Pertuzumab+Trastuzumab+Docetaxel and Prior Trastuzumab use: Yes
Ptz+T+D – No = Pertuzumab+Trastuzumab+Docetaxel and Prior Trastuzumab use: No
Pla+T+D – Yes = Placebo+Trastuzumab+Docetaxel and Prior Trastuzumab use: Yes
Pla+T+D – No = Placebo+Trastuzumab+Docetaxel and Prior Trastuzumab use: No

Up-dated overall survival and investigator-assessed PFS analyses based on a data cut-off date of 14 May 2012 were essentially unchanged compared with the primary analyses. Of note, the updated HR

for OS for patients with prior (neo)adjuvant trastuzumab was 0.68 (95% CI: 0.30, 1.55), which is consistent with the HR for the overall patient population of 0.66 (95% CI; 0.52; 0.84).

Patients with ECOG status 0 or 1+

An exploratory analysis indicated that a benefit in favour of Ptz+T+D was observed both in patients with an ECOG status of 0 (n = 522; HR= 0.70 [0.55, 0.90]) and in patients with an ECOG status of 1+ (n = 286, HR= 0.55 [0.40, 0.74]) at baseline.

Patients with docetaxel dose escalations (from 75 mg/m2 to 100 mg/m2)

Relatively few patients had the docetaxel dose uptitrated to 100 mg/2 (n= 109). The data indicate that the higher docetaxel dose did not have a major impact on the efficacy results as HR for PFS = 0.62 (0.50; 0.76) in patients who were not dose escalated compared to HR= 0.65 (0.37, 1.13) in patients who received the highest docetaxel dose.

SECONDARY ENDPOINTS

PFS (INV-assessed)

PFS based on INV assessment was in line with the result based on IRC assessment (HR for PFS (INV) = 0.65 (95% CI 0.54- 0.78, p< 0.0001), median PFS was 12.4 months in the Pla+T+D arm vs. 18.5 months in the Ptz+T+D arm.

The Applicant has performed an updated PFS analysis one year after the original, primary IRF-determined PFS analysis. At the time of the updated INV-based PFS analysis (data cut-off: 14 May 2012) 68% of patients had had a PFS event (72.9% in the Placebo arm and 63.9% in the Ptz arm). The updated HR = 0.69 (95% CI: 0.58, 0.81). The K-M curves demonstrated an early and clear separation. The median PFS was 12.4 months in the Placebo arm compared with 18.7 months in the Ptz arm. Consistent results were observed in the subgroup analyses. Thus, the previously observed PFS-benefit has been maintained and confirmed in this updated analysis.

Figure 24. Kaplan-Meier Curve of Investigator-Assessed Progression-Free Survival (Data cut-off 14 May 2012).

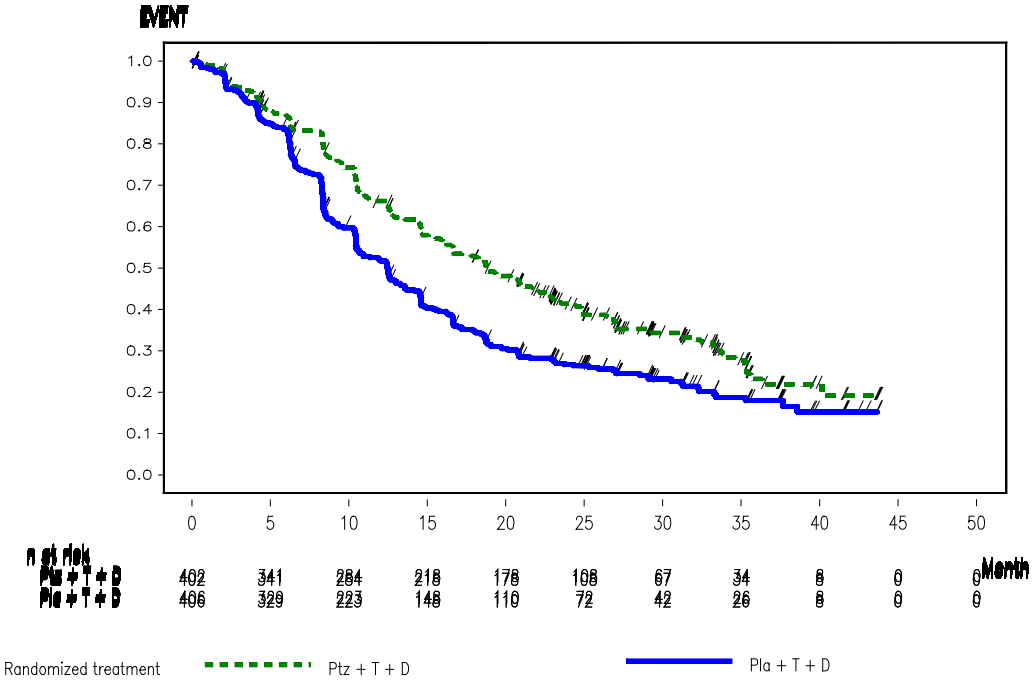
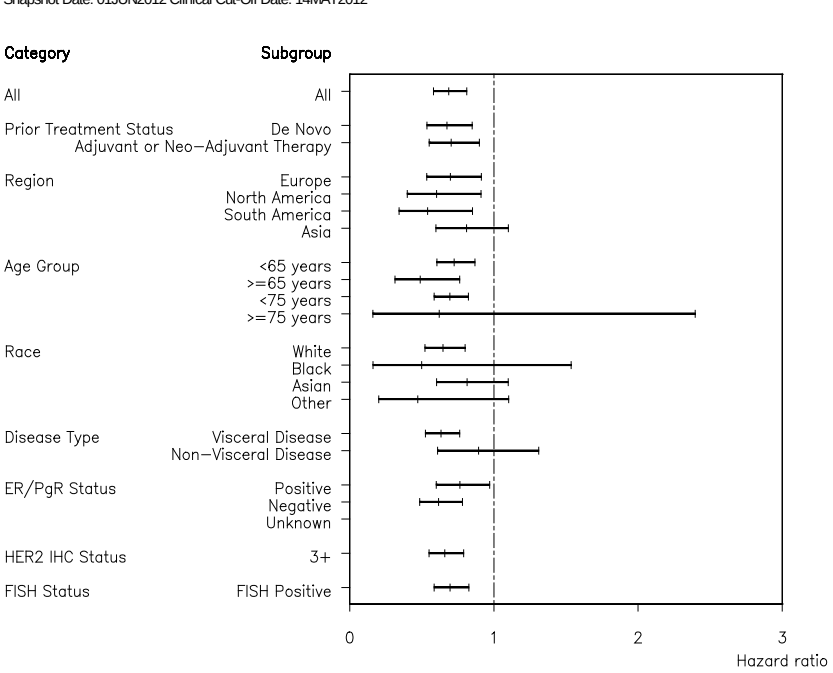

EVENT
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
35
40
45
50
Month
n at risk
Ptz + T + D
Pla + T + D
Randomized treatment
Ptz + T + D
Pla + T + D

Figure 25 Forest Plot Hazard Ratios and 95% Confidence Intervals for Investigator-Assessed Progression-Free Survival by Subgroup (Data cut off 14 May 2012)

f_hrscox_inv_pfs_i Forest Plot of Hazard Ratios and 95% Confidence Intervals for Investigator-Assessed Progression-Free Survival by Subgroup
Protocol: CD20698K
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 01JUN2012 Clinical Cut-Off Date: 14MAY2012



Race - other includes patients in the following eCRF race categories: 'American Indian or Alaska Native', 'Native Hawaiian or other Pacific Islander', 'Other'
Non-visceral disease defined as tumors located in the breast, bone, bone marrow, lymph nodes, skin or soft tissue
ER/PgR positive is defined as ER positive and/or PgR positive; ER/PgR negative is defined as ER negative and PgR negative

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Overall Survival (OS), First Analysis

OS data was not mature at the time of data cut-off for the primary analysis (13 May 2011). The duration of follow-up was similar across treatment arms (19.3 months). In the Placebo arm 96 patients had died (23.6%) compared to 69 deaths (17.2%) in the Ptz arm. The median time to death had not been reached in any of the treatment arms. The HR for OS was 0.64 (95% CI: 0.47; 0.88, p = 0.0053) but the O'Brien-Fleming stopping boundary was not met (HR ≤ 0.603, p ≤ 0.0012). The K-M curves show a separation in favor of the Ptz arm just before ten months. Of note, cross-over between treatment arms was not allowed per protocol.

Table 58

Summary of Overall Survival

t_ttev_str_os_i Summary of Overall Survival (months) by Trial Treatment, Stratified by Prior Treatment Status and Region
Protocol: WO20698
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 06JUL2011 Clinical Cut-Off Date: 13MAY2011

	Placebo + Trastuzumab + Docetaxel (N=406)		Pertuzumab + Trastuzumab + Docetaxel (N=402)
Patients included in analysis[1]	406 (100.0 %)		402 (100.0 %)
Patients with event	96 (23.6 %)		69 (17.2 %)
Patients without event*	310 (76.4 %)		333 (82.8 %)
Time to event(Months)			
Median#	.		.
95% CI for Median#	[30;.]		[.;.]
25% and 75%-ile#	21;.		26;.
Range##	0 to 38		0 to 38
p-value (Log-Rank test, stratified**)		0.0050	
Hazard Ratio (stratified**)		0.64	
95% CI		[0.47;0.88]	
P-value		0.0053	
1 year duration			
Patients remaining at risk	300		327
Event Free Rate#	0.89		0.95
95% CI for Rate#	[0.86;0.92]		[0.92;0.97]

[1] Number of patients in the respective treatment arms who are actually included in the analysis (patients for which records in the event data set are available, time-to-event is non-negative and non-missing and censoring variable is non-missing).
*censored.
Event = OS.
# Kaplan-Meier estimates.
including censored observations.
** Stratified by prior treatment status and region

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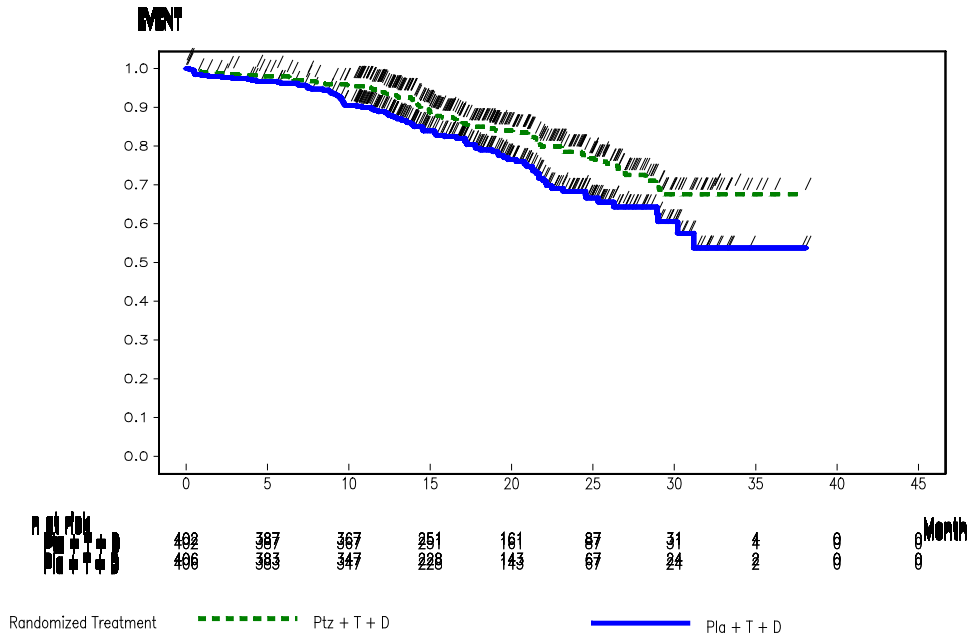
Output : $PROD/cdpl1450/j20698b/reports/t_ttev_str_os_i.out
08JUL2011 13:16 Page 1 of 1

Figure 26. Study WO20698/TOC4129g: Kaplan-Meier Plot of Overall Survival (ITT Population)

f_ttev1_os_i Kaplan-Meier Curve of Overall Survival (months) by Trial Treatment
Protocol: WO20698
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 06JUL2011 Clinical Cut-Off Date: 13MAY2011



Updated OS results

The second interim analysis of OS (data cut-off May 14th 2012) was based on events one year after the data cut-off of the primary analysis, and included 102 additional deaths. At the time of this second analysis, 267 deaths had occurred, specifically 154 events (37.9%) in the placebo arm and 113 events (28.1%) in the pertuzumab arm. Results from the second interim analysis of OS (considered as the final OS analysis) showed a significant survival benefit for patients randomized to receive pertuzumab (stratified by prior treatment status and region), with a HR of 0.66 (95% CI: 0.52; 0.84, p= 0.0008). Median survival was of 37.6 months in the placebo arm and was still not reached in the pertuzumab arm. There was a sustained survival advantage in the pertuzumab arm with 94%, 81% and 66% of patients surviving in the PTZ+T+D arm versus 89%, 69% and 50% in the Pl+T+D arm at 12, 24 and 36 months, respectively.

The results from subgroup analyses were consistent with those obtained for the overall ITT population with the exception of the HR obtained for the subgroup of patients with non-visceral disease (HR 1.42) where the number of events was low (33 deaths ≈ 18.5%)

Figure 27. Study WO20698/TOC4129g: Kaplan-Meier Curve of Overall Survival (months) (ITT Population)

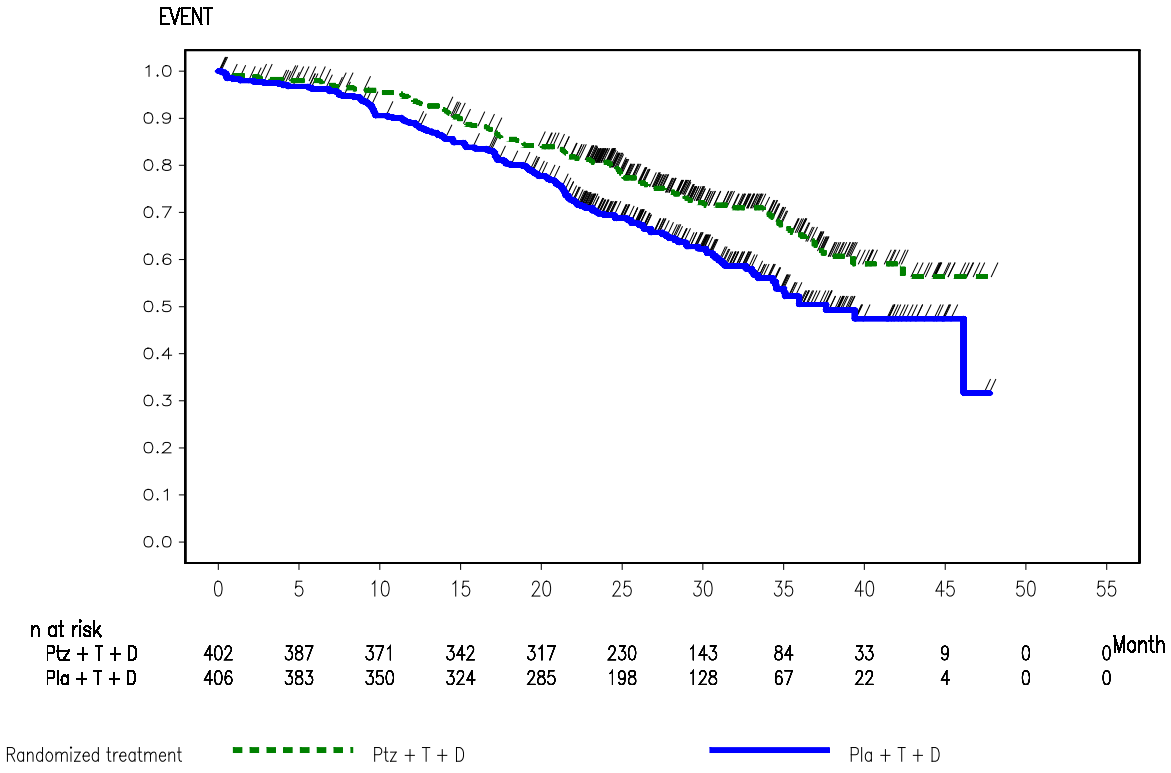
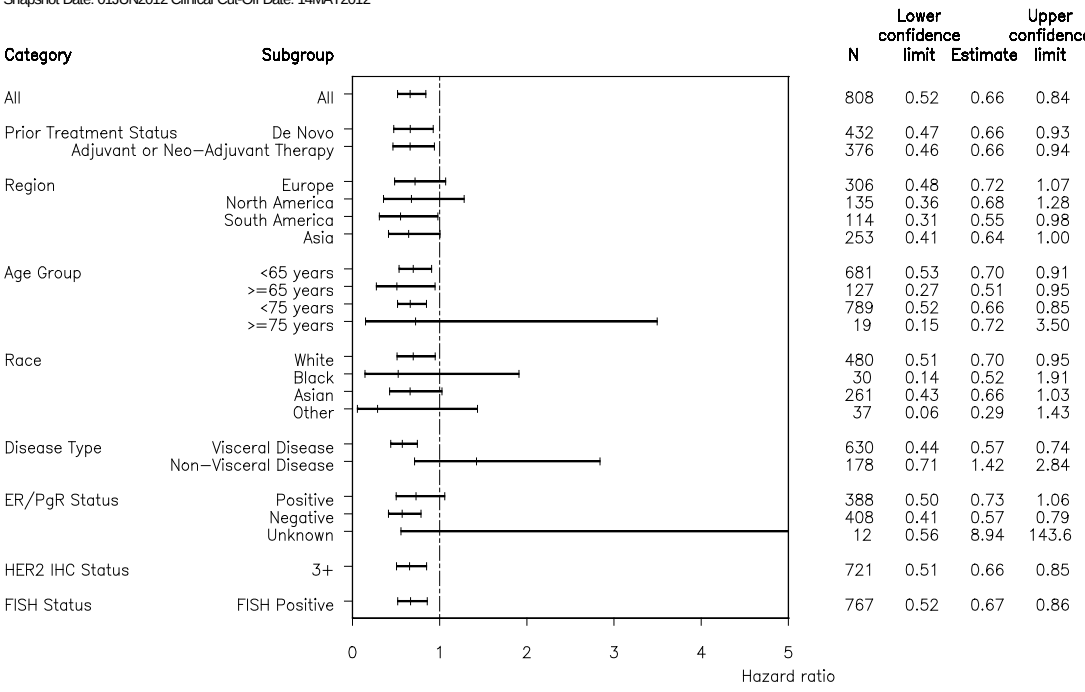


Figure 28. Study WO20698/TOC4129g: Forest Plot of Hazard Ratios and 95% Confidence Intervals for Overall Survival by Subgroup (ITT Population)

f_hrscox_os_i Forest Plot of Hazard Ratios and 95% Confidence Intervals for Overall Survival by Subgroup
Protocol: CD20698K
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 01JUN2012 Clinical Cut-Off Date: 14MAY2012



Race - other includes patients in the following eCRF race categories: 'American Indian or Alaska Native', 'Native Hawaiian or other Pacific Islander', 'Other'
Non-visceral disease defined as tumors located in the breast, bone, bone marrow, lymph nodes, skin or soft tissue
ER/PgR positive is defined as ER positive and/or PgR positive; ER/PgR negative is defined as ER negative and PgR negative

Program : $PROD/cdp11450/wo20698/f_hrscox.sas / Output : $PROD/cd11450k/k20698a/reports/f_hrscox_os_i.cgm
13JUN2012 11:57

Objective Response Rate and Duration of Response

A higher ORR was observed in the Ptz+T+D arm (80.2%) compared to the Pla+T+D arm (69.3%). The majority of responses in the Ptz arm were PRs. The median duration of responses was also longer in the Ptz+T+D arm (87.6 weeks) than in the Pla+T+D arm (54.1 weeks).

Table 59. Summary of IRF Best Overall Response (RECIST) for Objective Response

t_rr_irf_str_or_imd_i Summary of IRF Best Overall Response (RECIST) for Objective Response (OR) by Trial Treatment, Stratified by Prior Treatment Status and Region, Patients with IRF-Determined Measurable Disease at Baseline
Protocol: WO20698
Analysis: ITT (By Treatment Randomized)
Snapshot Date: 06JUL2011 Clinical Cut-Off Date: 13MAY2011

	Placebo + Trastuzumab + Docetaxel (N=336)	Pertuzumab + Trastuzumab + Docetaxel (N=343)
Responders *	233 (69.3 %)	275 (80.2 %)
Non-Responders	103 (30.7 %)	68 (19.8 %)
95% CI for Objective Response Rate**	[64.1; 74.2]	[75.6; 84.3]
Difference in Response Rates	10.83	
95% CI for Difference in Response Rates#	[4.2; 17.5]	
p-Value ##	0.0011	
Odds Ratio	1.79	
95% CI for Odds Ratio	[1.26;2.54]	
Complete response (CR)	14 (4.2 %)	19 (5.5 %)
95% CI for complete response rate**	[2.3; 6.9]	[3.4; 8.5]
Partial Response (PR)	219 (65.2 %)	256 (74.6 %)
95% CI for partial response rate**	[59.8; 70.3]	[69.7; 79.2]
Stable disease (SD)$	70 (20.8 %)	50 (14.6 %)
95% CI for stable disease rate**	[16.6; 25.6]	[11.0; 18.8]
Progressive disease (PD)	28 (8.3 %)	13 (3.8 %)
95% CI for progressive disease rate**	[5.6; 11.8]	[2.0; 6.4]

Number of patients in the respective treatment arms who are actually included in the analysis is the number with IRF-determined measurable disease at baseline
* Patients with best overall response of confirmed CR or PR by RECIST.
** 95% CI is the exact binomial using Pearson-Clopper method.
# Approximate 95% CI for difference of two rates using Hauck-Anderson method.
Mantel-Haenszel chi-square test stratified by prior treatment status and region.
$ SD maintained for at least least 42 days
Response based on IRF tumor assessments reported up to PD, death or start of next-line anti cancer therapy, whichever occurs earliest.

Time to Symptom Progression (HRQoL)

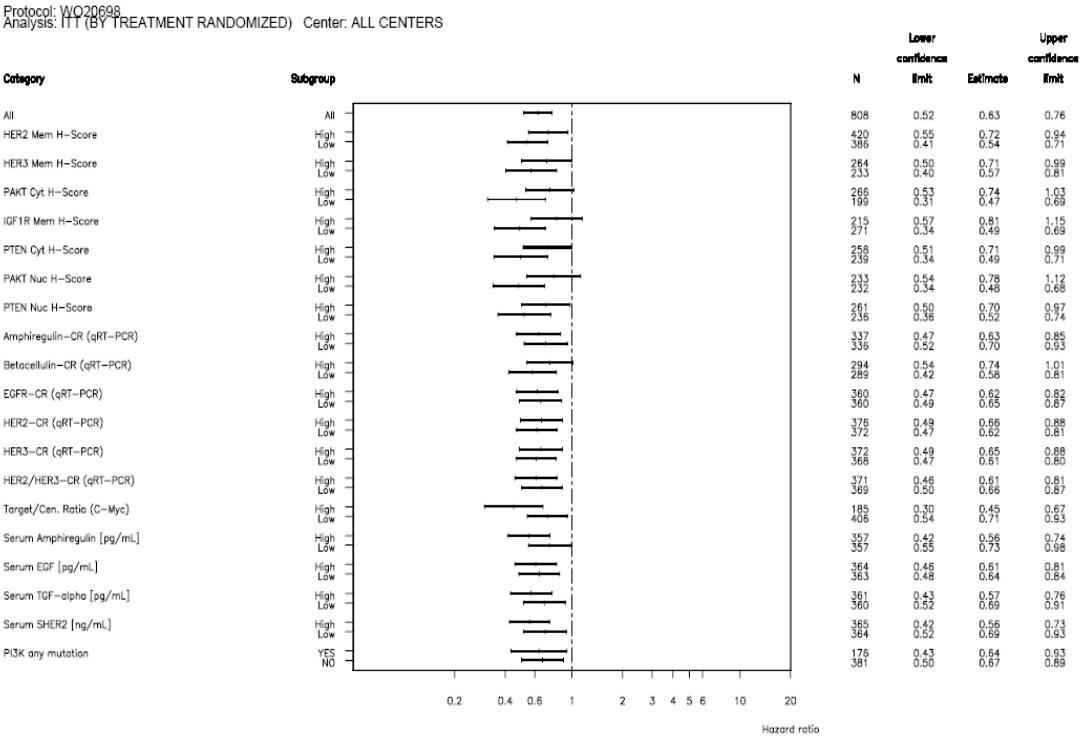
In this double-blinded trial the pre-specified analyses do not indicate a difference in QoL across treatment arms based on the FACT-B questionnaire.

Biomarkers

The potentially predictive value of a number of biomarkers (tumour/serum or whole blood based) was investigated. No specific hypotheses were predefined. The cut-point between “high” and ”low” levels of expression was for practical purposes set at the median level of each individual biomarker. No predictive biomarkers were identified that could be used to select patients with a better or poorer response to Ptz+T+D. All investigated subgroups seemed to benefit from the Ptz+T+D combination.

Figure 29

3 Forest Plot of Hazard Ratios and 95% Confidence Intervals for IRF-Assessed Progression-Free Survival



'Category' represents the biomarker
'Subgroup' represents low and high expression, where patients are divided into low and high expression according to the overall median expression for the biomarker
Cutoff for c-myc defined as Target/Cen. Ratio of 2. Cuttoff for IGF1R Mem H-score defined as 0.

Program : $PROD/cd11450c/b20698a/f_onco_km_cox_fplot_18.sas
Output : $PROD/cd11450c/b20698a/reports/f_onco_km_cox_fplot_18_i.cgm
05OCT2011 9:23

Immunogenicity

The incidence of positive ATA results for the pivotal study WO20698/TOC4129 was reported using a conservative approach by including all patients with any post-baseline positive result. With this approach, antibodies to pertuzumab were detected in 6.2% of patients in the Pla+T+D arm and 2.8% of patients in the Ptz+T+D arm.

Summary of main studies

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 60. Summary of Efficacy for trial WO20698C/TOC4129g (CLEOPATRA)

Title: A Phase III, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in previously untreated HER2-Positive Metastatic Breast Cancer			
Study identifier	WO20698C		
Design	Phase III, randomized, double blind, placebo controlled trial		
	Duration of main phase: Duration of Run-in phase: Duration of Follow-up phase:		Treatment cycles of 21 days each, until investigator-assessed progressive disease or unmanageable toxicity (minimum of 6 cycles of chemotherapy recommended 28 days 3 years
Hypothesis	Equivalence. H0: survival distributions of PFS in the treatment groups are the same. H1: survival distributions of PFS in the treatment and control arms are different.		
Treatments groups	Ptz + T + D		Pertuzumab, 840mg/kg (loading dose) followed by 420mg/kg IV,q3w+ Trastuzumab, 8mg/lg (loading dose) followed by 6mg/kg IV, q3w+ Docetaxel, 75 mg/m2 IV, q3W 6 cycles, 402 patients
	Pla + T + D		Placebo 840mg/kg (loading dose followed by 420mg/kg IV,q3w+ Trastuzumab, 8mg/lg (loading dose) followed by 6mg/kg IV q3w+ Docetaxel, 75 mg/m2 IV, q3W 6 cycles, 406 patients
Endpoints and definitions	Primary endpoint	IRF-PFS	Progression free survival assessed by an independent review facility.
	Secondary endpoint	OS	Overall Survival, time from date of randomization to date of death from any cause.
	Secondary Endpoint	PFS	Progression-free survival assessed by investigator
	Secondary endpoint	ORR	Objective Response Rate, complete response rate or partial response rate determined by independent review facility
	Secondary Endpoint	Duration of Response	Duration of objective response based on independent review facility
	Secondary Endpoint	Time to Symptom Progression	
Database lock	13 May 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT: all randomized patients were included in the intent to treat population.			
Descriptive statistics and estimate variability	Treatment group	Ptz + T + D	Pla + T + D	
	Number of subject	402	406	
	Median IRF-PFS	18.5 months	12.4 months	
	Median investigator assessed PFS	18.5 months	12.4 months	
	Number of deaths	69 (17.2%)	96(23.6%)	
	ORR 95% CI	80.2% (75.6; 84.3)	69.3% (64.1; 74.2)	
	Median duration of Response	87.6 weeks	54.1 weeks	
	95% CI	(71; 106)	(46; 64)	
	Median Time to Symptom Progression	18.4 weeks	18.3 weeks	
	95% CI	(18; 27)	(18; 27)	

Effect estimate per comparison	Primary endpoint	Comparison groups	Ptz + T + D vs. Pla + T + D
		Median IRF-PFS	6.1 months
		HR (95%CI)	0.62 (0.51, 0.75)
		P-value	P<0.0001
	Secondary endpoint	Comparison groups	Ptz + T + D vs. Pla + T + D
		Median investigator – assessed PFS	6.1 months
		HR (95% CI)	0.65 (0.54. 0.78)
		P-value	P<0.0001
	Secondary endpoint	Comparison groups	Ptz + T + D vs. Pla + T + D
		Overall Survival	Not available
		HR (95% CI)	0.66 (0.52,0.84)
		P-value	P=0.0008
Notes			
Analysis description	**Efficacy Analysis**		

	A fixed-sequence testing hierarchy was used at the time of the primary PFS analysis to adjust for multiple statistical testing of IRF-assessed PS, OS and ORR for the purpose of confirmatory statistical testing.

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

No pooled analyses performed across trials were submitted.

Clinical studies in special populations

No clinical studies across special populations were submitted.

Supportive study(ies)

Study WO20697 (NEOSPHERE)

Study WO20697 was a randomized, open-label study investigating 4 different regimens in the neoadjuvant setting. 417 treatment-naïve patients with HER2+, locally advanced, inflammatory or early stage breast cancer (EBC) of more than 2 cm in diameter were randomized in a 1:1:1:1 ratio to treatment with either T+D (Regimen A), PtZ+T+D (Regimen B), Ptz+T (Regimen C) or Ptz+D (Regimen D). The 4th treatment arm (Ptz+D) was introduced by amendment after the enrolment of just 29 patients in the trial. Doses given were in line with the doses used in the pivotal trial (T: 8 mg/kg loading dose, then 6 mg/kg, D: 75 mg/m2 at cycle 1, then increased to 100mg/m2 if there was no limiting toxicity, P: 840 mg loading dose, then 420 mg). The study regimens were administered for 4 cycles 3qw prior to surgery (neoadjuvant therapy). After surgery patients in arms A, B and D received 3 cycles of FEC whereas patients in arm C received 4 cycles of D followed by 3 cycles of FEC. All patients received T for a year in total (adjuvant therapy). The primary endpoint was pathological complete response (pCR) rate in the breast.. Secondary endpoints were clinical response rate, time to clinical response, rate of breast conserving surgery, evaluation of biomarkers, DFS and PFS.

Baseline characteristics were overall well-balanced between treatment arms. Approximately 60% of patients in all treatment arms had operable EBC. Overall, few patients withdrew prematurely from treatment; the highest number was noted in arm C (Ptz+T) and was caused by insufficient response. Almost all patients received all 4 cycles in the neoadjuvant setting and doses received were similar across treatment arms. For Ptz, 93-95% of patients across treatment arms received all 4 cycles of study treatment. The planned total dose was 2100 mg and 2048-2060 mg was received. For T, 93-98% of patients received all 4 cycles and the mean total dose received was balanced across treatment arms (1710-1785 mg). For D, 95-99% of patients completed all 4 cycles and the median dose received was 576-600 mg across treatment arms.

The results of the analysis of the primary endpoint demonstrate very similar pCR rates in the treatment arms A (T+D: 29%) and D (Ptz+D: 24.0%) so although activity was shown with Ptz without T, it was clearly better to add Ptz to T+D (Ptz+T+D: 45.8%). This justifies the lack of a Ptz+D arm in the pivotal study. The activity of Ptz+T (without D) was inferior to the other regimens (Ptz+T: 16.8%). DFS results are not mature.

Study BO17929

Study BO17929 was a Simon's two-stage, Phase II, single-arm study exploring the efficacy and safety of Ptz and T in patients with HER2+ MBC who had received ≤ 3 chemotherapy lines before study entry and who had lately progressed on T-based therapy. The last T dose should have been received ≤ 9 weeks prior to study day 1. Cohort 1 included 24 patients in whom Ptz was added to T that was continued (Ptz+T). Predefined criteria for continuation were met at an interim analysis so that 42

additional patients were enrolled into Cohort 2. Cohort 3 included 29 patients in whom T was stopped at study entry and treatment with Ptz was initiated as single-agent. If patients in Cohort 3 experienced PD, T could be added to Ptz (17 patients). Standard doses of T were used (loading dose of 4 mg/kg, then 2 mg/kg if weekly administration, loading dose of 8 mg/kg, then 6 mg/kg in 3 weekly administration).

At the time of the primary analysis, the median number of T+Ptz cycles received was 9 (range 1-26). The median total dose of Ptz received was 4.200 mg (range 840 – 11.340 mg). The median total dose of T received was 3897 mg (range 423 – 11.907 mg). Overall, baseline characteristics were balanced between treatment arms. Slightly more patients in Cohort 3 had a PS of 1, but this is of less importance since treatment arms were not directly compared. All patients had MBC.

When combining Cohorts 1+2, the ORR to Ptz+T was 24.2% despite the fact that these patients had recently progressed on a T-containing regimen. There were 12 patients with PR, and 4 patients with CR. 26% of patients had SD for at least 6 months so the CBR was 50% which is relatively impressive in this advanced disease setting. Patients in Cohort 3 who had failed on a T-containing regimen and stopped T at study entry had minor benefit of treatment with Ptz alone (ORR 3.4% (1 case of PR)). 2 patients experienced SD so the CBR was 10.3% (3 patients). In contrast, a better response was actually seen when re-introducing T at the time of PD as the ORR was 17.6% (3 patients) and the CBR 35.3% in this subgroup of cohort 3. This indicates that added activity is observed when Ptz+T are administered together.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy in the present submission is based on the pivotal study, WO20698/TOC4129g (CLEOPATRA), a well-designed and well-conducted phase III trial. This trial was a randomized, double-blind, placebo controlled study of Ptz+T+D compared to Pla+T+D in patients with untreated HER2-positive locally recurrent, unresectable or MBC.

Overall, the clinical development program of Ptz has been designed in accordance with recommendations in the “Guideline on the Evaluation of anticancer medicinal products in man” (CPMP/EWP/205/95/Rev.3/Corr. 2). According to this guideline (and to the new draft Guideline) PFS is an acceptable primary endpoint and a prolonged PFS as such is considered to represent a clinical benefit to the patient *per se*. However, the estimated treatment effect on OS as secondary endpoint should be precise enough to rule out a detrimental effect on OS, in most cases by showing trends towards a favourable outcome. In principle, a single pivotal trial is considered acceptable according to the guideline “Points to consider on application with 1. Meta-analyses; 2. One pivotal study” (CPMP/EWP/2330/99) provided that a statistically compelling and clinical relevant benefit as well as internal and external validity can be demonstrated and that the B/R-ratio is considered positive.

EMA scientific advice was sought in 2007 on the design of the phase III trial WO20698/TOC4129g (CLEOPATRA) and has overall been adhered to.

The pivotal study included patients with HER2+ disease (centrally confirmation of HER2 status according to standard criteria: 3+ by IHC or amplification ratio ≥ 2.0 by FISH) who had not previously received systemic treatment for advanced disease (1st line), however, prior hormonal treatment for MBC was allowed. Prior (neo)adjuvant treatment with trastuzumab and/or taxanes was allowed provided that the disease-free interval between end of adjuvant therapy and recurrence was ≥ 12 months thereby excluding patients who would be less likely to respond to rechallenge with trastuzumab/taxanes as previously recommended by the CHMP. Patients with a) a previous high

cumulative exposure to anthracyclines b) a pre-treatment LVEF value of ≤ 50%, c) a history of CHF, d) decreases in LVEF < 50% during prior trastuzumab therapy or e) other major cardiac conditions were excluded as a safety measure as HER2-targeting agents are known to be cardiotoxic. The study population is considered acceptable and representative of HER2+ patients with MBC who could be considered candidates for further HER-targeted therapy.

The biological rationale for combining pertuzumab and trastuzumab in order to obtain a complementary inhibition of the HER2 axis has been well justified. The lack of a Ptz+D arm in the pivotal trial was discussed during the scientific advice procedure. The applicant has argued that non-clinical data as well as data from the supportive studies, in particular study WO20697, clearly indicate that although both antibodies have activity as single-agents, the combination regimen is more active than either agent alone. Therefore, it was found unethical to include a Ptz+D only arm. This argumentation is accepted.

According to current standards, a first-line metastatic regimen consisting of T (traztuzumab) and a taxane seems appropriate for patients with an interval of more than 12 months between completion of an adjuvant T-containing regimen and relapse. T (loading dose 8 mg/kg) and repeated every 3 weeks (maintenance dose: 6 mg/kg) combined with D 100 mg /m2 every 3 weeks is considered an acceptable standard 1st line regimen. When designing the pivotal study it was decided to lower the initial D dose to 75 mg/m2 in both treatment arms as this dose is often used in clinical practice in order to reduce the risk of toxicity (particularly the risk of (febrile) neutropenia). However, given that 100 mg/m2 is the approved dose for D in combination with T in the EU and considering the previous advice obtained from the CHMP, the applicant introduced the option to dose escalate D to 100 mg/mg after the first dose based on individual patient tolerability which is endorsed.

PFS is considered an acceptable primary endpoint. The proposed secondary endpoints, including OS, ORR, QoL are also standard and in accordance with the current and draft Guideline regarding development of anticancer drugs. Evaluation of potential biomarkers has also been included as a secondary endpoint which is endorsed. The study was double-blind. No evident reasons for compromising the study blinding have been identified. The primary analysis of PFS was based on an Independent Review Facility (IRF) -derived assessment to further reduce the risk of bias. As recommended, a simple stratified (block) randomization was used and strata were kept at a minimum (prior treatment status and geographical region). Symmetrical and regular assessment schedules (every 9 weeks) were also applied for the two treatment arms in order to avoid bias. Tumour assessments were continued until IRF-confirmation of progression in order to avoid lack of follow-up in case progression was only determined by investigators but not confirmed by the IRC.

As recommended by the CHMP the sample size was increased from 600 to 800 patients in order to provide more statistically compelling results. A HR of 0.75 (a 33% improvement in median PFS) in favor of the P+T+D arm was assumed. In order to have 80% power to detect a benefit of this magnitude at a two-sided significance level of 5%, 381 IRF-assessed PFS events would be required. The basic assumptions are considered appropriate. An interim analysis of OS was planned at the time of the primary analysis of PFS. The pre-specified stopping boundary for the interim analysis was set at HR ≤ 0.603, p ≤ 0.0012. Standard statistical tests and a fixed-sequence testing hierarchy were used.

Efficacy data and additional analyses

The first patient was enrolled in the pivotal CLEOPATRA study on 12 February 2008. The date for data cut-off for the primary PFS analysis was on 13 May 2011. In total, 1196 patients were screened and 808 patients (N) were enrolled and randomized to one of two treatment arms: Pla+T+D (n=406) or

Ptz+T+D (n= 402). Patients were enrolled from 204 centres in 25 countries. All patients have been adequately accounted for.

Overall, *demographics* were representative of the proposed target population.

D*isease characteristics:* The number of patients with locally recurrent disease was very low in both treatment arms (19 patients in total). From a biological point of view there is no reason to support a different response to Ptz in patients with locally inoperable disease and in patients with MBC. Moreover, the clinical approach is very similar for locally advanced inoperable BC to that for metastatic disease. A statement to reflect the very limited data available in patients with unresectable locally recurrent disease has been mentioned in the SmPC section 5.1.

The median disease-free interval was 29.0 months in the Placebo arm vs. 31.0 months in the Ptz arm and prior therapies were also well-balanced across treatment arms. About one quarter of patients had received hormone therapy as adjuvant or 1st line treatment for metastatic disease (allowed by protocol). In general, patients with ER+ /HER2 + tumours have lower response rates and shorter time to progression when treated with endocrine therapy. Studies indicate that HER2 and ER interact (cross talk). Therefore, T in combination with chemotherapy is considered standard first-line therapy in patients with ER+/HER2+ tumours unless patients can't tolerate or do not wish treatment with chemotherapy (Reference: DBCG guidelines). The number of patients who received hormone therapy as 1st line therapy for MBC was limited (n= 49) and similarly distributed across treatment arms (29 in the Placebo arm and 20 in the Ptz arm). It seems that these patients had a more indolent disease as expressed by a long time from diagnosis to metastasis (median 45.16 months).

The main concern has been that only about half of patients in the pivotal study had received prior (neo-) adjuvant therapy which is a much lower percentage than expected from clinical practice in Western countries. Of particular concern was the fact that only about 10% of patients (10.1% (41 patients) in the Pla+T+D arm vs. 11.7% (47 patients) in the Ptz+T+D arm) had received prior trastuzumab (T) in the (neo-) adjuvant setting so the vast majority of patients were therefore trastuzumab-naïve. Overall, the patient population of the pivotal trial appeared to have been undertreated compared to the standard of care of today. According to current international standards an adjuvant T-containing regimen should be offered to all women with HER2+, node-positive BC or to women with HER2+ node-negative tumours > 1 cm in size. Even for patients with smaller tumours T may be considered due to the generally increased risk of recurrence in patients with HER2+ BC. The applicant has explained the relatively low usage of adjuvant T with reference to the unavailability of T in some regions of the world, a generally lower usage of trastuzumab in the EU in the beginning of the recruitment period (February 2008 – July 2010) compared to today and to the requirement of a one-year disease-free interval at minimum between adjuvant therapy and relapse. These are valid arguments. Reassurance on the interpretation of the study results derives from the fact that patients pretreated with (neo)adjuvant trastuzumab were well balanced between the two study arms. Therefore, the superiority of the combination of two anti-HER2 antibodies is not questioned. However, the estimated magnitude of the treatment effect in patients already exposed to T might differ from what has been observed. As expected, the majority of the 88 patients previously exposed to trastuzumab came from the EU or North America (72). The demography of these patients was comparable to demographics of the entire European population as well as the ITT population. Further reassurance derives from an exploratory *post-hoc* analysis showing that the efficacy of T+D+Ptz (IRF-assessed PFS) was comparable between the subgroup of patients pre-treated with trastuzumab (n= 88, HR = 0.62 (95% CI: 0.35; 1.07)) and the overall study population (N= 808, HR= 0.62 (95% CI: 0.51; 0.75). These results have been confirmed in the updated analysis presented (cut-off date 14 May 2012). Similarly, the updated OS results showed very similar outcomes in the subgroup of patients pretreated with trastuzumab (HR= 0.68 (95% CI: 0.30; 1.55)) and in the ITT population (HR = 0.66

(95% CI: 0.52, 0.84)). With all the limitations of a *post-hoc* exploratory analysis in mind, these data support the efficacy of pertuzumab also in the EU target patient population. In conclusion, the benefit of pertuzumab, both in the overall patient population as well as in patients pre-treated with trastuzumab, is considered clinically relevant and sufficiently supported by the available evidence. In support, study BO17929 documented the activity of Ptz in patients pre-treated with trastuzumab in the metastatic setting. The results of the ongoing studies PHEREXA (2^{nd} line MBC) and PERUSE (1^{st} line MBC) will be able to further confirm the effect size associated with Ptz in patients pre-treated with trastuzumab and should be submitted (Annex II conditions to the marketing authorisation).

Primary endpoint: At the time of data cut-off for the primary IRF-based PFS efficacy analysis 242 patients in the Placebo arm had an event (59.6%) compared to only 191 patients (47.5%) in the Ptz-arm. The K-M curves demonstrated a clear, consistent and early separation already at the time of the first tumour assessment at 9 weeks. The HR for IRF-assessed PFS was 0.62 (95% CI: 0.51; 0.75, $p < 0.0001$) (stratified analysis) in favour of the Ptz-containing arm. The median PFS was 18.5 months in the Ptz arm compared to 12.4 months in the Placebo arm, resulting in an absolute gain of 6.1 months in median PFS in patients treated with both Ptz+T+D. The result of the unstratified analysis (HR = 0.63, $p < 0.0001$) was in support of the stratified IRF-PFS result. Six pre-specified sensitivity analyses were performed that took account of the earliest PD data (IRF or investigator assessment), censored for use of next-line therapies, IRF-assessed PFS during treatment or treatment withdrawals due to toxicity or investigated the impact of missing assessments or included all early deaths as events. HRs in all of these analyses were very consistent with the primary analysis (HR from 0.58 to 0.66). For completeness, the result of the "worst-case" sensitivity analysis (including early withdrawals as events) also supported the result of the primary analysis confirming its robustness.

The robustness of the primary result was also tested by taking account of different prognostic factors in exploratory univariate and multivariate Cox regression analyses. None of the tested covariates had an impact on the treatment effect when adjusted for these covariates. Similarly, although ECOG status was found to be significantly associated with PFS, it did not have an influence on the adjusted treatment effect in the model (data not shown).

The pre-specified subgroup analyses demonstrated consistent benefits in most subgroups, specifically also in patients who had received prior (neo-) adjuvant therapy, in elderly patients ≥ 65 years of age and in patients with HR+ tumours. As expected, larger confidence intervals were observed in smaller populations. The estimate for European patients was slightly higher than for the overall population (HR=0.72 (0.53; 0.97)) but still the upper CI was below 1. The very elderly patients (≥75 years) did not appear to derive statistical significant benefit from pertuzumab, although this finding is likely to be due to the limited number of very elderly patients (n=19). The limited knowledge of the benefit of pertuzumab in the patient population ≥75 years old has been reflected in the SmPC.

It has been noted that the subgroup analysis detected very limited efficacy in patient with non visceral disease (n=178) (HR=0.96 (0.61; 1.52)). This is somewhat unexpected from a mechanistic point of view as HER2 blockade is also known to be efficacious in earlier disease stages. The relatively wide confidence intervals reveal that the estimate is not very precise in this subpopulation. It is agreed that the particular non-visceral subgroup characteristics (smaller sample size and a biological behaviour resulting in a lower event rate) may have resulted in the large variability of the point estimate and probability to capture a true treatment effect

In light of these considerations, a restriction of indication of pertuzumab treatment to the subgroup of patients with visceral disease status is not advisable. However, a Forest plot of the subgroup analysis results for PFS has been included in section 5.1 of the SmPC.

The applicant has performed a number of post-hoc exploratory investigations in order to further address the potential importance of the ECOG status, the HER2 IHC status and docetaxel dose escalations.

- Patients with HER2 IHC 2+ disease (n=79) seemed to have a smaller benefit (HR = 0.90 [0.53, 1.54]). It is agreed that the limited number of enrolled patients with IHC2+ tumours (n=79) hampers firm conclusions to be drawn but the results of secondary endpoints and across studies do not indicate a smaller benefit in this subgroup of patients.
- An exploratory analysis indicated that a benefit in favor of Ptz+T+D was observed both in patients with an ECOG status of 0 (n = 522; HR= 0.70 [0.55, 0.90]) and in patients with an ECOG status of 1+ (n = 286, HR= 0.55 [0.40, 0.74]) at baseline. The Ptz arm included a slightly higher percentage of patients with PS 0 (68.2%) compared to the Placebo arm (61.1%). Based on the results above, this small imbalance is unlikely to have biased the results in the overall population significantly.
- Relatively few patients had the docetaxel dose uptitrated to 100 mg/m2 (n= 109). Dose escalation of docetaxel did not have a major impact on the efficacy results as HR for PFS = 0.62 (0.50; 0.76) in patients receiving D 75mg/m2 compared to HR= 0.65 (0.37, 1.13) in patients who received the highest docetaxel dose (100 mg/m2). The applicant has provided an elaborate review of clinical practice in Europe regarding used dosages of docetaxel in MBC. Since patients in both treatment arms had the opportunity to dose-escalate docetaxel to 100 mg/m2, the overall exposure to docetaxel was similar in the two treatment arms and efficacy results similar whether patients received the high or low dose docetaxel, it is agreed that there is no indication that patients in the Placebo-containing arm were under-dosed.

Secondary endpoints: PFS based on INV assessment was in line with the result based on IRC assessment (HR for PFS (INV) = 0.65 (95% CI 0.54- 0.78, p< 0.0001), median PFS was 12.4 months in the Pla+T+D arm vs. 18.5 months in the Ptz+T+D arm. In general, there was good concordance between IRC and INV assessment. The agreement on occurrence of a PFS event was 86% in the Pla+T+D arm and 85% in the Ptz+T+D arm. When also taking the timing into account, agreement of a PFS event occurring within 30 days of each other was 67% in both arms.

The Applicant has performed an updated PFS analysis one year after the original, primary IRF-determined PFS analysis. At the time of the updated INV-based PFS analysis (data cut-off: 14 May 2012) 68% of patients had had a PFS event (72.9% in the Placebo arm and 63.9% in the Ptz arm). The updated HR = 0.69 (95% CI: 0.58, 0.81). The K-M curves demonstrated an early and clear separation. The median PFS was 12.4 months in the Placebo arm compared with 18.7 months in the Ptz arm. Consistent results were observed in the subgroup analyses. Thus, the previously observed PFS-benefit has been maintained and confirmed in this updated analysis

The study was fully powered to assess OS at 80% power. However, OS data was not mature at the time of the primary data cut-off where only 43% of the number of events required for the final OS analysis had occurred. The duration of follow-up was similar across treatment arms (19.3 months). In the Placebo arm 96 patients had died (23.6%) compared to 69 deaths (17.2%) in the Ptz arm. The median time to death had not been reached in any of the treatment arms. The HR for OS was 0.64 (95% CI: 0.47; 0.88, p = 0.0053) but the O'Brien-Fleming stopping boundary was not met (HR ≤ 0.603, p ≤ 0.0012). The K-M curves show a separation in favour of the Ptz arm just before ten months. Of note, cross-over between treatment arms was not allowed per protocol.

The second interim analysis of OS (data cut-off May 13th 2012) collected events one year after the data cut-off of the primary analysis, by adding 102 deaths. At the time of this second analysis, 267 deaths had occurred, specifically 154 events (37.9%) in the placebo arm and 113 events (28.1%) in

the pertuzumab arm. Results from the second and final OS analysis showed a significant survival benefit for patients randomized to receive pertuzumab (stratified by prior treatment status and region): HR of 0.66 (95% CI: 0.52; 0.84, p< 0.0008). Median survival was of 37.6 months in the placebo arm and was not still reached in the pertuzumab arm. Survival rates showed a sustained survival advantage in the pertuzumab arm 0.94, 0.81 and 0.66 for the PTZ+T+D arm and 0.89, 0.69 and 0.50 in the Pl+T+D arm at 12, 24 and 36 months, respectively.

The results from a subgroup analysis were consistent with those obtained for the overall ITT population. Only the HR obtained for the subgroup of patients with non-visceral disease showed a negative trend (HR 1.42; 95% CI: 0.71; 2.84) but the number of events in this subgroup was low (33 deaths ≈ 18.5%) as expressed by the wide confidence intervals. The particular non-visceral subgroup characteristics (smaller sample size and a biological behaviour resulting in a lower event rate) may have resulted in the large variability of the point estimate and the probability to capture a true treatment effect) in this subgroup.

More patients in the Placebo arm (64%) received subsequent lines of therapy or surgical procedures compared the Ptz-containing arm (56%). This imbalance may confound later OS results. The most frequently used 2nd line therapy was capecitabine in both treatment arms. A substantial number of patients also continued T upon progression or were switched to lapatinib, a dual HER1/HER2 tyrosine kinase inhibitor. Finally, the experimental drug trastuzumab emtansine (T-DM1) was also received by 10% of patients in both study arms.

A higher ORR was observed in the Ptz+T+D arm (80.2%) compared to the Pla+T+D arm (69.3%). The majority of responses in the Ptz arm were PRs. The median duration of responses was also longer in the Ptz arm (87.6 weeks) than in the Placebo arm (54.1 weeks). A subset of patients was classified as non responders (19.8% in the pertuzumab arm and 30.7 in the control arm) and a minority (5.5% in the pertuzumab arm and 4.2% in the control arm) obtained a CR. The assessment of the biomarkers panel in specific sub-populations (e.g. patients with complete response vs. patients with quick progression) was considered in defining the biologic characteristics of these two different subsets.

In this double-blinded trial the pre-specified analyses did not indicate a difference in QoL across treatment arms based on the FACT-B questionnaire.

The potentially predictive value of a number of biomarkers (tumour/serum or whole blood based) was investigated. No predictive biomarkers were identified that could be used to select patients with a better or poorer response to Ptz+T+D. All investigated subgroups seemed to benefit from the Ptz+T+D combination. As expected, the number of samples varied per biomarker, but overall the availability of samples was relatively high (58-99.8%). There was no significant difference in biomarker expression between primary and metastatic tumour samples. Therefore, only a total of 24 pairs (primary tumour/metastatic tumour) were available for this analysis and all markers could not be tested in all samples (due to lack of tumour tissue or for technical reasons). Only possible mechanisms involved in *intrinsic* resistance have been investigated. Biomarkers included molecules known to confer resistance to HER2 (e.g. PI3K mutation status, loss of PTEN). No *predictiv*e markers were identified. It is recommended that results regarding *acquired* resistance mechanisms are submitted when available (projected Q4 2012).

Immunogenicity: Patients in the pivotal trial CLEOPATRA were tested at multiple time-points for anti-therapeutic antibodies (ATA) to Perjeta. Approximately 2.8% (11/386 patients) of Perjeta-treated patients and 6.2% (23/372 patients) of placebo-treated patients tested positive for ATAs. Of these 34 patients, none experienced severe (NCI-CTCAE Grade >3) infusion or hypersensitivity reactions (anaphylaxis) that were clearly related to ATA. However, Grade 3 hypersensitivity reactions associated with detectable ATAs occurred in 2 of 366 Perjeta-treated patients (0.5%) in phase I and II studies.

There are currently insufficient data to evaluate the effects of ATA on the efficacy of Perjeta in combination with trastuzumab and docetaxel; a potential loss of efficacy based on ATA in individual patients cannot be ruled out.

Supportive studies: The applicant has submitted supportive data from 2 Phase II studies that were both performed in different study populations than proposed in the indication but the results confirm the added activity observed when combining Ptz and T.

2.5.4. Conclusions on the clinical efficacy

The addition of Ptz to T+D in the first-line treatment of locally advanced or MBC demonstrated a highly statistically significant and clinically relevant gain in IRF-based PFS (+ 6 months in median PFS, HR = = 0.62 [95% CI: 0.51; 0.75]). The primary result was shown to be robust and internally consistent in most subgroup analyses. It was supported by most results of secondary endpoints and it was maintained and confirmed in the updated INV-based PFS analysis. An exploratory subgroup analysis indicates consistent results in the small subgroup of patients pre-treated with T confirming the added benefit of the more complete HER2 blockade despite prior treatment status.

Importantly, results from the second interim OS analysis after 33% of patients had died, showed a significant survival benefit for patients randomized to receive pertuzumab (stratified by prior treatment status and region): HR of 0.66 (95% CI: 0.52; 0.84, p= 0.0008). Median survival was 37.6 months in the placebo arm and was not still reached in the pertuzumab arm. The updated OS results demonstrate very similar outcomes in the subgroup of patients pre-treated with trastuzumab (HR= 0.68 (95% CI: 0.30; 1.55)). Only the HR obtained for the subgroup of patients with non-visceral disease showed a negative trend (HR 1.42; 95% CI: 0.71; 2.84) but the number of events in this subgroup was low (33 deaths ≈ 18.5%) as expressed by the wide confidence intervals. The particular non-visceral subgroup characteristics (smaller sample size and a biological behaviour resulting in a lower event rate) may have affected the large variability of the point estimate and the probability to capture a true treatment effect (low power) in this subgroup.

In conclusion, the observed benefit of adding pertuzumab to a standard regimen is considered clinically relevant and sufficiently supported by the available evidence both in the overall patient population as well as in patients pre-treated with trastuzumab.

The CHMP considers the following measures necessary to address issues related to efficacy:

- The results of the ongoing studies PHEREXA (2nd line MBC) and PERUSE (1st line MBC) should be submitted to confirm the efficacy of Ptz in patients pre-treated with trastuzumab (Annex II obligations).
- It is recommended that results regarding *acquired* resistance mechanisms are submitted when available.

2.6. Clinical safety

The evaluation of safety is based on data from the pivotal WO20698/TOC4129g study, the two key supporting studies and 14 other studies. These studies provide safety data on patients exposed to the planned treatment regimen pertuzumab + trastuzumab + docetaxel (Ptz+T+D), as well as safety data

for patients exposed to pertuzumab in combination with trastuzumab, pertuzumab alone, and pertuzumab with other anti-cancer agents.

Patient exposure

Overall, a total of 1412 patients received at least one infusion of pertuzumab in the 14 studies evaluated. The median number of cycles received in "all Pertuzumab treated patients" was 4 (range 1-62) with a median exposure duration of 3 months (range 1-43).

In the pivotal study at the data cutoff for 2nd the second interim analysis of overall survival, the median number of placebo/pertuzumab cycles was 15 (range 1-62) vs. 24 (range 1-66). The median total dose of placebo was 6720 mg and the median total dose of pertuzumab received was 10500 mg (range 840-28140). The median exposure duration of placebo/pertuzumab was 11.4 months (range 1-46) vs. 17.4 months (range 1-47). A total of 16% of patients in the placebo arm and 26% of patients in the pertuzumab arm were yet to discontinue from treatment.

The long term safety data in the proposed indication is considered sufficient as in the pivotal study 24.3% of the patients were exposed to pertuzumab for >6 - <=12 months and 57.2% of the patients were exposed for more than 12 months and up to more than 2 years, at the time of the primary analysis.

Exposure to docetaxel was overall similar across treatment arms (median of eight cycles in both treatment arms, the median dose per cycle was 125 mg in the Pla+T+D arm vs. 123 mg in the Ptz+T+D arm).

Adverse events

Common adverse events

In the pivotal study almost all patients experienced at least one AE, 98.5% and 99.8 % in the placebo arm and pertuzumab arms, respectively. The majority of AE's were considered *treatment-related.* The most common (>25%) AEs in the pivotal study were alopecia (60.5% in the placebo arm/ 60.9% in the pertuzumab arm), diarrhoea (46.3%/66.8%), neutropenia (49.6%/52.8%), nausea (41.6%/42.3%), fatigue (36.8%/37.6%), rash (24.2%/33.7%), asthenia (30.2%/26.0%), decreased appetite (26.4%/29.2%), peripheral oedema (30.0%/23.1%) and mucosal inflammation 19.9%/27.8%). AE's (any grade) observed with a *higher* incidence (at least 5 percentage points) in the pertuzumab arm were diarrhoea (46.3% in the placebo arm, 66.8% in the pertuzumab arm), rash (24.2% in the placebo arm, 33.7 % in the pertuzumab arm), mucosal inflammation (19.9% in the placebo arm, 27.8 % in the pertuzumab arm), febrile neutropenia (7.6 % in the placebo arm, 13.8 % in the pertuzumab arm) and dry skin (4.3 % in the placebo arm, 10.6% in the pertuzumab arm). These events were mainly grade 1 or 2 and occurred less frequently after discontinuation of docetaxel. AE's observed with a *lower* incidence (at least 5 percentage points) in the pertuzumab arm were edema peripheral (30.0% in the placebo arm, 23.1% in the pertuzumab arm) and constipation (24.9% in the placebo arm, 15.0% in the pertuzumab arm). In addition,left ventricular systolic dysfunction LVSD (any grade) was observed more frequently in the placebo arm (8.3%) compared to the pertuzumab arm (4.4%).

Table 61. Summary Of Adverse Events Occurring In ≥5% Of Patients: Pivotal Study (WO20698/TOC4129g)

t_ae13_cl Summary Of Adverse Events With An Incidence Rate Of At least 5% By Trial Treatment: Pivotal Study, WO20698
Protocol(s): WO20698
Analysis: ALL PATIENTS Center: ALL CENTERS

Adverse Event	PLACEBO + TRASTUZUMAB + DOCETAXEL N = 397 No. (%)	PERTUZUMAB + TRASTUZUMAB + DOCETAXEL N = 407 No. (%)
ALOPECIA	240 (60.5)	248 (60.9)
DIARRHOEA	184 (46.3)	272 (66.8)
NEUTROPENIA	197 (49.6)	215 (52.8)
NAUSEA	165 (41.6)	172 (42.3)
FATIGUE	146 (36.8)	153 (37.6)
RASH	96 (24.2)	137 (33.7)
ASTHENIA	120 (30.2)	106 (26.0)
DECREASED APPETITE	105 (26.4)	119 (29.2)
OEDEMA PERIPHERAL	119 (30.0)	94 (23.1)
VOMITING	95 (23.9)	98 (24.1)
MUCOSAL INFLAMMATION	79 (19.9)	113 (27.8)
MYALGIA	95 (23.9)	93 (22.9)
NAIL DISORDER	91 (22.9)	93 (22.9)
ANAEMIA	75 (18.9)	94 (23.1)
NEUROPATHY PERIPHERAL	80 (20.2)	86 (21.1)
COUGH	74 (18.6)	87 (21.4)
CONSTIPATION	99 (24.9)	61 (15.0)
LEUKOPENIA	81 (20.4)	74 (18.2)
HEADACHE	67 (16.9)	85 (20.9)
PYREXIA	71 (17.9)	76 (18.7)
STOMATITIS	61 (15.4)	77 (18.9)
DYSGEUSIA	62 (15.6)	75 (18.4)
ARTHRALGIA	64 (16.1)	63 (15.5)
UPPER RESPIRATORY TRACT INFECTION	53 (13.4)	68 (16.7)
DYSPNOEA	62 (15.6)	57 (14.0)
LACRIMATION INCREASED	55 (13.9)	57 (14.0)
PAIN IN EXTREMITY	47 (11.8)	62 (15.2)
INSOMNIA	53 (13.4)	54 (13.3)
ABDOMINAL PAIN	49 (12.3)	57 (14.0)
PERIPHERAL SENSORY NEUROPATHY	56 (14.1)	49 (12.0)
BACK PAIN	46 (11.6)	55 (13.5)
DIZZINESS	48 (12.1)	51 (12.5)
NASOPHARYNGITIS	51 (12.8)	48 (11.8)
DYSPEPSIA	48 (12.1)	49 (12.0)
PRURITUS	40 (10.1)	57 (14.0)
OEDEMA	50 (12.6)	46 (11.3)
FEBRILE NEUTROPENIA	30 (7.6)	56 (13.8)
BONE PAIN	39 (9.8)	39 (9.6)
PARAESTHESIA	40 (10.1)	37 (9.1)
ABDOMINAL PAIN UPPER	39 (9.8)	37 (9.1)
EPISTAXIS	34 (8.6)	37 (9.1)
HYPERTENSION	32 (8.1)	37 (9.1)
MUSCULOSKELETAL PAIN	35 (8.8)	32 (7.9)
URINARY TRACT INFECTION	30 (7.6)	32 (7.9)
DRY SKIN	17 (4.3)	43 (10.6)
HYPOKALAEMIA	19 (4.8)	37 (9.1)
OROPHARYNGEAL PAIN	25 (6.3)	27 (6.6)
LEFT VENTRICULAR DYSFUNCTION	33 (8.3)	18 (4.4)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	22 (5.5)	28 (6.9)
WEIGHT DECREASED	16 (4.0)	34 (8.4)
CHILLS	15 (3.8)	33 (8.1)
RHINORRHOEA	21 (5.3)	26 (6.4)
HYPERSENSITIVITY	20 (5.0)	26 (6.4)
PAIN	22 (5.5)	24 (5.9)
MUSCLE SPASMS	15 (3.8)	29 (7.1)
PLEURAL EFFUSION	23 (5.8)	21 (5.2)
PARONYCHIA	14 (3.5)	29 (7.1)
DEPRESSION	19 (4.8)	23 (5.7)
HOT FLUSH	21 (5.3)	21 (5.2)
ERYTHEMA	19 (4.8)	22 (5.4)
CONJUNCTIVITIS	17 (4.3)	23 (5.7)
WEIGHT INCREASED	21 (5.3)	13 (3.2)
CHEST PAIN	20 (5.0)	13 (3.2)
DYSURIA	9 (2.3)	22 (5.4)

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE13 18JUL2011:21:00:10

Based on causality assessment, an overview of Adverse Drug Reactions in the Cleopatra Study is reported in the table below, and adequately reflected in the SmPC. .

Table 62 Summary of ADRs from the pivotal clinical trial CLEOPATRA

System organ class	***Very Common***	***Common***	***Uncommon***
Infections and infestations	Upper respiratory tract infection Nasopharyngitis	Paronychia	
Blood and lymphatic system disorders	Febrile neutropenia* Neutropenia Leucopenia Anaemia		
Immune system disorders	Hypersensitivity/ anaphylactic reaction° Infusion related reaction/cytokine release syndrome°°		
Metabolism and nutrition disorders	Decreased appetite †		
Psychiatric disorders	Insomnia		
Nervous system disorders	Neuropathy peripheral Peripheral sensory neuropathy Headache † Dizziness Dysgeusia		
Eye disorders	Lacrimation increased		
Cardiac disorders		Left ventricular dysfunction † (including congestive heart failure)	
Respiratory, thoracic and mediastinal disorders	Dyspnoea † Cough †	Pleural effusion	Interstitial lung disease
Gastrointestinal disorders	Diarrhoea † Vomiting † Stomatitis Nausea † Constipation † Dyspepsia		
Skin and subcutaneous tissue disorders	Alopecia Rash † Nail disorder Pruritus Dry skin		
Musculoskeletal and connective tissue disorders	Myalgia Arthralgia		
General disorders and administration site conditions	Mucositis/mucosal inflammation Pain † Oedema †	Chills	

System organ class	***Very Common***	***Common***	***Uncommon***
	Pyrexia Fatigue † Asthenia †		

* Including adverse reactions with a fatal outcome.
† Except for febrile neutropenia, neutropenia, leucopenia, lacrimation increased, interstitial lung disease, paronychia, and alopecia, all events in this table were also reported in at least 1% of patients participating in Perjeta monotherapy trials, although not necessarily considered causally related to Perjeta by the investigator. Very common events (reported in ≥ 10% of Perjeta monotherapy-treated patients) are marked in the Table with a †.
° Hypersensitivity/anaphylactic reaction is based on a group of terms.
°° Infusion related reaction/cytokine release syndrome includes a range of different terms within a time window, see "Description of selected adverse reactions" below.

Serious adverse event / deaths / other significant events

Severe adverse events

In the pivotal study no difference in experienced grade 3-4 events was observed between the placebo arm and the pertuzumab arms (72.0% and 73.5%, respectively). The most common grade 3-4 adverse events reported were neutropenia (45.8 % in the placebo arm, 48.9 % in the pertuzumab arm), febrile neutropenia (7.3 % in the placebo arm, 13.0 % in the pertuzumab arm), leukopenia (14.6 % in the placebo arm, 12.3 % in the pertuzumab arm) and diarrhoea (5.0 % in the placebo arm, 7.9 % in the pertuzumab arm). So it was mainly the rates of grade 3+ febrile neutropenia and diarrhoea that were higher in the pertuzumab arm compared to the control arm. LVSD of grade 3 or higher was reported less frequently in the pertuzumab arm (1.2%) compared to the placebo arm (2.8%).

Deaths

Overall in the pivotal study 94 patients (23.7%) died in the placebo arm and 69 patients (17%) died in the pertuzumab arm. The majority of deaths were due to PD (n=81 in the placebo arm and n= 57 in the pertuzumab arm), however, 13 deaths in the placebo arm and 12 deaths in the pertuzumab arm were due to other causes.

Table 62. Summary of All Deaths: Pivotal Study (WO20698 / TOC4129g)

t_dd11_cl Summary Of Deaths By Trial Treatment: Pivotal Study, WO20698
Protocol(s): WO20698
Analysis: ALL PATIENTS Center: ALL CENTERS

Cause of Death (incl. Underlying Cause of Death)	PLACEBO + TRASTUZUMAB + DOCETAXEL N = 397 No. (%)	PERTUZUMAB + TRASTUZUMAB + DOCETAXEL N = 407 No. (%)
Total No. of Deaths	94 (23.7)	69 (17.0)
DISEASE PROGRESSION	81 (20.4)	57 (14.0)
DEATH	1 (0.3)	3 (0.7)
FEBRILE NEUTROPENIA	1 (0.3)	3 (0.7)
INTESTINAL PERFORATION	2 (0.5)	1 (0.2)
NO CODING AVAILABLE	1 (0.3)	1 (0.2)
BREAST CANCER METASTATIC	-	2 (0.5)
MYOCARDIAL INFARCTION	2 (0.5)	-
PNEUMONIA	2 (0.5)	-
SEPSIS	1 (0.3)	1 (0.2)
BREAST CANCER	-	1 (0.2)

CEREBROVASCULAR ACCIDENT	1 (0.3)	-
COLON CANCER	-	1 (0.2)
GASTROINTESTINAL HAEMORRHAGE	1 (0.3)	-
GENERAL PHYSICAL HEALTH DETERIORATION	1 (0.3)	-
HEPATIC FAILURE	1 (0.3)	-
METASTASES TO LIVER	1 (0.3)	-
NEOPLASM MALIGNANT	-	1 (0.2)
NEUTROPENIC SEPSIS	1 (0.3)	-
RESPIRATORY FAILURE	1 (0.3)	-
RESPIRATORY TRACT INFECTION	-	1 (0.2)
SEPTIC SHOCK	-	1 (0.2)
SOMNOLENCE	-	1 (0.2)
UNEVALUABLE EVENT	1 (0.3)	-

Investigator text for Cause of Death encoded using MedDRA version 14.0.
Percentages are based on N.
Note that 'Causes of Death' may exceed 'Total No.of Deaths' as patients may have more than one cause of death reported.
DD11 18JUL2011:22:19:16 (1 of 1)
Footnote modified by PDRD (Source: t_dd11_cl)

Serious Adverse Events

Overall, in the pivotal trial 34.4% of patients in the Ptz-T-D arm reported a SAE compared to 26.2% in the Pla+T+D arm. The most common SAEs were febrile neutropenia (11.3% in the Ptz arm vs. 5.0% in the Placebo arm), and infections (10.8% in the Ptz arm vs. 7.3% in the Placebo arm).

Table 63. Summary Of Serious Adverse Events By Body System And Trial Treatment: Pivotal Study (WO20698/TOC4129g)

t_ae11_s_cl Summary Of Serious Adverse Events By Body System And Trial Treatment: Pivotal Study, WO20698
Serious Adverse Events. Protocol(s): WO20698
Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO + TRASTUZUMAB + DOCETAXEL N = 397 No. (%)	PERTUZUMAB + TRASTUZUMAB + DOCETAXEL N = 407 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	104 (26.2)	140 (34.4)
Total Number of AEs	149	221
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	42 (10.6)	65 (16.0)
FEBRILE NEUTROPENIA	20 (5.0)	46 (11.3)
NEUTROPENIA	19 (4.8)	18 (4.4)
ANAEMIA	3 (0.8)	3 (0.7)
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	29 (7.3)	44 (10.8)
PNEUMONIA	7 (1.8)	5 (1.2)
CELLULITIS	2 (0.5)	7 (1.7)
NEUTROPENIC INFECTION	1 (0.3)	4 (1.0)
HERPES ZOSTER	3 (0.8)	1 (0.2)
SEPSIS	3 (0.8)	1 (0.2)
URINARY TRACT INFECTION	1 (0.3)	3 (0.7)
GASTROENTERITIS	1 (0.3)	2 (0.5)
LOWER RESPIRATORY TRACT INFECTION	-	3 (0.7)
NEUTROPENIC SEPSIS	2 (0.5)	-
PHARYNGITIS	-	2 (0.5)
UPPER RESPIRATORY TRACT INFECTION	-	2 (0.5)
UROSEPSIS	-	2 (0.5)
VIRAL INFECTION	2 (0.5)	-
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	17 (4.3)	18 (4.4)
DIARRHOEA	5 (1.3)	11 (2.7)
VOMITING	1 (0.3)	2 (0.5)
CONSTIPATION	2 (0.5)	-
INTESTINAL PERFORATION	2 (0.5)	-
OESOPHAGITIS	-	2 (0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	8 (2.0)	14 (3.4)
PYREXIA	3 (0.8)	6 (1.5)
CHEST PAIN	2 (0.5)	1 (0.2)
FATIGUE	1 (0.3)	2 (0.5)
ASTHENIA	-	2 (0.5)
GENERAL PHYSICAL HEALTH DETERIORATION	2 (0.5)	-

INFLUENZA LIKE ILLNESS	-	2 (0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	8 (2.0)	13 (3.2)
PLEURAL EFFUSION	4 (1.0)	2 (0.5)
DYSPNOEA	2 (0.5)	2 (0.5)
PULMONARY EMBOLISM	-	4 (1.0)
INTERSTITIAL LUNG DISEASE	-	2 (0.5)
CARDIAC DISORDERS		
Total Pts With at Least one AE	13 (3.3)	5 (1.2)
LEFT VENTRICULAR DYSFUNCTION	7 (1.8)	4 (1.0)
ATRIAL FIBRILLATION	2 (0.5)	-
MYOCARDIAL INFARCTION	2 (0.5)	-
IMMUNE SYSTEM DISORDERS		
Total Pts With at Least one AE	4 (1.0)	7 (1.7)
DRUG HYPERSENSITIVITY	3 (0.8)	3 (0.7)
HYPERSENSITIVITY	-	3 (0.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts With at Least one AE	1 (0.3)	7 (1.7)
FEMUR FRACTURE	1 (0.3)	2 (0.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	3 (0.8)	5 (1.2)
BACK PAIN	1 (0.3)	2 (0.5)
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	4 (1.0)	4 (1.0)
VASCULAR DISORDERS		
Total Pts With at Least one AE	2 (0.5)	6 (1.5)
DEEP VEIN THROMBOSIS	-	3 (0.7)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	3 (0.8)	4 (1.0)
DEHYDRATION	2 (0.5)	1 (0.2)
RENAL AND URINARY DISORDERS		
Total Pts With at Least one AE	3 (0.8)	3 (0.7)
RENAL FAILURE ACUTE	2 (0.5)	-

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 18JUL2011:20:21:29
Abridged by PDRD:PT incidence ≥0.5% in any arm (Source: t_ae11_s_cl)

Adverse events of Special Interest

Cardiac safety data

In the pivotal trial symptomatic Left Ventricular Systolic Dysfunction (LVSD) was reported for 11 patients (7 in the Placebo arm (1.8%) vs. 4 (1%) in the Ptz arm) by investigators. These cases were reported as cardiac failure SAEs and were all considered treatment-related. The CRC identified 4 cases (1%) in each treatment arm. All 4 cases in the Placebo arm were categorized as NYHA class II events whereas 3 events in the Ptz arm were categorized as NYHA class III-IV events. These cases led to treatment discontinuation and supportive therapy.

Significant LVEF (defined as a decline of at least 10% points from baseline to an absolute value of , 50%) declines other than symptomatic CHF were observed in 5.5% of patients in the Placebo arm vs. 3.2% in the Ptz arm.

Table 64. Key Cardiac Safety Data from the Company Integrated Safety Database

Safety Parameter	Patients Experiencing Event								
	WO20698/TOC4129g		WO20697				BO17929	Single Agent Ptz	All Ptz-Treated Pts
	Pla+T+D n=397	Ptz+T+D n=407	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T n=83	Ptz n=386	Various n=1412
Any CHF SAE or significant LVEF decline	7.3%	4.2%	0.9%	2.8%	0.9%	1.1%	7.2%	6.5%	4.2%
Significant LVEF decline*	5.5%	3.2%	0.9%	2.8%	0	1.1%	7.2%	5.2%	3.3%
CHF SAE	1.8%	1.0%	0	0	0.9%	0	0	1.3%	1.0%
Gr ≥ 3 CHF SAE	1.8%	1.0%	0	0	0.9%	0	0	0.5%	0.8%

NB: patients may appear in more than one group/column. Dark grey columns: data for patients treated with Ptz+T+D (proposed licensed treatment regimen).
Mid grey columns: data for patients treated with Ptz+T.
Pale grey columns: data for patients treated with single agent pertuzumab.
CHF: congestive heart failure (symptomatic left ventricular dysfunction) SAEs analyzed by SMQ (wide) 'Cardiac failure'.
LVEF: left ventricular ejection fraction.
*LVEF declines other than those counted as CHF SAE (significant LVEF decline defined as LVEF decline of $\geq$ 10% from baseline to an absolute value <50%).

In the pivotal study QT prolongation was reported as AE in 2.0% of patients in the Placebo arm vs. 1.3% in the Ptz-containing arm.

Infusion-Associated Reactions

In the pivotal study, relatively few patients experienced an event during a placebo/Ptz infusion (5.0% in the placebo arm vs. 8.8% in the Ptz+T+D arm). Most of these events were mild or moderate in severity. Events observed on Day 1 in Cycle 1 were of particular interest, as this was the only day when Ptz or Placebo was administered without T or D. On this day, 3.9% receiving Ptz experienced an AE during the infusion compared to 2.0% in the Placebo arm. The most frequent events reported in the Ptz arm were nausea, pyrexia, diarrhea, chills, fatigue, headache, asthenia, hypersensitivity and vomiting.

Table 65. Summary of AEs on the Day of or the Day After a Placebo/Pertuzumab Infusion from the Integrated Safety Database

Safety Parameter	Patients Experiencing Event								
	WO20698/TOC4129g		WO20697				BO17929	Single Agent Ptz	All Ptz-Treated Pts
	Pla+T+D n=397	Ptz+T+D n=407	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T n=83	Ptz n=386	Various n=1412
AEs starting during a placebo/pertuzumab infusion*									
Any AE	5.0%	8.8%	0	7.5%	13.0%	1.1%	6.0%	2.3%	5.9%
Grade ≥ 3	0.3%	0.2%	0	0.9%	1.9%	0	0	0.5%	0.5%
AEs on the day of a placebo/pertuzumab infusion*									
Any AE	78.6%	82.8%	51.4%	60.7%	46.3%	61.7%	73.5%	57.3%	68.6%
Grade ≥ 3	10.6%	12.3%	1.9%	4.7%	2.8%	3.2%	6.0%	6.2%	9.6%
AEs on the day of or the day after a placebo/pertuzumab infusion*									
Any AE	85.1%	88.2%	72.9%	78.5%	52.8%	80.9%	78.3%	66.3%	77.4%
Grade ≥ 3	14.9%	16.5%	2.8%	6.5%	2.8%	5.3%	7.2%	8.8%	12.2%
Average no. AEs per pt	4.3	5.1	1.9	2.3	1.2	2.0	2.7	2.0	3.6

NB: patients may appear in more than one group/column. Dark grey columns: data for patients treated with Ptz+T+D (proposed licensed treatment regimen).
Mid grey columns: data for patients treated with Ptz+T.
Pale grey columns: data for patients treated with single agent pertuzumab.
*Or day of trastuzumab administration for the T+D arm of WO20697.

Anaphylaxis and hypersensitivity

Anaphylaxis or hypersensitivity reactions (occurring at any time and regardless of causality) were reported for 9.1% of patients in the Placebo arm vs. 10.8% of patients in the Ptz arm. These events were severe in 2.5% and 2.0% of patients, respectively.

Table 66. Summary of Anaphylaxis/Hypersensitivity Reactions from the Integrated Safety Database

Safety Parameter	Patients Experiencing Event								
	WO20698/TOC4129g		WO20697				BO17929	Single Agent Ptz	All Ptz-Treated Pts
	Pla+T+D n=397	Ptz+T+D n=407	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T n=83	Ptz n=386	Various n=1412
Anaphylaxis / hypersensitivity All Grades	9.1%	10.8%	1.9%	5.6%	5.6%	6.4%	4.8%	2.1%	6.6%
Anaphylaxis / hypersensitivity Grade ≥ 3	2.5%	2.0%	0	0.9%	1.9%	0	0	0.3%	1.3%

NB: patients may appear in more than one group/column.

Leucopenia

Leucopenic events (which include neutropenia envents and febrile neutropenia events) were reported in 58.2% of patients in the Pla+T+D arm vs. 62.4% in the Ptz+T+D arm in the pivotal trial. Most of these events were ≥ grade 3 (53.1% and 58.2%, respectively). Of most interest is the incidence of febrile neutropenia that was slightly higher in the Ptz-containing arm (13.8%) compared to the Placebo arm (7.6%).

Table 67. Summary of Leucopenia AEs from the Integrated Safety Database

Safety Parameter	Patients Experiencing Event								
	WO20698/TOC4129g		WO20697				BO17929	Single Agent Ptz	All Ptz-Treated Pts
	Pla+T+D n=397	Ptz+T+D n=407	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T n=83	Ptz n=386	Various n=1412
Any leucopenia AE*	58.2%	62.4%	74.8%	56.1%	0.9%	69.1%	0	0.5%	33.0%
Gr ≥ 3	53.1%	58.2%	68.2%	51.4%	0.9%	60.6%	0	0.5%	28.9%
Related	55.9%	60.4%	74.8%	56.1%	0	69.1%	0	0	30.0%
Neutropenia	49.6%	52.8%	62.6%	50.5%	0.9%	62.8%	0	0	28.3%
Gr ≥ 3	45.8%	48.9%	57.0%	44.9%	0.9%	55.3%	0	0	24.7%
FN	7.6%	13.8%	7.5%	8.4%	0	7.4%	0	0	5.3%
Gr ≥ 3	7.6%	13.8%	7.5%	8.4%	0	7.4%	0	0	5.3%

NB: patients may appear in more than one group/column.
Dark grey columns: data for patients treated with Ptz+T+D (proposed licensed treatment regimen).
Mid grey columns: data for patients treated with Ptz+T.
Pale grey columns: data for patients treated with single agent pertuzumab.
* Defined using the SMQ [narrow] "Hematopoietic leukopenia" which includes neutropenia events and febrile neutropenia events.
FN: febrile neutropenia.

Diarrhoea

Diarrhoea was more commonly reported in patients treated with Ptz+T+D (66.8%) than with Pla+T+D (46.3%) in the pivotal trial. It was also potentiated by treatment with docetaxel since only a minority of patients (<10%) experienced diarrhoea after Cycle 6.

Table 68. Summary of Diarrhea AEs from the Integrated Safety Database

Safety Parameter	Patients Experiencing Event								
	WO20698/TOC4129g		WO20697				BO17929	Single Agent Ptz	All Ptz-Treated Pts
	Pla+T+D n=397	Ptz+T+D n=407	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T n=83	Ptz n=386	Various n=1412
Diarrhea All Grades	46.3%	66.8%	33.6%	45.8%	27.8%	54.3%	56.6%	57.3%	58.1%
Diarrhea Grade ≥ 3	5.0%	7.9%	3.7%	5.6%	0	4.3%	3.6%	6.5%	6.4%
Diarrhea Related	38.3%	57.7%	26.2%	43.0%	26.9%	48.9%	51.8%	47.7%	48.7%
Diarrhea requiring treatment	23.2%	46.2%	14.0%	19.6%	14.8%	30.9%	26.5%	28.2%	34.1%

NB: patients may appear in more than one group/column
Dark grey columns: data for patients treated with Ptz+T+D (proposed licensed treatment regimen).
Mid grey columns: data for patients treated with Ptz+T.
Pale grey columns: data for patients treated with single agent pertuzumab.

Rash

The incidence of rash was higher in the Ptz-containing arm (45.2%) compared to the Placebo arm (36.0%) of the pivotal trial.

Table 69. Summary of Rash (Identified using AE Grouped Terms) from the Integrated Safety Database

Safety Parameter	Patients Experiencing Event								
	WO20698/TOC4129g		WO20697				BO17929	Single Agent Ptz	All Ptz-Treated Pts
	Pla+T+D n=397	Ptz+T+D n=407	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T n=83	Ptz n=386	Various n=1412
Rash All Grades	36.0%	45.2%	29.0%	40.2%	18.5%	40.4%	31.3%	23.8%	36.0%
Rash Grade ≥ 3	1.3%	2.7%	1.9%	2.8%	0	1.1%	1.2%	0.5%	1.4%
Rash Related	28.0%	37.3%	26.2%	34.6%	15.7%	38.3%	24.1%	19.9%	30.0%
Rash Requiring treatment	20.2%	29.2%	14.0%	22.4%	5.6%	21.3%	16.9%	8.8%	18.5%

NB: patients may appear in more than one group/column.

Mucositis

More patients in the Ptz-arm experienced mucositis (48.6%) vs. 37.0% in the Placebo arm in the pivotal trial.

Table 70. Summary of Mucositis AEs (Grouped Term) from the Integrated Safety Database

Safety Parameter	Patients Experiencing Event								
	WO20698/TOC4129g		WO20697				BO17929	Single Agent Ptz	All Ptz-Treated Pts
	Pla+T+D n=397	Ptz+T+D n=407	T+D n=107	Ptz+T+D n=107	Ptz+T n=108	Ptz+D n=94	Ptz+T n=83	Ptz n=386	Various n=1412
Mucositis All Grades	37.0%	48.6%	33.6%	45.8%	9.3%	43.6%	24.1%	14.8%	32.2%
Mucositis Grade ≥ 3	1.8%	2.9%	0	1.9%	0	0	1.2%	0.8%	1.3%

NB: patients may appear in more than one group/columnDark grey columns: data for patients treated with Ptz+T+D (proposed licensed treatment regimen).
Mid grey columns: data for patients treated with Ptz+T.
Pale grey columns: data for patients treated with single agent pertuzumab.

Laboratory findings

Most patients had normal laboratory values. As expected, the most common Grade 3+ laboratory values at any time in the pivotal trial were Grade 3+ neutropenia with a balanced frequency across treatment arms (86.6% in the Placebo arm vs. 86.0% in the Ptz arm). In general, shifts from baseline were also comparable between treatment arms for hematologic parameters. For biochemistry parameters grade 3-4 shifts occurred most frequently for uric acid (as an indicator of increased cell turnover) and liver function tests, potassium, sodium, magnesium and fasting glucose. Minor differences were observed between treatment arms.

Safety in special populations

Age

In the pivotal trial there were very few patients of age ≥ 75 years (19 in total, 5 in the Ptz arm) so data in this subgroup is difficult to interpret. There were 126 patients of age ≥ 65 years. The incidence of neutropenic events was slightly higher in patients < 65 years of age and the incidence of febrile neutropenia was highest in the Ptz+T+D arm in the younger age group. In contrast, the elderly patients experienced slightly more diarrhea but the absolute difference between young and elderly patients was < 10%. The incidence of cardiac events was overall comparable across age groups.

Gender

The pivotal study only included 2 male patients and the proposed target population will mainly be represented by women.

Race

Asian patients (who represented approximately 30% of the pivotal study population) experienced more neutropenia, and particularly more febrile neutropenia in the Ptz+T+D arm (26%) compared to other races, most probably due to a higher docetaxel exposure in Asians.

Patients with hepatic impairment

The safety of pertuzumab has not been studied in patients with hepatic impairment. Patients with inadequate liver function were excluded from Study WO20698/TOC4129g (defined as total bilirubin < ULN, AST or ALT< 2.5 ULN).

Patients with reduced kidney function

The safety of pertuzumab has not been studied in patients with renal impairment. No dedicated renal impairment study has been conducted for pertuzumab. Study WO20698/TOC4129g enrolled patients with serum creatinine levels ≤ 2.0 mg/dL or 177 µmol/L.

Immunological events

The incidence of clinically relevant safety sequelae related to unwanted immunogenicity of pertuzumab was low and in line with what may be expected for a humanized monoclonal antibody. It is agreed with the Applicant that the occurrence of ATA per se do not necessarily warrant discontinuation of pertuzumab, since patients may, with appropriate management, still benefit from pertuzumab.

Safety related to drug-drug interactions and other interactions

No safety studies related to drug-drug interactions were submitted as no drug-drug interactions have been indentified for pertuzumab.

Discontinuation due to adverse events

When excluding events leading to discontinuation of docetaxel alone, relatively few patients in the pivotal trial stopped study medication due to AEs and the proportion was similar across treatment arms (5.3% in the Placebo arm vs. 6.1% in the Ptz arm). In both treatment arms the most common reason for discontinuing was left ventricular dysfunction (2.0% in the Placebo arm and 1.5% in the Ptz arm). Other reasons reported in the Ptz arm were hypersensitivity reactions, diarrhea and rash reported in 0.5% of patients, respectively.

Table 71 Summary Of AEs Leading To Discontinuation Of Study Medication (Excluding Events Leading To Discontinuation Of Docetaxel only): Pivotal Study (WO20698/TOC4129g)

t_ae11_dc_cl Summary Of Adverse Events Leading To Discontinuation Of Study Medication, Excluding Events Leading To Discontinuation Of Docetaxel Only, By Body System And Trial Treatment: Pivotal Study, WO20698
Protocol(s): WO20698. Analysis: ALL PATIENTS Center: ALL CENTERS

Body System/ Adverse Event	PLACEBO + TRASTUZUMAB + DOCETAXEL N = 397 No. (%)	PERTUZUMAB + TRASTUZUMAB + DOCETAXEL N = 407 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	21 (5.3)	25 (6.1)
Total Number of AEs	22	26
CARDIAC DISORDERS		
Total Pts With at Least one AE	10 (2.5)	8 (2.0)
LEFT VENTRICULAR DYSFUNCTION	8 (2.0)	6 (1.5)
CARDIOVASCULAR INSUFFICIENCY	-	1 (0.2)
MYOCARDIAL ISCHAEMIA	1 (0.3)	-
PERICARDIAL EFFUSION	1 (0.3)	-
VENTRICULAR FIBRILLATION	-	1 (0.2)
Total Number of AEs	10	8
IMMUNE SYSTEM DISORDERS		
Total Pts With at Least one AE	2 (0.5)	4 (1.0)
HYPERSENSITIVITY	1 (0.3)	2 (0.5)
DRUG HYPERSENSITIVITY	1 (0.3)	1 (0.2)
ANAPHYLACTIC REACTION	-	1 (0.2)
Total Number of AEs	2	4
GASTROINTESTINAL DISORDERS		

Total Pts With at Least one AE	2 (0.5)	2 (0.5)
DIARRHOEA	1 (0.3)	2 (0.5)
INTESTINAL PERFORATION	1 (0.3)	-
Total Number of AEs	2	2
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	2 (0.5)	2 (0.5)
HERPES SIMPLEX	1 (0.3)	-
POSTOPERATIVE WOUND INFECTION	1 (0.3)	-
SEPSIS	-	1 (0.2)
URINARY TRACT INFECTION	-	1 (0.2)
Total Number of AEs	2	2
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	1 (0.3)	3 (0.7)
RASH	-	2 (0.5)
DERMATITIS ALLERGIC	-	1 (0.2)
RASH ERYTHEMATOUS	1 (0.3)	-
Total Number of AEs	1	3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	2 (0.5)	1 (0.2)
FATIGUE	1 (0.3)	1 (0.2)
ASTHENIA	1 (0.3)	-
Total Number of AEs	2	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	2 (0.5)	1 (0.2)
DYSPNOEA	1 (0.3)	-
INTERSTITIAL LUNG DISEASE	-	1 (0.2)
PLEURAL EFFUSION	1 (0.3)	-
Total Number of AEs	2	1

Investigator text for Adverse Events encoded using MedDRA version 14.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 18JUL2011:20:17:27

The number of cycle delays was also similar across treatment arms (6.3% in the Placebo arm vs. 5.8% in the Ptz arm). In contrast, dose interruptions or modifications were slightly more frequent in the Ptz+T+D arm (60.0%) compared to the Pla+T+D arm (53.1%). The most common AEs leading to dose modifications in the Ptz-containing arm were as expected febrile neutropenia, hypersensitivity and diarrhea.

Post marketing experience

No post-marketing reports were submitted.

2.6.1. Discussion on clinical safety

Pivotal trial

Overall, standard reporting methods for safety parameters have been used. However, additional cardiac safety measures were instituted, including separate collection of LVEF data and a cardiac event evaluation by a Cardiac Review Committee (CRC) which is endorsed based on the known risk of cardio toxicity associated with other HER2 targeting agents. The *exposure* to pertuzumab is considered sufficient to allow a representative safety evaluation.

Common AEs associated with docetaxel are nausea, vomiting, diarrhoea, fluid retention, dyspnoea, neutropenia, infections, myalgia, alopecia, peripheral neuropathy and allergic reactions. Common AEs associated with trastuzumab are asthenia, fatigue, flu-like symptoms, headache, dyspnoea, infusion-related reactions, nausea, diarrhoea, abdominal pain, febrile neutropenia, cardiotoxicity (Ejection Fraction decreased), arthralgia and myalgia.

In the pivotal study almost all patients experienced at least one AE, 98.5% and 99.8 % in the placebo and pertuzumab arms, respectively. The majority of AE's were considered *treatment-related.*

Common AEs in the pivotal study (incidence >25%) were alopecia (60.5% in the placebo arm, 60.9% in the pertuzumab arm), diarrhoea (46.3%/66.8%), neutropenia (49.6%/52.8%), nausea (41.6%/42.3%), fatigue (36.8%/37.6%), rash (24.2%/33.7%), asthenia (30.2%/26.0%), decreased appetite (26.4%/29.2%), peripheral oedema (30.0%/23.1%) and mucosal inflammation 19.9%/27.8%). So when pertuzumab was added to trastuzumab + docetaxel the safety profile was generally not changing, however, more diarrhoea, rash, mucosal inflammation, dry skin and (febrile) neutropenia were seen. Importantly, no increase in LVSD was observed.

Overall, no difference in *grade 3-4 events* was observed between the placebo arm and the pertuzumab arms (72.0% and 73.5%, respectively). It was mainly the rates of febrile neutropenia and diarrhoea of grade 3+ that were higher in the pertuzumab arm compared to the control arm. LVSD of grade 3 or higher was reported les frequently in the pertuzumab arm (1.2%) compared to the placebo arm (2.8%).

Deaths: In the pivotal trial 23.7% of patients died in the placebo arm vs. 17% in the pertuzumab arm. The majority of patients died due to PD (20.4% and 14.0%, respectively) and most deaths occurred more than 42 days after last treatment. AEs resulting in death were observed in 2.5% of patients in the placebo arm and in 2.0% of patients in the pertuzumab arm. No accumulation of specific causes was noted. In particular, no deaths were attributed to heart failure. There were 6 deaths in the Placebo arm and 5 deaths in the Ptz arm considered *treatment-related* by Investigator. As expected, febrile neutropenia was the most common fatal treatment-related AE in the Ptz arm (3 cases). Of note, there was however also two patients in the Placebo arm who died of treatment-related sepsis/febrile neutropenia.

SAEs: Overall, a higher number of patients in the Ptz arm reported a SAE (34.4%) compared to 26.2% in the Pla+T+D arm. The most common SAEs were febrile neutropenia and infections. The incidence of febrile neutropenia almost doubled in the Ptz-treated patients (11.3% in the Ptz arm vs. 5.0% in the Placebo arm), whereas only a modest increase in the incidence of infections was actually noted (10.8% in the Ptz arm vs. 7.3% in the Placebo arm). The incidence of all other SAEs was < 5% in both treatment arms. SAEs that considered related to treatment by Investigators could be related to all components of the regimen. Treatment-related SAEs were reported in 25.1% of patients in the Ptz arm vs. 17.9% in the Placebo arm. The difference was mainly due to a larger incidence of SAEs of febrile neutropenia in the Ptz arm (11.3% vs. 4.8% in the Placebo arm).

The Applicant has provided an additional 6 months of safety data (new safety cut-off date: 7 November 2012, previous safety cut-off dates were 13 May 2011 and 14 May 2012 respectively). Reassuringly, the updated safety profile is very consistent to what was reported in the MAA.

Summary of safety update (data cut-off, 7 November 2012): The incidence of SAEs was still higher in the Ptz arm (35.6%) compared with the Placebo arm (28.0%), especially because of more cases of febrile neutropenia in the Ptz arm. In contrast, more patients had died in the Placebo arm (28.7%) compared with the Ptz arm (22.4%). Most patients died because of PD. Since the first safety report (data cut-off,13 May 2011), two more deaths from other causes than PD were reported (one unrelated case of myocardial infarction in the Placebo arm and one unevaluable death in the Ptz arm). Two additional patients in the Placebo arm had Grade ≥ 3 LVSD and one additional patient in the Ptz arm had developed CHF. More common AEs associated with Ptz were still diarrhea, rash, mucosal inflammation, febrile neutropenia and dry skin. Pruritus had also been added. The severity of events was overall similar to what was previously reported. No new safety events were identified.

Events of special interest

A number of events of special interest were pre-defined by the applicant based on the mechanism of action of pertuzumab.

Cardiac safety: HER family members play a crucial role in normal cardiac development thus cardiac safety in patients treated with the combination of pertuzumab and trastuzumab is an important issue (Portera CC et al., CCR 2008). In order to limit the possible occurrence of cardiac toxicity, the enrolment criteria for all the pertuzumab studies were aimed to select patients having a good cardiac function (LVEF cut-off value at baseline: 50-55%) and stable LVEF values (a decline of LVEF value below 50% during prior or after Trastuzumab was not accepted). Moreover, several measures were used to monitor cardiac safety including independent cardiac event evaluation by a Cardiac Review Committee (CRC).

In the pivotal study, the addition of pertuzumab to trastuzumab and docetaxel did not seem to increase the incidence of cardiac toxicity. The number of patients who had cardiac AEs of any type reported during the treatment period was roughly comparable between the two arms (16.4% of patients in the Pla+T+D arm, and 14.5% of patients in the Ptz+T+D arm). As expected, left ventricular systolic dysfunction (LVDS) was the most common cardiac AE (reported more frequently in the Pla+T+D arm (8.3%) than in the Ptz+T+D arm (4.4%). Symptomatic LVSD was reported for 11 patients by investigators (7 in the Placebo arm vs. 4 in the Ptz arm). These cases were reported as cardiac failure SAEs and were all considered treatment-related. The CRC identified 4 cases (1%) in each treatment arm. All 4 cases in the Placebo arm were categorized as NYHA class II events whereas 3 events in the Ptz arm were categorized as NYHA class III-IV events. These cases led to treatment discontinuation and supportive therapy. The ventricular dysfunction was reversible as the majority of cases had resolved at the time of data-cut off. Significant LFEV declines other than symptomatic CHF (defined as a decline of at least 10% points from baseline to an absolute value of <50%) were observed in 5.5% of patients in the Placebo arm vs. 3.2% in the Ptz arm. The analysis of patient characteristics in the pivotal study showed that the median LVEF was 65.0% (range 50-88%) and that patients with a lower baseline LVEF in the range of 50-55% only represented 7.8% of the total study population why a selection bias was suspected. As only a minority of the patients had been exposed to trastuzumab and/or anthracyclines in the adjuvant setting, there were concerns that the risk of cardiotoxicity had been underestimated. The baseline LVEF data did not differ from what has been observed in other 1st line studies in MBC. Patient characteristics such as baseline LVEF values, age, smoking status, prior radiotherapy and prior anthracycline therapy were well balanced across treatment arms.

The cardiac safety profile of Ptz has been described in details and updated. No differences were observed between the two treatment arms in terms of incidence of cardiac AEs. Left ventricular dysfunction, was the most common cardiac AE (Pla+T+D: 8.6% and PTZ+T+D: 5.2%). Risk factors of cardiotoxicity have been identified (mainly prior anthracycline therapy and prior radiotherapy). Based on data from the pivotal trial, the incidence of cardiac dysfunction was 5.6% in the Placebo arm compared with 0.8% in the Ptz arm in the subgroup of patients who had never received prior anthracyclines or trastuzumab (n=477). Prior anthracycline therapy (n = 239) resulted in a higher incidence of cardiac dysfunction (mainly LVEF declines) in both treatment arms, the increase was however slightly more marked in the Ptz arm (Placebo: 8.9%, Ptz: 12.1%) which could be a chance finding. Prior trastuzumab exposure did not seem to increase the risk of cardiotoxicity. The cardiac dysfunction was reversible in the majority of patients. The updated cardiac safety review did not identify new concerns.

Relevant information about risk factors and exclusion criteria in the pivotal trial has been provided in the SmPC as for trastuzumab. Cardiac disorders have been included in the RMP. Of note, oncologists are experienced with the surveillance and management of these adverse events.

Infusion-Associated Reactions (IARs): The applicant has used 3 "time-windows" for registration of IARs in the pivotal trial instead of investigator-assessed causality or event terms. Relatively few patients experienced an event during a placebo/Ptz infusion (5.0% in the Placebo arm vs. 8.8% in the Ptz+T+D arm). Most of these events were mild or moderate in severity. Events observed on Day in Cycle 1 were of particular interest, as this was the only day when Ptz or Placebo was administered without T or D. On this day, 3.9% receiving Ptz experienced an AE during the infusion compared to 2.0% in the Placebo arm.**.** The applicant has identified patients with a history of asthma, eczema or hay fever to have a slightly higher risk of developing Infusion-Associated Reactions.

Anaphylaxis or *hypersensitivity reactions* were reported for 9.1% of patients in the Placebo arm vs. 10.8% of patients in the Ptz arm. These events were severe in 2.5% and 2.0% of patients, respectively. Only 1.5% of patients in the Pla+T+D arm vs. 1.0% of patients in the Ptz+T+D arm discontinued study medication due to anaphylaxis/hypersensitivity reactions, indicating that most of these reactions could be handled by interrupting or slowing the infusion or by reducing the dose of docetaxel. No potential risk factors were identified.

The incidence of *leucopenic event*s was only slightly higher in the Ptz+T+D arm (62.4%) compared to the Pla+T+D arm (58.2%). Most of these events were ≥ grade 3 (58.2% and 53.1%, respectively). Of most interest is the incidence of febrile neutropenia that was also slightly higher in the Ptz-containing arm (13.8%) compared to the Placebo arm (7.6%). These frequencies are however not high enough to recommend prophylactic G-CSF usage (FN risk ≥ 20%). Similarly, the incidence of (febrile) leucopenic infections was also slightly higher in the Ptz arm than in the placebo arm [(3.4%) 12.5% vs. (0.8%) 9.8%]. The median time to the most severe leucopenic event was 29 days in both treatment arms. The incidence of leucopenic events was clearly associated with the administration of docetaxel as leucopenic events were almost not observed in treatment arms without administration of docetaxel in the supportive studies (0.9% in the Ptz+T arm of study WO20697 and 0% in study BO17929 (Ptz+T)). Asian race was identified as a risk factor for leucopenia.

Exacerbation of chemotherapy/docetaxel-associated neutropenia was identified as an important risk to be monitored in the post marketing surveillance.

A wording advising monitoring of patients for complications of neutropenia in case of treatment-induced myelosuppression together with reference to docetaxel dose modifications has been included in the SmPC section 4.2. The reported data do not support a clear role of pertuzumab in affecting the docetaxel nadir and the recovery from neutropenia

Diarrhea was more commonly reported in patients treated with Ptz (66.8%) than with Placebo (46.3%). This was expected as diarrhea is thought to be an off-target intestinal effect caused by the inhibition of HER1/HER2 and HER2/HER heterodimers. Although diarrhea episodes also lasted longer in Ptz-treated patients (median duration of longest episode 17 days compared to 8 days in the control arm), most of these events were mild or modest in severity (the incidence of Grade ≥ 3 events was 7.9% in the Ptz+T+D arm vs. 5.0% in the Pla+T+D arm) and few patients actually discontinued study medication due to diarrhea so it was overall considered manageable. Many patients experienced diarrhea early in the course of treatment. Risk factors were Asian race, patients with a history of bowel disease and patients receiving concomitant chemotherapy.

Rash is another expected off-target effect involving HER1 (EGFR). The incidence of rash increased when adding Ptz to T+D (45.2% in the Ptz+T+D arm) compared to the Pla+T+D arm (36.0%).

However, severe events (≥ grade 3) were rare (2.7% in the Ptz arm vs. 1.3% in the Placebo arm) and few patients discontinued treatment due to rash that often occurred early in the course of treatment. The supportive studies confirm that rash was also seen in Ptz+T arms (18.5% in study WO20697 and 31.3% in study BO17929) as well as in Ptz single-agent studies (23.8%).

Similarly, more patients in the Ptz-arm experienced *mucositis* (48.6%) vs. 37.0% in the Placebo arm. The incidence of patients experiencing Grade 3+ events was generally low (2.9% in the Ptz arm vs. 1.8% in the Placebo arm). Docetaxel seemed to be a contributing factor since patients in Ptz single-agent studies and in Ptz+T arms of the supportive studies had a much lower incidence of mucositis. With regard to the potential relationship between neutropenia and mucositis, the Applicant provided exhaustive information. The reported data confirm the onset of mucositis whenever the nadir of neutrophil count is expected. The simultaneous occurrence of neutropenia and mucositis is clinically expected.

The incidence of all grade *hepatic disorders* was balanced between treatment arms (10.1% in the Placebo arm vs. 9.6% in the Ptz arm). Grade ≥ 3 events were rare (1.3% in the Placebo arm vs. 1.7% in the Ptz arm). The most common event was increased ALAT. No potential risk factors for hepatic disorders were identified. Liver metastases were not a risk factor according to the applicant but of note, only patients with a preserved liver function were included in the pivotal study. No studies have been performed in patients with impaired liver function.

Age: In the pivotal trial there were very few patients of age ≥ 75 years (19 in total, 5 in the Ptz arm) why data in this subgroup is difficult to interpret. There were 126 patients of age ≥ 65 years. The incidence of neutropenic events was slightly higher in patients < 65 years of age and the incidence of febrile neutropenia was highest in the Ptz+T+D arm of the younger age group. In contrast, the elderly patients experienced slightly more diarrhea but the absolute difference between young and elderly patients was < 10%. The incidence of cardiac events was overall comparable across age groups.

Race: Asian patients (who represented approximately 30% of the study population) experienced more neutropenia, and particularly more febrile neutropenia in the Ptz+T+D arm (26%) compared to other races, most likely due to a higher docetaxel exposure in Asians. This information has been included in the SmPC.

Discontinuations/Dose interruptions/Delays: The proportion of patients stopping docetaxel treatment due to toxicity was similar across treatment arms (23.2% of patients in the Placebo arm vs. 23.6% of patients in the Ptz arm). The most common reasons were edema, fatigue and peripheral neuropathy. The number of patients who discontinued due to neutropenia was also similar (7 patients in each arm), but in addition, 4 patients in the Ptz+T+D arm stopped docetaxel due to febrile neutropenia vs. none in the Placebo arm. When excluding events leading to discontinuation of docetaxel alone, relatively few patients stopped study medication due to AEs and the proportion was similar across treatment arms (5.3% in the Placebo arm vs. 6.1% in the Ptz arm). This indicates that although added toxicity was observed in the Ptz-containing arm, the tolerability of the triple regimen was overall acceptable. In both treatment arms the most common reason for discontinuing treatment was left ventricular dysfunction (2.0% in the Placebo arm and 1.5% in the Ptz arm). In the Ptz arm hypersensitivity reactions, diarrhea and rash were other reasons reported in 0.5% of patients, respectively. The number of cycle delays was also similar across treatment arms (6.3% in the Placebo arm vs. 5.8% in the Ptz arm). In contrast, dose interruptions or modifications were slightly more frequent in the Ptz+T+D arm (60.0%) compared to the Pla+T+D arm (53.1%). The most common AEs leading to dose modifications in the Ptz-containing arm were febrile neutropenia, hypersensitivity and diarrhoea as expected.

Supportive studies

It is of interest that patients who received Ptz + T (but without D) in study WO20697 in general experienced considerably fewer AEs compared to the patients in the other 3 docetaxel containing arms of the study. This was also observed in the other supportive study BO17929 in which no concurrent chemotherapy was given (Ptz +/- T). In addition, a very low frequency of leucopenia was observed in the supportive studies without docetaxel-containing regimens and in the single-agent pertuzumab studies indicating that the chemotherapy component (docetaxel) is likely to be the main cause of this AE in the pivotal study. The same is evident for alopecia. Similarly, few grade 3-4 AEs were observed for the combination of Ptz+T compared to those arms which included docetaxel. In the key supporting studies 3 deaths were observed in total. In the neo-adjuvant study WO20697, only 16.8% of patients reported a SAE (probably due the shorter treatment duration), however the most commonly reported SAE was febrile neutropenia in all arms containing docetaxel (T+D: 7.5%, Ptz+T+D: 8.4%, Ptz+T: 0%, P+D: 12.8%). Only one SAE of cardiac failure was observed in the Ptz + T arm. Significant LVEF declines were also observed at low numbers but with the highest incidence in the Ptz+T+D arm (T+D: 0.9%, Ptz+T+D: 2.8%, Ptz-T: 0%, Ptz-D: 1.1%). In the other supportive study BO17929 in advanced MBC, the incidence of SAEs was 14.5%, but no SAEs were reported for the Ptz+T combination. The incidence of significant LVEF declines was higher (7.2%) in the BO17929 study that in the WO20697 study which probably reflects the fact that all patients had been pre-treated in the BO17929 study with T and > 70% had received anthracyclines. There were no reports of CHF SAEs in this study.

Single-agent studies

Common AEs (>20%) associated with pertuzumab as single agent were diarrhoea (57.3%), fatigue (31.6%), nausea (30.8%), vomiting (22.3%) and decreased appetite (21.2%). Diarrhoea (6.5%) was the most common Grade 3+ AE. There were no SAE reports of neutropenia/febrile neutropenia. Deaths during study treatment (n=30, 7.8%) were mainly due to PD (7.0%).

2.6.2. Conclusions on the clinical safety

The safety of a pertuzumab (Perjeta) has been evaluated in more than 1,400 patients either in the pivotal trial CLEOPATRA or in phase I and II trials conducted in patients with various malignancies and predominantly treated with Perjeta in combination with other antineoplastic agents.

407 patients received at least one dose of Perjeta in combination with trastuzumab and docetaxel. The most common adverse drug reactions (ADRs) (>50%) were diarrhoea, alopecia and neutropenia. The most common NCI-CTCAE (version 3) Grade 3-4 ADRs (> 10%) were neutropenia, febrile neutropenia and leucopenia, and the most common serious adverse events were febrile neutropenia, neutropenia and diarrhoea. Treatment-related deaths occurred in 1.2% of patients in the Perjeta-treated group and 1.5% of patients in the placebo-treated group and were mainly due to febrile neutropenia and/or infection. Left ventricular dysfunction occurred at a frequency of <10% in the pivotal trial CLEOPATRA (4.4% in the Perjeta-treated group and 8.3% in the placebo-treated group, including symptomatic LVSD in 1.2% in the Perjeta-treated group and 2.8% of patients in the placebo-treated group).

The safety of Perjeta in phase I and II studies was generally consistent with that observed in the CLEOPATRA trial, though the incidence and most common ADRs varied depending on whether Perjeta was administered as monotherapy or with concomitant anti-neoplastic agents.

Therefore the CHMP included the following statements in the SmPC:

- Decreases in LVEF have been reported with medicinal products that block HER2 activity, including Perjeta. Patients who have received prior anthracyclines or prior radiotherapy to the

chest area may be at higher risk of LVEF declines. In the pivotal trial CLEOPATRA, Perjeta in combination with trastuzumab and docetaxel was not associated with a greater incidence of symptomatic left ventricular systolic dysfunction (LVSD) or LVEF declines compared with placebo and trastuzumab and docetaxel.

- Perjeta has not been studied in patients with:a pre-treatment LVEF value of ≤50%; a prior history of congestive heart failure (CHF); LVEF declines to <50% during prior trastuzumab adjuvant therapy; or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to >360 mg/m^2 of doxorubicin or its equivalent.

- Assess LVEF prior to initiation of Perjeta and every three cycles during treatment to ensure that LVEF is within the institution's normal limits. If LVEF is <40% or 40-45% associated with ≥10% points below the pretreatment value, Perjeta and trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If the LVEF has not improved, or has declined further, discontinuation of Perjeta and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

- Perjeta has been associated with infusion and hypersensitivity reactions. Close observation of the patient during and for 60 minutes after the first infusion and during and for 30-60 minutes after subsequent infusions is recommended following the administration of Perjeta. If an infusion reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Perjeta must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome.

- Patients treated with Perjeta, trastuzumab and docetaxel are at increased risk of febrile neutropenia compared with patients treated with placebo, trastuzumab and docetaxel, especially during the first 3 cycles of treatment. As nadir neutrophil counts were similar in Perjeta-treated and placebo-treated patients, the higher incidence of febrile neutropenia in Perjeta-treated patients may be associated with the higher incidence of mucositis and diarrhoea in these patients. Symptomatic treatment for mucositis and diarrhoea should be considered. In the pivotal trial, CLEOPATRA, no events of febrile neutropenia were reported after cessation of docetaxel.

- In the pivotal trial CLEOPATRA, ADRs were reported less frequently after discontinuation of docetaxel treatment. After discontinuation of docetaxel, all ADRs in the Perjeta and trastuzumab treated group occurred in <10% of patients with the exception of diarrhoea (19.1%), upper respiratory tract infection (12.8%), rash (11.7%), headache (11.4%) and fatigue (11.1%).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. .

The CHMP considered that a Global Perjeta pharmacovigilance programme was adequate to address the potential risk of the use of this medicinal product in pregnant women.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

Table 71

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important identified risk		
Exacerbation ofchemotherapy/ docetaxel -associated neutropenia	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** Cumulative data presented in PSURs.	**Routine activities:** Section 4.8 of the EU SmPC states "In the pivotal trial CLEOPATRA, the majority of patients in both treatment groups experienced at least one leucopenic event (62.4% of patients in the Perjeta-treated group and 58.2% of patients in the placebo-treated group), of which the majority were neutropenic events. Febrile neutropenia occurred in 13.8% of Perjeta-treated patients and 7.6% of placebo-treated patients. In both treatment groups, the proportion of patients experiencing febrile neutropenia was highest in the first cycle of therapy and declined steadily thereafter. An increased incidence of febrile neutropenia was observed for Asian patients in both treatment groups compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the Perjeta-treated group (26%) compared with the placebo-treated group (12%)". **Additional activities:** None

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Infusion reactions / Hypersensitivity/Anaphylaxis	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** Cumulative data presented in PSURs.	**Routine activities:** Section 4.4 of the EU SmPC states "Perjeta has been associated with infusion and hypersensitivity reactions . Close observation of the patient during and for 60 minutes after the first infusion and during and for 30 minutes after subsequent infusions is recommended following the administration of Perjeta. If an infusion reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Perjeta must be permanently discontinued in case of NCI-CTCAE Grade 4 hypersensitivity reactions (anaphylaxis), bronchospasm or acute respiratory distress syndrome." **Additional activities:** None

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Congestive heart failure	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** Cumulative data presented in PSURs. Studies BO22280, BO25126, MO22324, MO28047, WO20698	**Routine activities:** Perjeta and trastuzumab should be withheld for at least 3 weeks for any of the following: symptoms and signs suggestive of congestive heart failure (Perjeta should be discontinued if symptomatic heart failure is confirmed) a drop in left ventricular ejection fraction (LVEF) to less than 40% a LVEF of 40%-45% associated with a fall of ≥ 10% points below pre-treatment values. Perjeta and trastuzumab may be resumed if the LVEF has recovered to > 45% or 40-45% associated with < 10% points below pretreatment value. If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinuation of Perjeta and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. **Additional activities:** None.
Mucositis (including diarrhoea)	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** Cumulative data presented in PSURs.	**Routine activities:** Included in table of ADRs presented in the EU SmPC. **Additional activities:** None.
≥ 3 grade diarrhoea	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** Cumulative data presented in PSURs.	**Routine activities:** In section 4.8 of the EU SmPC it states “In the pivotal clinical trial CLEOPATRA, diarrhoea occurred in 66.8% of Perjeta-treated patients. Most events were mild-moderate in severity and occurred in the first few cycles of receiving treatment. The incidence of NCI-CTCAE grade 3-4 diarrhoea was 7.9% in Pejeta treated patients vs 5.0% in placebo-treated patients. The median duration of the longest episode was 17 days in Perjeta-treated patients and 8 days in placebo-treated patients. Diarrhoeal events responded well to proactive management with anti-diarrhoeal agents.” **Additional activities:** None.
Interstitial lung disease	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** Checklist Cumulative data presented in PSURs.	**Routine activities:** Included in table of ADRs presented in the EU SmPC. **Additional activities:** None.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important potential risk		
Oligohydramnios	Routine pharmacovigilance as detailed in Section 2.1. **Additional activities:** MotHER pregnancy registry annual report. Cumulative data presented in PSURs. Proposed Pregnancy PV Program and follow up infants for the first year after exposure to pertuzumab and trastuzumab.	**Routine activities:** Section 4.6 of the EU SmPC states "There is limited amount of data from the use of pertuzumab in pregnant women. Studies in animals have shown reproductive toxicity. Perjeta is not recommended during pregnancy and in women of childbearing potential not using contraception." **Additional activities:** None

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important mssing information		
Risk in patients aged 75 years or older	Routine pharmacovigilance as detailed in Section 2.1. **Additional activities:** Cumulative data presented in PSURs.	**Routine activities:** Section 4.2 of the EU RMP states "Very limited data are available in patients >75 years". **Additional activities:** None
Risk in pregnant women	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** MotHER U.S. pregnancy registry annual reports Cumulative data presented in PSURs. Proposed Pregnancy PV Program	**Routine activities:** Section 4.6 of the EU SmPC states "There is limited amount of data from the use of pertuzumab in pregnant women. Studies in animals have shown reproductive toxicity. Perjeta is not recommended during pregnancy and in women of childbearing potential not using contraception." **Additional activities:** None
Risk in lactating women	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** MotHER U.S. pregnancy registry annual reports Cumulative data presented in PSURs. Proposed Pregnancy PV Program and follow up infants for the first year after exposure to pertuzumab and trastuzumab.	**Routine activities:** Because human IgG is secreted in human milk and the potential for absorption and harm to the infant is unknown, a decision should be made to discontinue nursing or pertuzumab, taking into account the importance to the mother and the half life of pertuzumab. **Additional activities:** None
Risk in fertility in humans	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** Cumulative data presented in PSURs.	**Routine activities:** Section 4.6 of the EU SmPC states "No specific fertility studies in animals have been performed to evaluate the effect of pertuzumab. Only very limited data are available from repeat-dose toxicity studies with respect to the risk for adverse effects on the male reproductive system. No adverse effects were observed in sexually mature female cynomolgus monkeys exposed to pertuzumab". **Additional activities:** None
Risk in male patients	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** Cumulative data presented in PSURs.	**Routine activities:** Safety in male patients is not discussed in the EU SmPC. Section 4.6 of the EU SmPC states "male patients with female partners of childbearing potential, must use effective contraception while receiving Perjeta and for 6 months following the last dose of Perjeta." **Additional activities:** None

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Risk in patients with cardiovascular impairment	Routine pharmacovigilance as detailed in Section 2.1. **Additional activities:** Studies BO22280, BO25126, MO22324, MO28047 Cumulative data presented in PSURs.	**Routine activities:** Section 4.2 Posology provides algorithm for dose interuptions. Section 4.4 states "Perjeta has not been studied in patients with: a pre-treatment LVEF value of $\leq$ 50%; a prior history of congestive heart failure (CHF); LVEF declines to <50% during prior trastuzumab adjuvant therapy; or conditions that could impair left ventricular function such as uncontrolled hypertension, recent myocardial infarction, serious cardiac arrhythmia requiring treatment or a cumulative prior anthracycline exposure to > 360 mg/m^2 of doxorubicin or its equivalent." **Additional activities:** None
Risk in patients with hepatic impairment	Routine pharmacovigilance as detailed in Section 2.1 Cumulative data presented in PSURs.	**Routine activities:** Section 4.2 of the EU RMP states "The safety and efficacy of Perjeta have not been studied in patients with hepaticimpairment." **Additional activities:** None
Risk in patients with renal impairment	Routine pharmacovigilance as detailed in Section 2.1 Cumulative data presented in PSURs.	**Routine activities:** Section 4.2 of the EU SmPC states "Dose adjustment of Perjeta are not needed in patients with mild or moderate renal impairment. No dose recommendations can be made for patients with severe renal impairment because of the limited pharmacokinetic data available." **Additional activities:** None

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Risk of lack of efficacy due to immunogenicity	Routine pharmacovigilance as detailed in Section 2.1 **Additional activities:** Ongoing and updated immunogenicity information from on-going and planned clinical trials will be collected. Cumulative data presented in PSURs.	**Routine activities:** Section 5.1 of the EU SmPC states "There are currently insufficient data to evaluate the effects of ATAs on the efficacy of Perjeta in combination with trastuzumab and docetaxel." **Additional activities:** None

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

The Applicant is recommended to include a special review and discussion of Venous Thromboembolic Events in upcoming PSURs.

2.8. 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.*

3. Benefit-Risk Balance

HER2 positive breast cancer (BC) represents approximately 20% of all breast cancers. They are known to have a more aggressive phenotype, a higher recurrence rate and a poor prognosis. Trastuzumab (T) has revolutionized the treatment of HER2+ BC. It is now the standard of care and is used in combination with chemotherapy in the (neo-) adjuvant and metastatic setting for patients with intervals of more than 12 months between completion of adjuvant T and relapse. Despite the improvements made, patients with advanced HER2+disease will eventually progress on trastuzumab-containing regimens. There is a growing body of evidence supporting continued HER2 blockade upon disease progression, so that patients are often switched to other trastuzumab- or lapatinib- containing regimens. More agents are currently under development.

Pertuzumab (Ptz) represents the first drug in a new class of targeted therapy called "HER2 dimerisation inhibitors". It is a recombinant, humanized, IgG mAb which also targets HER2, but Ptz binds to a different epitope (domain II) than T (domain IV) and prevents dimerisation of HER2 with other members of the HER family (HER1 (=EGFR), HER3 and HER4). These dimers (homodimers or heterodimers) are responsible for signal transduction that is involved in the survival, growth and division of BC cells. Thereby, it is believed that Ptz will result in a more complete inhibition of the HER2 axis when combined with T (dual HER2 blockade).

The pivotal study in this submission is the Phase III study WO20698/TOC4129g (CLEOPATRA), a randomized, double-blind, placebo controlled phase III study of Ptz+T+D compared to Pla+T+D in patients with untreated HER2-positive locally recurrent, unresectable or MBC.

Benefits

Beneficial effects

In the primary efficacy analysis the addition of Ptz to T+D resulted in a HR of 0.62 for IRF-assessed PFS (95% CI: 0.51; 0.75, p < 0.0001) (stratified analysis) in favour of the Ptz-containing arm. The median PFS was 18.5 months in the Ptz arm compared to 12.4 months in the Placebo arm.

The result of the primary analysis was supported by the results of secondary endpoints. PFS based on INV assessment was in line with the result based on IRC assessment (HR for PFS (INV) = 0.65 (95% CI 0.54- 0.78, p< 0.0001)), median PFS was 12.4 months in the Pla+T+D arm vs. 18.5 months in the Ptz+T+D arm). The PFS-benefit has been maintained and confirmed in an updated INV-based PFS analysis one year after the original, primary, IRF-based PFS analysis. At the time of the updated INV-based PFS analysis (data cut-off: 14 May 2012) 68% of patients had had a PFS event (72.9% in the Placebo arm and 63.9% in the Ptz arm). Updated HR for PFS (INV) = 0.69 (95% CI: 0.58, 0.81). The K-M curves demonstrated an early and clear separation. The median PFS was 12.4 months in the Placebo arm compared with 18.7 months in the Ptz arm. Consistent results were also observed in the subgroup analyses.

At the time of the primary PFS analysis 96 patients had died in the Placebo arm (23.6%) compared to 69 deaths (17.2%) in the Ptz arm. The median time to death had not been reached in any of the treatment arms. The HR for OS was 0.64 (95% CI: 0.47; 0.88, p = 0.0053) but the O'Brien-Fleming stopping boundary was not met (HR ≤ 0.603, p ≤ 0.0012).

The second interim analysis of OS (data cut-off May 13th 2012) collected events one year after the data cut-off of the primary analysis, by adding 102 deaths. At the time of this second analysis (considered as the final OS analysis), 267 deaths had occurred, specifically 154 events (37.9%) in the placebo arm and 113 events (28.1%) in the pertuzumab arm. Results from the second and final OS analysis showed a significant survival benefit for patients randomized to receive pertuzumab (stratified by prior treatment status and region): HR of 0.66 (95% CI: 0.52; 0.84, p= 0.0008). Median survival was of 37.6 months in the placebo arm and was not still reached in the pertuzumab arm. Survival rates showed a sustained survival advantage in the pertuzumab arm 0.94, 0.81 and 0.66 for the PTZ+T+D arm and 0.89, 0.69 and 0.50 in the Pl+T+D arm at 12, 24 and 36 months, respectively.

A higher ORR was observed in the Ptz+T+D arm (80.2%) compared to the Pla+T+D arm (69.3%). The majority of responses in the Ptz arm were PRs. The median duration of responses was also longer in the Ptz arm (87.6 weeks) than in the Placebo arm (54.1 weeks).

No difference in QoL was observed between treatment arms based on the FACT-B questionnaire.

Uncertainty in the knowledge about the beneficial effects.

Patients with non-visceral disease (n=178) appeared to get the smallest benefit from the addition of Ptz based on a subgroup analysis (HR=0.96 (0.61; 1.52)). This is somewhat unexpected from a mechanistic point of view as HER2 blockade is also known to be efficacious in earlier disease stages. The relatively wide confidence intervals reveal that the estimate is not very precise in this subpopulation. As pointed out, in this small size subgroup, events occurred at lower rate (only 33 deaths in 178 pts) when compared to the visceral disease status subgroup. The CHMP agreed that the subgroup characteristics (small size and low rate of event occurrence) may have affected the large variability of the point estimate and the probability to capture a true treatment effect (low power).

In addition, imbalances in certain demographics/disease characteristics may also have contributed to the reduced treatment effect observed in the non visceral disease subgroup. Further studies have not been requested.

Risks

Unfavourable effects

Common AEs in the pivotal study (incidence >25%) were alopecia (60.5% in the placebo arm, 60.9% in the pertuzumab arm), diarrhoea (46.3%/66.8%), neutropenia (49.6%/52.8%), nausea (41.6%/42.3%), fatigue (36.8%/37.6%), rash (24.2%/33.7%), asthenia (30.2%/26.0%), decreased appetite (26.4%/29.2%), peripheral oedema (30.0%/23.1%) and mucosal inflammation 19.9%/27.8%). So when Ptz was added to T + D the safety profile was generally not changing, however, more diarrhoea, rash, mucosal inflammation, dry skin and (febrile) neutropenia were seen.

Overall, no difference in *grade 3-4 events* was observed between the placebo and pertuzumab arms (72.0% and 73.5%, respectively). It was mainly the rates of febrile neutropenia and diarrhoea of grade 3+ that were higher in the pertuzumab arm compared to the control arm. LVSD of grade 3 or higher was reported less frequently in the pertuzumab arm (1.2%) compared to the placebo arm (2.8%).

AEs resulting in death were observed in 2.5% of patients in the placebo arm and in 2.0% of patients in the pertuzumab arm. No accumulation of specific causes was noted. In particular, no deaths were attributed to heart failure. Although neutropenia and febrile neutropenia were observed more often in the pertuzumab arm, the number of deaths because of febrile neutropenia or infections was similar in the two treatment arms.

A higher number of patients in the pertuzumab arm reported *SAEs* (34.4%) compared to 26.2% in the Pla+T+D arm. The most common SAEs were febrile neutropenia and infections. The incidence of febrile neutropenia almost doubled in the Ptz-treated patients (11.3% in the Ptz arm vs. 5.0% in the Placebo arm), whereas only a modest increase in the incidence of infections was actually noted (10.8% in the Ptz arm vs. 7.3% in the Placebo arm). The incidence of all other SAEs was < 5% in both treatment arms.

The proportion of patients stopping docetaxel treatment due to toxicity was similar across treatment arms (23.2% of patients in the Placebo arm vs. 23.6% of patients in the Ptz arm). The most common reasons were oedema, fatigue and peripheral neuropathy. The number of patients who discontinued due to neutropenia was also similar (7 patients in each arm), but in addition, 4 patients in the Ptz+T+D arm stopped docetaxel due to febrile neutropenia vs. none in the Placebo arm. When excluding events leading to *discontinuation* of docetaxel alone, relatively few patients stopped study medication due to AEs and the proportion was similar across treatment arms (5.3% in the Placebo arm vs. 6.1% in the pertuzumab arm).

Safety update: An additional 6 months of safety data has been provided (new safety cut-off date: 7 November 2011, the original safety cut-off date was 13 May 2011). Reassuringly, the updated safety profile is very consistent to what was reported in the original MAA. The incidence of SAEs was still higher in the Ptz arm (35.6%) compared with the Placebo arm (28.0%), especially because of more cases of febrile neutropenia in the Ptz arm. In contrast, more patients had died in the Placebo arm (28.7%) compared with the Ptz arm (22.4%). Most patients died because of PD. Since the first safety report, two more deaths from other causes than PD were reported (one unrelated case of myocardial infarction in the Placebo arm and one unevaluable death in the Ptz arm). Two additional patients in the Placebo arm had Grade ≥ 3 LVSD and one additional patient in the Ptz arm had developed CHF. More

common AEs associated with Ptz were still diarrhea, rash, mucosal inflammation, febrile neutropenia and dry skin. The severity of events was overall similar to what was previously reported. No new safety events were identified.

The cardiac safety profile of Ptz has been described in detail and updated. No differences were observed between the two treatment arms in terms of incidence of cardiac AEs. Left ventricular dysfunction, as in the previous report, was the most common cardiac AE (Pla+T+D: 8.6% and PTZ+T+D: 5.2%).

Risk factors of cardiotoxicity have been identified (mainly prior anthracycline therapy and prior radiotherapy). Based on data from the pivotal trial, the incidence of cardiac dysfunction was 5.6% in the Placebo arm compared with 0.8% in the Ptz arm patients who had never received prior anthracyclines or trastuzumab (n=477). Prior anthracycline therapy (n = 239) resulted in a higher incidence of cardiac dysfunction (mainly LVEF declines) in both treatment arms, the increase was however slightly more marked in the Ptz arm (Placebo: 8.9%, Ptz: 12.1%) which could be a chance finding. Prior trastuzumab exposure did not seem to increase the risk of cardiotoxicity. The cardiac dysfunction was reversible in the majority of patients. The updated cardiac safety review did not identify new concerns.

Relevant information about risk factors and exclusion criteria in the pivotal trial has been provided in the SmPC. Cardiac disorders have been included in the RMP.

Uncertainty in the knowledge about the unfavourable effects

Only patients with a preserved cardiac function and no known risk factors for cardiotoxicity were included in the pivotal trial. These exclusion criteria are provided in the SmPC.

No studies have been performed in patients with impaired liver function. This may be considered a deficiency since patients with MBC will often have liver involvement and abnormal liver function tests. However, it is considered that the SmPC and RMP adequately reflects the missing data and provide sufficient reassurance and information.

Benefit-risk balance

Importance of favourable and unfavourable effects

A HR for PFS (IRF-assessed) of 0.62 (95% CI: 0.51; 0.75, p < 0.0001) translates into a 38% reduction in the risk of progression or death in patients treated with the Ptz+T+D combination. The median PFS was 18.5 months in the Ptz arm compared to 12.4 months in the Placebo arm, resulting in an absolute gain of 6.1 months in median PFS in patients treated with Ptz+T+D. A PFS gain of this magnitude is considered important from a clinical point of view and it is statistically compelling. A number of sensitivity analyses have confirmed the robustness of the result. The pre-specified subgroup analyses demonstrated very consistent benefits in most subgroups, also in patients who had received prior (neo-) adjuvant therapy (50%), in elderly patients and in patients with HR+ tumours.

A statistically significant OS benefit in favour of the Ptz-containing arm was demonstrated in the second (and final) OS interim analysis.

Overall, the addition of Ptz to T+D did not change the known safety profile of the T+D combination, but increased toxicity was observed, primarily diarrhoea, rash, mucosal inflammation and (febrile)

neutropenia. Higher incidence of grade 3+ febrile neutropenia and diarrhoea and as well as more SAEs (mainly febrile neutropenia and infections) were observed in the pertuzumab arm compared to the control arm. On the other hand, more patients died in the placebo arm, mainly because of PD. The incidence of AEs resulting in death was similar between treatment arms. Indeed, relatively few patients stopped study medication due to AEs and the proportion was also similar across treatment arms (5.3% in the Placebo arm vs. 6.1% in the Ptz arm) indicating that the tolerability of the regimen was overall acceptable. Importantly, there is currently no indication that the addition of Ptz to T+D significantly increased the risk of cardiotoxicity.

Benefit-risk balance

Discussion on the benefit-risk balance

The totality of data indicates that Ptz offered substantial and consistent benefits of clinical relevance in a patient population with a limited number of treatment options. Although added toxicity was observed, the safety profile was overall acceptable.

In summary, the benefit of pertuzumab, both in the overall patient population as well as in patients pre-treated with trastuzumab, is considered clinically relevant and sufficiently supported by the available evidence. In support, study BO17929 documented the activity of Ptz in patients pre-treated with trastuzumab in the metastatic setting. The results of the ongoing studies PHEREXA (2nd line MBC) and PERUSE (1st line MBC) will be able to further confirm the size of effect associated with Ptz in patients pre-treated with trastuzumab and will be submitted (Annex II obligations).

Concerns had been raised that the risk of cardiotoxicity might have been underestimated in the pivotal trial. This issue has also been adequately addressed and it has been concluded that there is no indication of a significantly increased risk of cardiotoxicity when adding Ptz to T+D.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Perjeta, in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease, is favourable and 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).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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 agreeed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, 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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
MO22324 (PHEREXA) A randomized Phase II study comparing combination of trastuzumab +capecitabine, +/- Pertuzumab Patients with HER2-positive metastatic breast cancer that have progressed after one line of trastuzumab-based therapy in the metastatic setting	March 2015
MO28047 (PERUSE) A multicenter, open-label, single-arm study of pertuzumab in combination with trastuzumab and a taxane in first line treatment of patients with HER2- positive advanced (metastatic or locally recurrent) breast cancer	December 2016

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

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that pertuzumab is qualified as a new active substance.