Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Petuzumab

Proprietary Product Name: Perjeta

Sponsor: Roche Products Pty Ltd

Date of first round CER:5 July 2012

Date of second round CER: 17 December 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. Minor corrections to typeographical errors have been made to the orginal text in response to errors of fact identified by the sponsor. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AEGT	Adverse event grouped terms
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATA	Anti-therapeutic antibodies
BCS	Breast cancer scale
CBR	Clinical benefit response
CEVA	Clinical Event Validation and Adjudication
CHF	Congestive heart failure
CI	Confidence interval
CLEOPATRA	Clinical evaluation of pertuzumab and trastuzumab
Cmax	Maximum plasma concentration
CR	Complete response
CRC	Cardiac Review Committee
CRF	Case report form
CSF	Colony stimulating factors
CT	Computed tomography
DFI	Disease-free interval
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
ECD	Extracellular domain
ECG	Electrocardiogram

Abbreviation	Meaning
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EORTC	European Organization for Research and Treatment of Cancer
EWB	Emotional well-being
FACT-B	Functional assessment of cancer therapy–Breast
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FFPE	Formalin-fixed paraffin-embedded
GGT	Gamma-glutamyl transferase
β-HCG	β-human chorionic gonadotropin
FWB	Functional well-being
HAHA	Human anti-human antibody
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICH	International Conference on Harmonization
IGF-1R	Insulin-like growth factor-1 receptor
IHC	Immunohistochemistry
ILD	Interstitial lung disease

Abbreviation	Meaning
INN	International non-proprietary name
IRB/IEC	Institutional review board/Independent ethics committee
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
LFT	Liver function test
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Health care products Regulatory Agency
MRI	Magnetic resonance imaging
MUGA	Multigated angiogram
NACT	Next-line anti-cancer therapy
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common terminology criteria for adverse events
NYHA	New York Heart Association
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazard
PK	Pharmacokinetics
Pla+T+D	Placebo in combination with trastuzumab and docetaxel
PR	Partial response

Abbreviation	Meaning
PS	Performance status
PT	Preferred term
Ptz+T+D	Pertuzumab in combination with trastuzumab and docetaxel
aPTT	Activated partial thromboplastin time
PWB	Physical well-being
QC	Quality Control
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SD	Stable disease
SMQ	Standardized MedDRA queries
SOPs	Standard Operating Procedures
SWB	Social well-being
TOI-PFB	Trial outcome index–physical/functional/breast
ULN	Upper limit of normal

1. Introduction

Pertuzumab (rhuMAb 2C4) is the first in a new class of targeted cancer treatments called HER2 dimerization inhibitors. It is a recombinant, humanized, immunoglobulin (Ig)G1κ monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2, also known as c-erbB-2). This receptor is a transmembrane glycoprotein with intrinsic tyrosine kinase activity. By binding to the subdomain 2 epitope of the extracellular domain of HER2, pertuzumab prevents heterodimerization of HER2 with other members of the HER family (HER1, HER3 and HER4), and blocks ligand-activated downstream signalling. Pertuzumab is also capable of activating antibody-dependent cell-mediated cytotoxicity (ADCC).

The proposed indication is:

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

1.1. Clinical rationale

The sponsor's covering letter (4 April 2012) bases the clinical rationale for the submission on the unmet clinical need for therapies to treat HER2 positive metastatic breast cancer (mBC). The sponsor notes that HER2 positive breast cancer represents 15% to 20% of breast cancers and

without treatment is associated with aggressive tumour growth and poor clinical outcomes. Furthermore, the sponsor comments that although Herceptin "represents a major advance in the treatment of HER2 positive mBC, almost all patients with HER2 positive mBC will eventually progress on HERCEPTIN-based regimens, with median survival still approximately three years".

Comment: The sponsor's clinical rationale is acceptable.

1.2. Orphan drug designation

Pertuzumab was designated as an orphan drug by the Therapeutic Goods Administration (TGA) on 19 January 2012 for "the treatment of patients with HER-2 positive metastatic (Stage IV) or locally recurrent breast cancer". The sponsor estimates the prevalence of HER2+ mBC patients in Australia to be 1300 (i.e., 535 incident population x 2.4 mean years overall survival).

1.3. Guidance

The sponsor indicates that no pre-submission meeting with the TGA was held, and states that the "submission is consistent with pre-submission form lodged"

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5
  - 12 studies providing pharmacokinetic data and 1 study providing pharmacodynamic data;
  - 2 population pharmacokinetic analyses;
  - 1 pivotal efficacy/safety study;
  - 10 other efficacy/safety studies;
  - Other data included 19 bioanalytical reports; and
  - literature references.
- Module 1
  - Letter of application; comprehensive table of contents; application forms; medicine information documents (proposed Australian draft PI and CMI), packaging and labelling; information about the experts; good manufacturing information; statement regarding individual patient data; overseas regulatory status; justification for not providing pharmaceutical studies; Risk Management Plan proposed for Australia.
- Module 2
  - Clinical Overview; Clinical Summaries (Biopharmaceutics and Associated Analytical Methods; Clinical Pharmacology; Clinical Efficacy; Clinical Safety); references; and synopses of individual studies.

2.2. Formulation and assay methods

[Note: Information from the CER on formulation, including Table 1, which provides a description of formulations used; and information on assay methods, including Table 3, which provides details of assays used in the PK studies, is not included in this Extract from the CER.**]**

2.3. Paediatric data

The sponsor states that it has confirmation for a class waiver from the EMEA for pertuzumab regarding the conduct of studies based on the proposed indication.

2.4. Good clinical practice

All studies are stated to have complied with the principles of good clinical practice (GCP).

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

3.1.1. Individual studies

The submission included 12 individual clinical studies in approximately 480 patients with cancer, assessing the pharmacokinetics of pertuzumab administered as a single agent or in combination with other chemotherapeutic agents (see Table 2, below). There were no pertuzumab PK data in healthy subjects. The PK parameters in the individual studies were standard and were derived from serum concentrations (pertuzumab/trastuzumab) or plasma concentrations (chemotherapeutic agents) using non-compartmental analysis (NCA). Relevant PK data from the 12 clinical studies in patients with cancer are included in the body of this CER.

Table 2: Individual studies with pharmacokinetic data.

Study	Phase	Indication	Dose/Regimens	N/PK
Single-agent studies (pertuzumab)				
TOC22976	Ia	Advanced solid tumours	Dose-escalation: 0.5, 2, 5, 10, and 15 mg/kg	21
JO17076	I	Advanced solid tumours	Dose-escalation: 5, 10, 15, and 25 mg/kg	18
TOC26896	II	Advanced ovarian cancer	Cohort 1: 840 mg loading, then 420 mg q3w Cohort 2: 1050 mg q3w	61 62
BO16934	II	MBC, low HER2 expression	Arm A: 840 mg loading, then 420 mg q3w Arm B: 1050 mg q3w	40 37
BO17004	II	HRPC, chemotherapy	Cohort 1: 840 mg loading, then 420 mg q3w	35 33

Study	Phase	Indication	Dose/Regimens	N/PK
		naive	Cohort 2: 1050 mg q3w	
TOC2682g	II	CRPC, pre-treated with DOX	840 mg loading, then 420 mg q3w	40
TOC2572g	II	Advanced, recurrent NSCLC	840 mg loading, then 420 mg q3w	43
Combination-studies (pertuzumab plus various other chemotherapeutic agents)				
BO17003	Ib	Advanced solid tumours	PTZ: 1050 mg q3w + CAP: 825, 1000, 1250 mg/m^2	18
BO17021	Ib	Advanced solid tumours	PTZ: 1050 mg q3w + DOX: 60, 75 mg/m^2. PTZ: 840 mg loading, then 420 mg q3w + DOX: 75, 100 mg/m^2	19
WO20024	Ib	Advanced NSCLC	PTZ: 840 mg loading, then 420 mg q3w + ERL: 100, 150 mg/day	15
TOC3258g	II	Ovarian, peritoneal, or fallopian cancer, platinum resistant	PTZ: 840 mg loading, then 420 mg q3w + GEM: 800 mg/m^2 GEM: alone	16 11
WOC20698 Pivotal	III	MBC HER2+	PBO: q3w + DOX: 75 mg/m^2 for 6 cycles at least + TTZ: 8 mg/kg loading, then 6 mg/kg, q3w PTZ: 840 mg loading, then 420 mg q3w + DOX 75 mg/m^2 for 6 cycles at least + TTZ: 8 mg/kg loading, then 6 mg/kg	17 20

PTZ = pertuzumab; TTZ = trastuzumab; DOX = docetaxel; GEM = gemcitabine; CAP = capecitabine; PBO = placebo; MBC = metastatic breast cancer; NSCLC = non-small cell lung cancer; CRCP = castrate resistant prostate cancer; HRPC = hormone resistant prostate cancer.

3.1.2. Population-pk analyses

The submission included two population-pk analyses (Ng et al., 2006; and report 11-2998). The preliminary analysis (Ng et al., 2006) was based on the PK results from one Phase I study (TOC2297g), and two Phase II studies (TOC2689g; BO16934). This study showed that the PK characteristics of pertuzumab were similar to those reported for other monoclonal IgG1 antibodies. The pivotal population-pk analysis was report 11-2998 which included PK data from all 12 Phase I/II/III clinical studies listed above in Table 2. Relevant population-pk data from report 11-2998 have been included in the body of this CER and additional tables and figures provided in the dossier, while relevant data from Ng et al., 2006 have also been included in this CER. In addition, a brief synopsis of the population-pk analysis from report 11-2998 has been

provided. No brief synopses of the population-pk data from Ng et al., 2006 has been provided as the data from the 3 studies included in this analysis were included in report 11-2998, together with data from an additional 9 studies. However, the data from the preliminary population-pk analysis have been examined and were consistent with the data from the subsequent pivotal population-pk analysis.

3.2. Pharmacokinetics of pertuzumab in patients

3.2.1. Overview

3.2.1.1. Pharmacokinetics – individual studies

Pertuzumab was administered as monotherapy in two, Phase I, weight-based dosing studies and five, Phase II, fixed, non-weight-based dosing studies in patients with cancer. In addition, pertuzumab in fixed, non-weight-based dose regimens was administered in combination with chemotherapeutic agents in 5 Phase I/II/III studies in cancer.

Fixed, non-weight-based pertuzumab dosing was supported by the results of the preliminary population-pk analysis (Ng et al., 2006). In this analysis, simulated serum pertuzumab concentration-time profiles were very similar after fixed non-weight-based, weight-based, and BSA-based dosing regimens. All simulated subjects received an initial 840 mg, 12.2 mg/kg, or 485 mg/m^2 iv infusion over 90 minutes, followed by 420 mg, 6.1 mg/kg, or 242.5 mg/m^2 iv infusions over 30 minutes on days 21, 42, and 63. Simulated serum pertuzumab concentrations were consistently above the therapeutic targeted serum concentration of 20 µg/mL in each of the three regimens. The target pertuzumab concentration of 20 µg/mL was based on preclinical mouse xenograft tumour models showing that suppression of tumour growth was achieved when steady-state trough concentrations were within the range 5 to 20 µg/mL.

Of the single-agent studies, relevant PK data on the proposed pertuzumab 840/420 regimen are available from studies BO16934 (metastatic breast cancer with low expression of HER2) and BO17004 (hormone refractory prostate cancer). In both studies, serum samples for pharmacokinetic assessment were taken at baseline, just before the start of the pertuzumab infusion and within 15 minutes of the end of infusion in all cycles, and once on days 8 and 15 in Cycles 1 and 2. PK sampling was sparse in both studies, and the data would have been more appropriately analyzed using population-pk methods rather than non-compartment analysis. In BO16934 and BO17004, in Cycle 1 following the pertuzumab 840 mg iv loading dose (single-agent), clearance (CL), volume of distribution at steady state (Vss), and terminal half-life ($t_{1/2}$) were similar (see Table 4, below).

Table 4: Mean (CV%) pharmacokinetic parameters following pertuzumab 840 mg in Cycle 1.

Study	Cmax (µg/mL)	AUC_{inf} (µg.day/mL)	AUC_{last} (µg.day/mL)	t_{max} (day)	CL (mL/day)	$t_{1/2}$ (day)	V_{ss} (mL)	MRT (day)
BO16934 [a], Cycle 1	289 (37)	3598 (39)	2517 (36)	0.42 (365)	270 (42)	12.2 (31)	4122 (40)	16 (30)
BO17004 [b], Cycle 1	255 (23)	3488 (44)	2305 (22)	0.073 (11)	270 (29)	13.7 (39)	4452 (26)	18.1 (42)

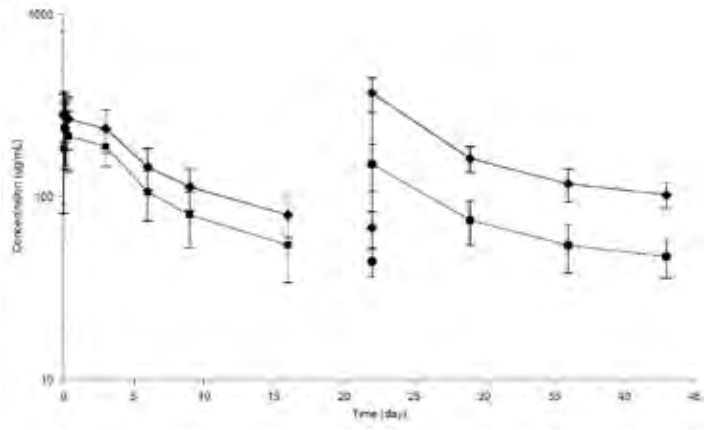
a BO16934: n = 38 (t1/2, AUCinf, CL, Vss); n=40 (tmax, Cmax, AUClast).
b BO17004: n=35 (all parameters).

Of the pertuzumab combination studies, relevant PK data on the pertuzumab 840/420 regimen are available from studies BO17021 (advanced solid tumours) and WO202004 (advanced NSCLC), and the results are summarized below in Table 5. In study BO17021, docetaxel 75 mg/m^2 q3w was administered with pertuzumab 840/420 mg to 6 patients, while docetaxel 100 mg/m^2 q3w was administered with pertuzumab 840/420 mg to 5 patients. In Cycle 1, serum samples for pertuzumab PK assessment were taken pre-dose and then 15 minutes, 1.5 hours, 4 hours and 8 hours after completion of the infusion, and then at Days 1, 6, 9, and 16. In Cycle 2, sparse serum samples for pertuzumab PK assessment were taken pre-dose and then 15 minutes after the infusion, and then on Days 8, 15, and 22. The principal pertuzumab PK parameters of interest were C_{max}, $t_{½}$, AUC_{inf}, V_z and CL, and these were estimated using non-compartmental analysis. The mean serum concentration-time profiles for pertuzumab in combination with docetaxel in Cycles 1 and 2 for the two pertuzumab regimens used in this study (840/420 and 1050) are summarized below in Figure 1.

Table 5: Mean (CV%) PK parameters (cycle 1) following pertuzumab 840/420 mg regimen in combination with docetaxel (B017021) and erlotinib (WO202004).

Study	Cycle	Cmax (µg/mL)	AUC_{inf} (µg.day/mL)	$AUC_{0\text{-last}}$ (µg.day/mL)	CL mL/day	$t_{1/2}$ (day)	V_D (mL)
BO17021	1 (n=11)	255 (33)	2796 (35)	1749 (31)	329 (29)	12.1 (45)	5355 (31)
	2 (n=12)	150 (29)	2762 (32)	1491 (32)	169 (35)	19.1 (50)	4233 (37)
WO202004	2 (n=6,8)	231 (24)	3000 (19)		240 (19)	17.9 (12)	4900 (27)

Figure 1: Study BO17021 - Mean serum concentration-time profiles for pertuzumab in combination with docetaxel in cycle 1 and 2.

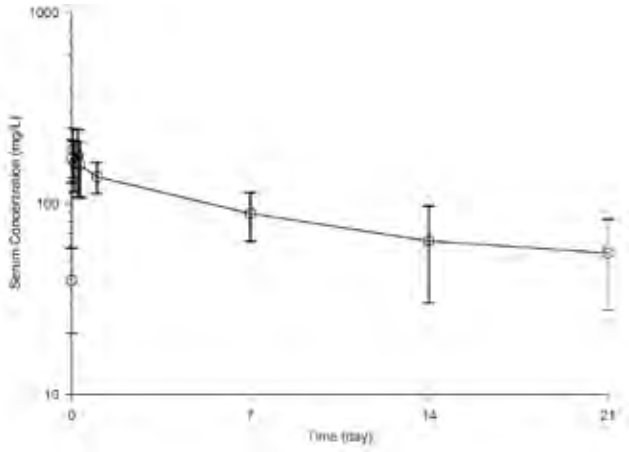


Note: Filled Diamond = 1050 mg dose in both Cycle 1 and 2. Filled Squares = 840 mg loading dose in Cycle 1 and Filled Circles = 420 mg maintenance dose in Cycle 2.

In study WO20024, erlotinib 100 mg orally once daily was administered with pertuzumab 840/420 mg to 6 patients, and erlotinib 150 mg once daily was administered with pertuzumab 840/420 mg to 9 patients. In Cycle 2, serum samples for pertuzumab PK assessment were taken pre-dose, and then post-dose at 0.5, 1.5, 3.0, 6.0, 8.0, 24, 168, 336, and 504 hours. The principal pertuzumab PK parameters of interest were C_{max}, t_{max}, $t_{½}$, $AUC_{0\text{-}21d}$, AUC_{inf}, V_{ss} and CL, derived

using non-compartmental analysis. The serum concentration-time profile for pertuzumab in combination with erlotinib in Cycle 2 is summarized below in Figure 2.

Figure 2: Study WO20024 - Mean (±SD) serum concentration-time profile for pertuzumab in combination with erlotinib in cycle 2.

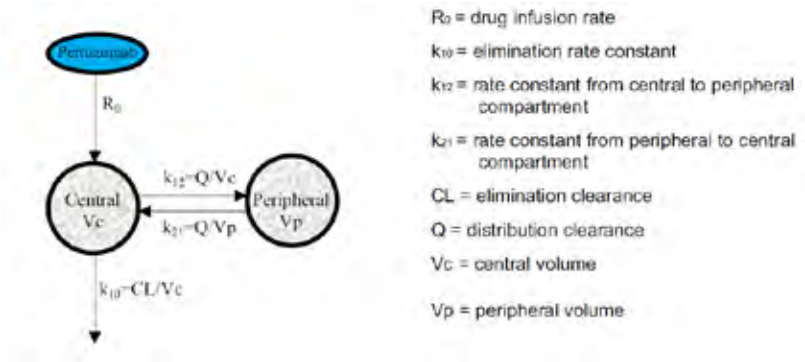


3.2.1.2. Population pharmacokinetics

As mentioned previously, there were two PopPK reports in the submission (Ng et al., 2006; and 11-2998). The preliminary PopPK analysis was based on the PK results of the Phase I study TOC2297g and two Phase II studies (TOC2689g and BO16934), and included data from 153 patients and 1458 samples (Ng et al., 2006). In this study, the population-pk analysis showed that a linear two-compartment model best described the data. The estimated central volume of distribution (V_c) was 2.74 L and the estimated clearance (CL) was 0.214 L/day. Pertuzumab CL was significantly influenced by body weight, serum albumin and serum alkaline phosphatase, while V_c was significantly influenced by BSA. Inclusion in the final model of the covariate effect of body weight alone and BSA alone explained about 8.3% and 40% of the inter-individual variance of CL and V_c, respectively.

Subsequent to the initial PopPK report, a larger PopPK report was undertaken pooling data from 440 cancer patients from eleven Phase I/II studies and one Phase III study treated with pertuzumab at doses ranging from 2 mg/kg to 25 mg/kg (Report 11-2998). This dose range covered the pertuzumab 840/420 mg regimen proposed for the treatment of mBC. The PopPK analysis demonstrated that the pertuzumab PK data were best described by a two-compartment model with first order elimination from the central compartment. The PK model was parameterized in terms of clearance (CL), central volume (V_c), distribution clearance (Q), and peripheral volume (V_p) (see Figure 3, below). CL and Vc were estimated to be 0.239 (±2.1% SE) L/day and 3.07 (±1.2% SE) L, respectively. Inter-individual variability (IIV) in CL and V_c expressed as coefficients of variation were 34.5% and 19.3%, respectively. Q was 0.558 L/day (8.4% SE), and 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.

Figure 3: Pertuzumab two-compartment PK model with first order elimination in cancer patients.



Lean body weight (LBW) and serum albumin concentration (ALBU) were identified as statistically significant covariates for the pharmacokinetics of pertuzumab. Pertuzumab CL decreased in patients with higher ALBU, and increased in patients with greater LBW. After inclusion of ALBU and LBW in the final model, the inter-individual variance in pertuzumab CL decreased by 21.7%, and LBW alone reduced the variance in CL by 4.6%. Both pertuzumab V_c and V_p increased in patients with greater LBW, and LBW decreased the variance of these two parameters by 29.3% and 8.1%, respectively. No other tested covariates were found to have statistically significant effects on the pharmacokinetics of pertuzumab (i.e., age, race [Japanese vs non-Japanese], sex, ALT, AST, TBIL, SerCr, ALK, performance status [ECOG/KPS], presence/absence of MBC, number of metastatic sites, liver metastases, and concomitant chemotherapy).

A sensitivity analysis was performed to examine the influence of CL and ALBU on the pertuzumab 840/420 mg regimen. The exposure parameters of interest were steady-state peak concentration ($C_{max,ss}$), trough concentration ($C_{min,ss}$), and steady state area under the curve (AUC_{ss}). The results suggested that ALBU is the most important determinant of $C_{min,ss}$ and AUC_{ss}, while the effect of LBW on these two parameters is relatively small. Compared with the effect of ALBU, LBW had a bigger impact on $C_{max,ss}$. Overall, the effects of both ALBU and LBW on the pertuzumab exposure parameters assessed were encompassed within the inter-individual variability of these parameters in the entire population, suggesting that dose adjustment based on ALBU and LBW are not required.

The population-pk analysis investigated the impact of baseline body weight on pertuzumab steady state peak concentration ($C_{max,ss}$), trough concentration ($C_{min,ss}$) and average exposure (AUC_{ss}). PK variables were simulated using the Bayesian post-hoc PK parameters for a loading dose of 840 mg following by 420 mg q3w. Of particular relevance was the percentage of patients with steady state trough concentrations < 20 µg/mL. Median $C_{min,ss}$ decreased from 58.4 µg/mL to 40.8 µg/mL in the lightest 25% to heaviest 25% of patients, respectively. The percentage of patients not achieving a steady-state trough concentration > 20 µ g/mL (occurs after 1 cycle for this loading dose regimen) increased from 3.6% in the lightest 25% to 11.8% in the heaviest 25%. In total, 8.2% (36/440) of the population had trough concentrations < 20 µg/mL, while 91.8% (404/440) had values ≥ 20 µg/mL.

3.2.2. Absorption

Absorption data were not applicable as pertuzumab is administered by iv infusion.

3.2.3. Linearity

In study TOC2297g, the pharmacokinetics of pertuzumab were linear over the dose range 2.0 to 15.0 mg/kg in patients with advanced solid tumours (see Table 6, below). Mean clearance was relatively constant over the 2.0 to 15.0 mg/kg dose range, while the $t_{½}$ ranged from about 15 to

22 days. The lowest dose (0.5 mg/kg) showed non-linearity, and the sponsor postulates that only partial saturation of the target binding site on the HER2 receptor occurs at lower doses.

Table 6: Study TOC2297g. Selected pertuzumab PK 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; t1/2 initial = initial distribution half-life; t1/2 terminal = terminal half-life; Vc = volume of central compartment; Vss = steady-state volume of distribution. 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.

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

In study JO170706, the pharmacokinetics of pertuzumab (Cycle 1) were also linear over the dose range 5.0 to 25.0 mg/kg in Japanese patients with advanced solid tumours (see Table 7, below). CL values were similar across the dose range, while $t_{½}$ values ranged from 11 to 17 days. The AUC_{last}, AUC_{inf} and C_{max} all increased with dose over the range 5.0 to 25.0 mg/kg. The Day 21 serum trough concentrations were ≥ 20 µg/mL at doses ≥ 10 mg/kg for all subjects.

Table 7: Study JO170706 - Pertuzumab PK (mean±SD) estimates following iv infusion (Cycle 1).

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

3.2.4. Steady state

Pertuzumab serum concentrations for the first three treatment cycles (Day 1 to 43) from study TOC2682g (single-agent study) in patients with castration resistant prostate cancer after the 840/420 mg regimen are summarized below in Table 8. The results showed that pre-dose pertuzumab concentrations were similar on Day 22 (after the loading dose) and on Day 43 (after the first maintenance dose), while post-dose pertuzumab concentrations on Day 22 (after the first maintenance dose) and Day 43 (after the second maintenance dose) were similar. In this single-agent study, steady state was reached by the second treatment cycle. In addition, targeted serum trough pertuzumab concentrations of > 20 µg/mL were obtained for 31 of 32 subjects (96.9%) and 25 of 26 subjects (96.2%) with evaluable sample data at the beginning of Cycle 2 and Cycle 3, respectively. Similar results were observed in study TOC2572g (single-agent study) in patients with recurrent NSCLC following pertuzumab 840/420 mg. In addition, in study TOC3258g (combination study), steady-state pertuzumab concentrations were reached by the second treatment cycle when pertuzumab 840/420 mg was co-administered with gemcitabine

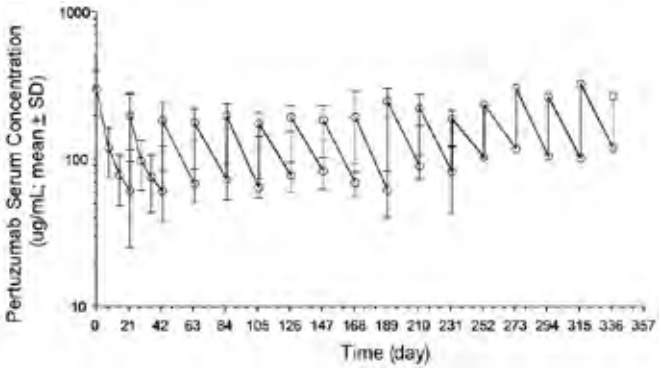
Table 8: TOC2682g - Pertuzumab serum concentrations for the first three treatment cycles (Day 1 to Day 43).

Treatment Cycle	Dose (mg)	Sampling Event (Study Day)	Nominal Time (days)	n	Mean (±DS) Serum Pertuzumab (µg/mL)
1	840	Day 1: pre-dose	-0.01402	40	LTR
		Day 1: post-dose	0.01402	38	254.7±46.9
		Day 8	7.0	39	97.5±25.9
		Day 15	14.0	38	69.2±19.1
2	420	Day 22: pre-dose	20.98958	33	52.4±15.2
		Day 22: post-dose	21.01042	31	175.9±34.7
		Day 29	28.0	30	88.2±27.8
		Day 36	35.0	32	67.5±21.5
3	420	Day 43: pre-dose	41.98958	26	53.1±19.5
		Day 43: post-dose	42.01042	23	176.2±32.4

LTR=less than range. Less than range=≤MCQ (0.25–0.40 µg/mL of serum pertuzumab).

In study BO16934, a pertuzumab loading dose of 840 mg achieved trough and peak concentrations within the range of those observed at steady state by the second treatment cycle in women with mBC (n=40). Mean serum concentration of 289 µg/mL was reached with the 840/420 mg regimen, and at the end of the cycles mean serum concentrations dropped to approximately 100 µg/mL (see Table 9, below).

Table 9: Study BO16934 - Serum concentration-time plots of pertuzumab following iv infusion of 420 mg q3w after a loading dose of 840 mg.



Note: 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.

In study JO17076, for Japanese patients receiving three or more treatment cycles, the observed pertuzumab accumulation ratio was 2.30 (i.e., Cycle 3: Cycle 1 trough concentration).

3.2.5. Distribution

The volume of distribution in the population-pk analysis (report 11-2998) was estimated to be 5.43 L (i.e., Vc 3.07 L [1.2% SE] + Vp 2.36 L [3.5% SE]). The estimated Vc (3.07 L) approximates plasma volume (3L). Both Vc and Vp increased in patients with greater lean body weight (LBW). However, sensitivity analyses for estimated steady state C_{min}, C_{max}, and AUC following pertuzumab 840/420 mg showed that the effect of LBW on these parameters was well within the estimated inter-individual variability of these parameters in the entire population.

3.2.6. Metabolism

There were no data in the submission investigating the metabolism of pertuzumab. However, it is expected that this large MW (~148 kDa) protein will undergo catabolism to small peptides and individual amino acids.

3.2.7. Excretion

There were no data in the submission investigating the excretion of pertuzumab. The TGA adopted EU "guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins" (CHMP/EWP/89249/3004) states that "the main elimination pathway should be identified". However, the guideline also states that "for therapeutic proteins [the elimination pathways] could be predicted, to a large extent, from the molecular size and specific studies may not be necessary". The MW of pertuzumab is ~148 kDa and from this it can be predicted that it will be not undergo renal filtration, but is likely to undergo elimination in other tissue through catabolism.

In the population-pk analysis (report 11-2998), the clearance of pertuzumab was 0.239 L/day (2.1% SE), with a coefficient or variation of 34.5%. Clearance decreased in patients with higher serum albumin concentrations and increased in patients with greater lean body weight. However, sensitivity analyses for estimated steady state C_{min}, C_{max}, and AUC following pertuzumab 840/420 mg showed that the effects of serum albumin and lean body weight on these parameters were well within the estimated inter-individual variability of these parameters in the entire population. In the population-pk analysis (report 11-2998), the median terminal elimination half-life was 17.2 days (95% range: 7.8 to 32 days).

3.2.8. Inter-individual variability in pharmacokinetics

In the population-pk analysis (report 11-2998), inter-individual variability in the pharmacokinetics of pertuzumab were modest. In this analysis, the clearance 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 (IIV) in clearance and central compartment volume expressed as the coefficient of variation was 34.5% and 19.3%, respectively.

3.2.9. Pharmacokinetics in special populations

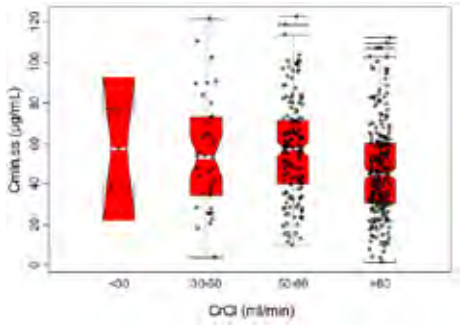
3.2.9.1. Hepatic impairment

There were no specific studies in the submission investigating the influence of hepatic impairment on the pharmacokinetics of pertuzumab. However, it is unlikely that hepatic impairment will significantly affect the pharmacokinetics of pertuzumab since the liver is unlikely to be involved in elimination.

3.2.9.2. Renal impairment

There were no specific studies in the submission investigating the influence of renal impairment on the pharmacokinetics of pertuzumab. However, it is unlikely that renal impairment will significantly affect the pharmacokinetics of pertuzumab since the kidney is unlikely to be involved in elimination. This was confirmed by the results of the population-pk analysis (report 11-2988), which analyzed the pharmacokinetics of pertuzumab following a simulated 840/420 mg regimen in patients groups by severity of renal measured by CrCL: i.e., < 30 mL/min severe impairment (n=3); 30-50 mL/min moderate impairment (n=38); 50-80 mL/min mild impairment [n=158]; and > 80 mL/min normal renal function (n=241). The steady state trough concentrations vs renal function defined by CrCL are summarized below in Figure 4. The results showed that renal impairment defined by CrCL had no significant effects on pertuzumab steady state trough concentrations. However, the number of patients with severe renal impairment was small (n=3). The median pertuzumab steady state trough levels were 45 μg/mL, 77 μg/mL and 54 μg/mL for patients with normal renal function, mild renal impairment, and moderate renal impairment, respectively.

Figure 4: Report 11-2998 – Steady state trough concentrations vs CrCL.



Note: The PK variables were simulated for a loading dose of 840 mg followed by 420 mg q3w using Bayes posthoc PK parameters of the final model and grouped by renal function. Points are individual values and box plots show the median, 25th and 75th percentiles.

3.2.9.3. Age

There were no specific studies in the submission investigating the influence of age on the pharmacokinetics of pertuzumab. However, the population-pk analysis (report 11-2998) showed that age had no significant effects on the pharmacokinetics of pertuzumab as regards clearance and volumes of the central and peripheral compartments. In this analysis, the mean±SD age of the total population (n=444) was 58.9±11.3 years (range: 18, 84), with 67.8% (n=301) being aged < 65 years, 23.4% (n=103), aged 65 to 75 years, and 9.1% (n=40) aged ≥ 75 years.

3.2.9.4. Sex

The population-pk analysis (11-2998), showed that the pharmacokinetics of pertuzumab did not significantly differ between male (n=147) and female (n=297) patients as regards clearance, and volumes of the central and peripheral compartments.

3.2.9.5. Race

The population-pk analysis (report 11-2998), included a comparison between the pharmacokinetics of pertuzumab in Japanese patients (n=22) and non-Japanese patients (n=422). The analysis showed no significant differences between the two populations as regards clearance, and volumes of the central and peripheral compartments. The submission also included a pharmacokinetic study in 18 Japanese patients treated with pertuzumab 5 to 25 mg/kg (study JO17076). Cross-study comparison between the 5, 10 and 15 mg/kg dose groups from this study in Japanese patients with advanced solid tumours (JO17076), and the study in non-Japanese patients with advanced solid tumours (TOC2297g) showed that pertuzumab clearance, steady state volume of distribution, and elimination were similar for the two populations.

3.2.9.6. Children and adolescents

There were no data in children and adolescents.

3.2.10. Pharmacokinetic interactions

3.2.10.1. Overview

There were no specific drug-drug PK interaction studies in humans, nor were there *in vitro* studies investigating the effect of pertuzumab on relevant metabolic enzyme systems or transporter proteins. However, there were five Phase II/III clinical efficacy and safety studies that included relevant drug-drug PK interaction data, and these studies are reviewed below.

3.2.10.1.1. Pivotal efficacy and safety study WO20698/TOC44129g (substudy 2) Overview

Study WO20698/TOC4129g was the pivotal Phase III, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of the combination of pertuzumab, trastuzumab, and docetaxel compared with the combination of placebo, trastuzumab and docetaxel in patients with previously untreated HER2-positive metastatic breast cancer.

Pertuzumab/placebo was administered as an IV loading dose of 840 mg on Day 1 of Cycle 1, and then as a maintenance dose of 420 mg for subsequent q3w cycles. Trastuzumab was administered as an IV loading dose of 8 mg/kg on Day 2 of Cycle 1, and then as a maintenance dose of 6 mg/kg IV on Day 1 of subsequent cycles following pertuzumab. Docetaxel was administered as an IV dose of 75 mg/m^2 on Day 2, Cycle 1, following trastuzumab and then on Day 1 of subsequent cycles following trastuzumab.

Protocol WO20698/TOC4129g included substudy 2. This substudy was designed to: (a) evaluate the effect of pertuzumab on the corrected QT (QTc) interval (Report GENE-RAS-002); (b) further evaluate the pharmacokinetics of pertuzumab; (c) characterize the potential drug-drug interaction of pertuzumab on trastuzumab pharmacokinetics (in the presence of docetaxel); and (d) characterize the potential drug-drug interaction of pertuzumab on docetaxel pharmacokinetics (in the presence of trastuzumab). In addition, samples were drawn from all pertuzumab treated patients for anti-therapeutic antibody (ATA) specific to pertuzumab.

3.2.10.1.2. Pharmacokinetic parameters and blood sampling schedule

PK parameters of pertuzumab and trastuzumab in serum, and docetaxel in plasma were calculated using standard non-compartmental methods. The planned blood sampling schedule for the pharmacokinetic analyses are summarized below in Table 10.

Table 10: Substudy 2 – Blood sampling schedule for pharmacokinetic analyses.

Cycle	1	2	3	6	9	12	15	18	Discontinuation[a]
placebo	X[b]		X						
trastuzumab	X		X						
pertuzumab	X		X	X	X	X	X	X	X
docetaxel		X[c]							

a 28-42 days after the last dose of the treatment;
b Pre-infusion (15 minutes prior) and 15 minute after the end of infusion (EOI) and;
c Preinfusion (15 minutes prior), 0.5hr during the infusion, at the EOI and 15 minutes, 1, 5, 7 and 24 hours post-infusion following the start of study drug administration on Day 1 of Cycle 2.

3.2.10.1.3. Results

a. Datasets analyzed

The PK analysis population consisted of all patients who had PK samples collected at Cycle 1 and/or Cycle 3 as a minimum. A total of 40 evaluable patients were enrolled, and blood samples were available for the PK evaluation of pertuzumab, trastuzumab and docetaxel in 20, 37 and 37 patients, respectively. The demographic characteristics of patients included in the PK analyses are summarized below in Table 11.

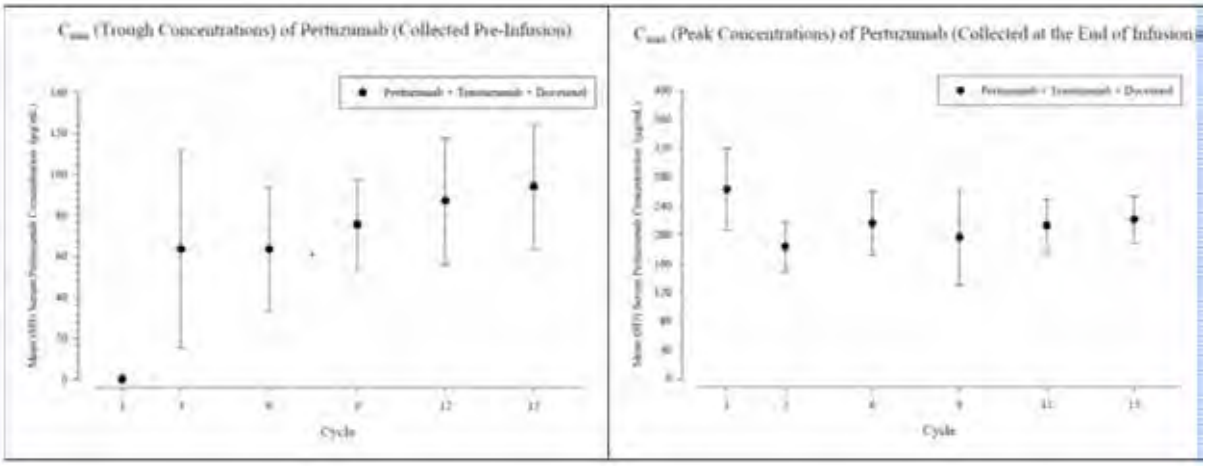
Table 11: Demographic characteristics of the PK analysis population.

Continuous		Mean (±SD)		
		Treatment Arm A: Placebo + Trastuzumab + Docetaxel (N=17)	Treatment Arm B: Pertuzumab + Trastuzumab + Docetaxel (N=20)	Treatment Arms Combined (N=37)
Age	(years)	56.2 (9.45)	51.8 (10.60)	53.9 (10.18)
Weight at baseline	(kg)	71.0 (10.49)	70.9 (14.8)	70.9 (12.83)
Height at Screening	(cm)	161.8 (7.11)	159.0 (7.25)	160.3 (7.23)
Categorical		N (%)	N (%)	N (%)
Gender	Female	17 (100)	20 (100)	37 (100)
Race	Asian	4 (23.5)	5 (25.0)	9 (24.3)
	Other	2 (11.7)	1 (5.0)	3 (8.1)
	White	11 (64.7)	14 (70.0)	25 (67.6)

b. Potential effect of docetaxel and trastuzumab (in combination) on pertuzumab PK

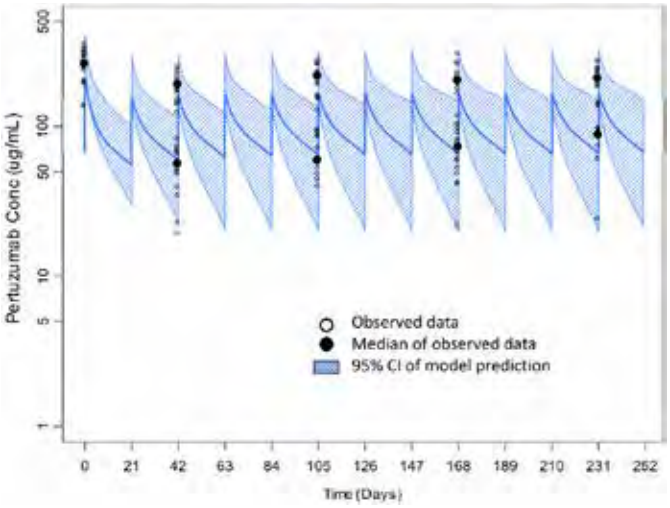
Mean (±SD) C_{min} (serum trough concentrations) and C_{max} (serum peak concentrations) for pertuzumab from Cycles 1, 3, 6, 9, 12 and 15 are shown below in Figure 5. Both mean trough concentrations (C_{min}) mean peak (C_{max}) serum pertuzumab concentrations increased from Cycles 3 to 15. In Cycle 1 (n=18), mean (CV%) pertuzumab Cmax was 263 µg/mL (21.5%), and in Cycle 3 (n=18) mean (CV%) pertuzumab Cmax was 183 µg/mL (18.3%) and mean Cmin was 63.6 µg/mL (75.6%). Inter-subject variability was more marked in Cmin than in Cmax across the first 15 treatment cycles.

Figure 5: Mean (±sd) serum C_{min} (left panel) and C_{max} (right panel) of pertuzumab in the presence of trastuzumab and docetaxel at Cycles 1, 3, 6, 9, 12 and 15.



The observed results from substudy 2 were superimposed on the simulated population pertuzumab PK profile from the population-pk analysis (report 11-2998), and the results are shown below in Figure 6. Comparison between the observed pertuzumab C_{min} and C_{max} values in the presence of docetaxel and trastuzumab showed that the majority of individual values were within the predicted 95% confidence interval for serum docetaxel estimated from the population-pk analysis. The results suggest that docetaxel and trastuzumab, when administered with pertuzumab, do not significantly affect the predicted pertuzumab serum concentration-time profile over at least 13 treatment cycles.

Figure 6: Observed and population model predicted serum concentrations of pertuzumab; semi-log.



c. Effect of pertuzumab in combination with docetaxel on trastuzumab PK

Mean trough (C_{min}) and peak (C_{max}) serum trastuzumab concentrations from Cycles 1 and 3 were similar when trastuzumab was administered with placebo/docetaxel and with pertuzumab/docetaxel. The results of an ANOVA model comparing the effects of placebo/docetaxel and pertuzumab/docetaxel on the C_{min} and C_{max} of trastuzumab in Cycles 1 and 3 are summarized below in Table 12. The results showed that both trastuzumab C_{max} and C_{min} were similar in Cycles 1 and 3 when trastuzumab was combined with pertuzumab and docetaxel and when trastuzumab was combined with placebo and docetaxel. The point estimates for the ratios were less than 1 for each of the comparisons, indicating that trastuzumab C_{min} and C_{max} concentrations were lower for pertuzumab/docetaxel than for the placebo/docetaxel, and the 90% CIs for the ratios were marginally outside the accepted bioequivalence interval of 80% to 125%. However, the results suggest that pertuzumab in combination with docetaxel is unlikely to significant affect exposure to trastuzumab.

Table 12: Substudy 2 – Serum trastuzumab – GLSM and 90% CI of the Ratio of GLSM of C_{max} and C_{min} (Treatment B [pertuzumab/docetaxel] vs Treatment A [placebo/docetaxel]).

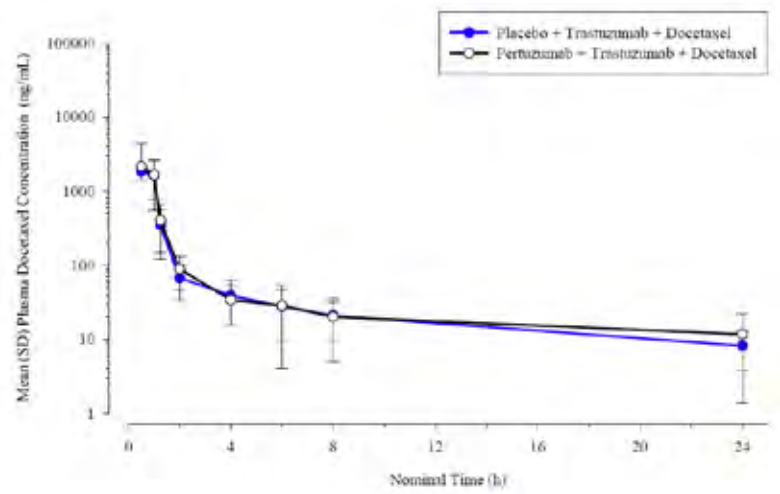
Parameter	Unit	Cycle	Geometric LSmeans		Ratio of Geometric LSmeans x100 (90% CI) Treatment B / Treatment A
			Treatment B (With Pertuzumab)[a]	Treatment A (With Placebo)[a]	
C_{max}	(µg/mL)	1	174	193	90.29 (78.15-104.33)
C_{min}[b]	(µg/mL)	3	21.0	21.9	95.94 (70.72-130.13)
C_{max}	(µg/mL)	3	119	147	81.02 (62.68-104.71)

[a] in the presence of docetaxel
[b] Patients 9861 and 9900 were excluded from ANOVA calculations for Cycle 3 C_{max} due to aberrant values

d. Effect of pertuzumab in combination with trastuzumab on docetaxel PK.

The mean (±SD) plasma concentration – time profiles of docetaxel (in the presence of trastuzumab and placebo) and docetaxel (in the presence of pertuzumab and trastuzumab) are shown below in Figure 7. Mean docetaxel plasma concentration declined in a multi-exponential manner following the end of the infusions given in Cycle 1, Day 2, and remained above the lower limit of quantification of the assay (LLOQ > 5 ng/mL) up to 24 hours after the start of infusion when combined with placebo/trastuzumab and pertuzumab/trastuzumab. There were no marked differences in the pharmacokinetics of docetaxel following a dose of 75 mg/m^2 between the placebo/trastuzumab and pertuzumab/trastuzumab combinations.

Figure 7: Substudy 2 - Mean (±sd) plasma concentration-time profiles of docetaxel (in the presence of trastuzumab) with either placebo or pertuzumab in Cycle 1; semi-log plot.



The results of an ANOVA model comparing the effects of placebo/trastuzumab and pertuzumab/trastuzumab on AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of docetaxel in Cycles 1 and 3 are summarized below in Table 13. In the ANOVA, the 90% CIs for the relevant ratios were outside the accepted bioequivalence interval of 80% to 125%. However, the results suggest that pertuzumab in combination with trastuzumab is unlikely to significantly affect exposure to docetaxel.

Table 13: Substudy 2 – Plasma docetaxel – GLSM and 90% CI of the Ratio of GLSM of PK parameters (Treatment B [pertuzumab/trastuzumab] vs Treatment A [placebo/trastuzumab]).

Parameter	Unit	Geometric LSmeans		Ratio of LSmeans x 100 (90% CI) Treatment B / Treatment A
		Treatment B (With Pertuzumab)[a]	Treatment A (With Placebo)[a]	
AUC_{0-t}	(ng•h/mL)	2190	2088	104.90 (73.90 – 148.90)
$AUC_{0-\infty}$	(ng•h/mL)	2660	2622	101.42 (75.66 – 135.96)
C_{max}	(ng/mL)	1881	2034	92.50 (65.22 – 131.18)

[a] in the presence of trastuzumab

3.2.10.2. Study BO17003

Study BO17003, was a Phase Ib, open-label, multicentre study of the safety and pharmacokinetics of pertuzumab and capecitabine in combination in patients with advanced solid tumors. Pertuzumab was administered to 18 patients at a dose of 1050 mg q3w IV. Capecitabine was administered orally at escalating doses of 825 mg/m^2 BID (Dose Level 1 Cohort), 1000 mg/m^2 BID (Dose Level 2 Cohort) and 1250 mg/m^2 BID (Dose Level 3 Cohort), and was given twice daily starting on day 1 of each 3 week cycle and continuing through Day 14 of each cycle.

Pharmacokinetic (PK) assessments were carried out in all patients to determine potential PK interactions between pertuzumab and capecitabine, and assessments focused on the potential influence of pertuzumab on capecitabine exposure. To determine the effects of pertuzumab on the PK of capecitabine, relevant PK parameters for capecitabine and its metabolites (5'-DFCR, 5'-DFUR, 5- FU and FBAL) obtained in the pre-cycle treatment phase (Day -7) were compared with those obtained on Day 1 of Cycle 1. The determine the effects of capecitabine on the PK of pertuzumab, relevant PK parameters were assessed in Cycle 1 (Day 1) and Cycle 2 and the final assessment was made on Day 22 (i.e., Day 1, Cycle 3) just before administration of capecitabine

3.2.10.2.1. PK results for pertuzumab

The PK parameters for pertuzumab are summarized below in Table 14, and the results were compared with single-agent data from other studies. The results showed that CL, V_{ss}, C_{max}, and $t_{½}$ for pertuzumab in combination with gemcitabine (Cycle 1) were consistent with the corresponding results from pertuzumab single-agent studies.

Table 14: Mean (±SD) pertuzumab PK parameters.

Study	Dose	n	$t_{1/2}$ (day)	Cmax (µg/mL)	AUC (µg/mL/day)	Vss (mL)	CL (mL/day)
BO17003 (C1)	1050 mg	18	14.6±4.1	355±59	4097±1282	5202±1007	283±98
TOC2297g *	15.0 mg/kg	8	18.6±8.8			5971±2569	257±102
TOC2689g **	1050 mg	62	15.8±5.2	388±105		5390±1310	285±119
BOC16935 ***	1050 mg	35	20.5±8.1	426±167		5110±1120	225±112

* TOC2297g Phase I dose escalation data, CL and Vss were adjusted because of dosing per kg and assumes average 70kg adult.
** TOC2689g Phase II Ovarian Cancer, Cycle 1 peak concentration.
*** BOC16935 Phase II Metastatic Breast Cancer, Cycle 1 peak concentration.

3.2.10.2.2. PK results for capecitabine

Overall, the mean PK parameters for capecitabine and its metabolites (5'-DFCR, 5'-DFUR, 5-FU, FBAL) following capecitabine 825 BID, 1000 BID and 1250 BID mg/m^2, and the relevant mean concentration-time profiles suggest that the effects of pertuzumab (1050 mg) on the pharmacokinetics of capecitabine are unlikely to be clinically significant.

3.2.10.3. Study BO17021

Study BO17021 was a Phase Ib, open-label, multicentre study of the safety and pharmacokinetics of pertuzumab in combination with docetaxel in patients with advanced solid tumors. Pertuzumab was administered to 19 patients as a loading dose of 840 mg followed by a maintenance dose of 420 mg q3w or as a dose of 1050 q3w. Patients also received docetaxel either as a 60, 75 or 100 mg/m^2 IV infusion q3w. In Cycle 1, docetaxel was administered on Day 1 and pertuzumab was administered at least 24 hours later on Day 2. In subsequent cycles, pertuzumab was administered on Day 1 immediately followed by docetaxel.

Pharmacokinetic (PK) assessments were performed in all patients to determine potential PK interactions between pertuzumab and docetaxel, and assessments focused on the potential modification of docetaxel exposure by pertuzumab. In Cycle 1, docetaxel was administered on Day 1 followed by analysis of docetaxel PK parameters, and pertuzumab was administered at least 24 hours later on Day 2 followed analysis of pertuzumab PK parameters. In the Cycle 2, pertuzumab was given on Day 1, immediately followed by the administration of docetaxel and PK assessments were performed for both compounds. To determine the influence of pertuzumab on the PK of docetaxel, the PK parameters for docetaxel from Day 1, Cycle 1 were compared with the PK parameters for docetaxel from Day 1, Cycle 2, within each dose level cohort. The PK parameters of pertuzumab were compared with historical data.

3.2.10.3.1. PKs for pertuzumab

The principal PK parameters of interest for pertuzumab were the C_{max}, $t_{½}$, $AUC_{0-\infty}$, V_{ss} and CL. The results from Cycle 1 (when pertuzumab was given 24 hours after docetaxel) showed V_{ss} and CL values were consistent with the corresponding PK results from pertuzumab single agent studies, while the $t_{½}$was shorter and the C_{max} was lower. Presumably the results for the pharmacokinetics of pertuzumab following pertuzumab 1050 mg in the presence of docetaxel (n=8) represent the mean values of patients from Cohort 1 (n=6, docetaxel 60 mg/m² + pertuzumab 1050 mg) and Cohort 2 (n=2, docetaxel 75 mg/m² + pertuzumab 1050 mg).

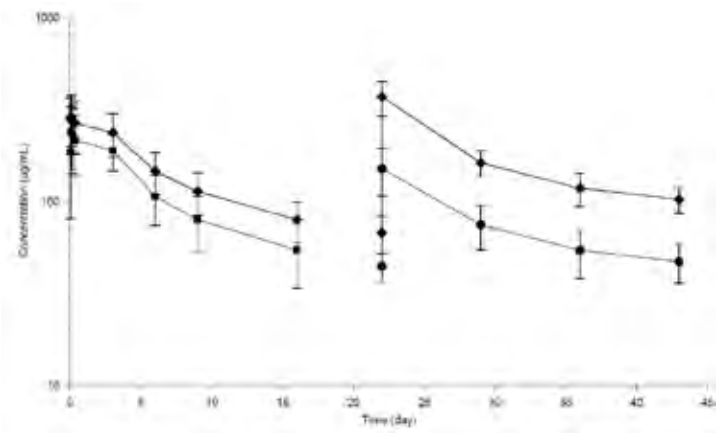
Table 15: Mean (±SD) pertuzumab PK parameters.

Study	Dose	n	$t_{1/2}$ (day)	Cmax (µg/mL)	AUC (µg/mL/day)	Vss (mL)	CL (mL/day)
BO17021 (C1)	1050 mg	8	13.4±4.2	301±93	3951±919	5214±1386	282±63
TOC2297g *	15.0 mg/kg	8	18.6±8.8			5971±2569	257±102
TOC2689g **	1050 mg	62	15.8±5.2	388±105		5390±1310	285±119
BOC16935 ***	1050 mg	35	20.5±8.1	426±167		5110±1120	225±112

* TOC2297g Phase I dose escalation data, CL and Vss were adjusted because of dosing per kg and assumes average 70kg adult.
** TOC2689g Phase II Ovarian Cancer, Cycle 1 peak concentration.
*** BOC16935 Phase II Metastatic Breast Cancer, Cycle 1 peak concentration.

The mean serum concentration time-profile for pertuzumab in combination with docetaxel for both pertuzumab treatment regimens are shown below in Figure 8.

Figure 8: Study BO17021 - Mean serum concentration-time profiles for pertuzumab in combination with docetaxel in cycle 1 and 2.



Filled Diamond = 1050 mg dose in both Cycle 1 and 2. Filled Squares = 840 mg loading dose in Cycle 1 and Filled Circles = 420 mg maintenance dose in Cycle 2.

3.2.10.3.2. PKs for docetaxel

The PK results for docetaxel alone and in combination with pertuzumab were shown. The C_{max}, AUC and CL values for docetaxel alone and in combination with pertuzumab were similar. In addition, the mean concentration-time profiles for docetaxel alone and in combination with pertuzumab were similar suggesting that pertuzumab has no significant affects on docetaxel plasma concentrations. Overall, the data suggest that pertuzumab is unlikely to significantly affect the pharmacokinetics of docetaxel. In this study, the MTD was estimated to be docetaxel 75 mg/m^2 plus pertuzumab 840 mg loading followed by 420 mg 3wq.

3.2.10.4. Study WO20024

Study WO20024 was a Phase Ib, open-label, multicentre study designed to assess the combination of pertuzumab and erlotinib in patients with locally advanced or metastatic (stage IIIb/IV) NSCLC after failure of at least one prior chemotherapy regimen. Pertuzumab was administered to 15 patients at an initial IV loading dose of 840 mg followed by 420 mg q3w. Erlotinib was administered as single agent starting eight days prior to pertuzumab at a dose level of 100 mg in the first cohort, escalating to a dose level of 150 mg in the second cohort.

Pharmacokinetic (PK) assessments were performed on all patients Day -1 before Cycle 1 and on study Days 1, 8, 15, and 22 of Cycle 2. To assess the impact of concomitant pertuzumab administration on the PK of erlotinib, the AUC0-24h from Days -1 before Cycle 1 and study Day 1 of Cycle 2 were compared graphically. To assess the impact of concomitant erlotinib on the PK of pertuzumab, the $AUC_{0\text{-}21d}$ obtained on study Day 1 of Cycle 2 were compared graphically with those obtained from Cycle 2 in previous study BO17021.

3.2.10.4.1. PK results for pertuzumab

The PK results for pertuzumab (Cycle 2) in the presence of erlotinib at steady state are summarized below in Table 16. Overall, the results were similar to those for pertuzumab 840/420 mg (Cycle 2) in combination with docetaxel seen in study BO17021.

Table 16: Study WO20024 – Pertuzumab PK parameters in the presence of erlotinib; Cycle 2.

Patient ID	C_{max} (mg/L)	t_{max} (day)	$t_{1/2}$ (day)	$AUC_{0\text{-}21d}$ (mg.day/L)	$AUC_{0\text{-}\infty}$ (mg.day/L)	V_{ss} (L)	CL (L/day)
N	8	8	6	8	7	7	8
Mean	231	0.23	17.9	1780	3000	4.9	0.24
SD	55.3	0.11	2.18	340	815	1.3	0.05
Min	163	0.06	15.4	1320	2070	2.7	0.18
Median	223	0.25	17.9	1720	2960	4.8	0.24
Max	348	0.33	20.6	2360	4220	6.7	0.32
CV%	23.9	47.9	12.2	19.1	27.1	26.5	18.7
Geo Mean	226	0.20	17.8	1750	2910	4.8	0.24

3.2.10.4.2. PK results for erlotinib

The PK results for erlotinib given alone and in the presence of pertuzumab (Cycle 2), and the erlotinib plasma concentration time-curves are provided. When pertuzumab 840/420 mg was combined with erlotinib 100 mg there was a reduction of about 18% in erlotinib mean C_{max} and $AUC_{0\text{-}24h}$ values in Cycle 2, and similar reductions in exposure to the primary erlotinib metabolite (OSI-420). However, when pertuzumab 840/420 mg was combined with erlotinib 150 mg there was an increase of about 28% and 42% respectively in mean erlotinib C_{max} and $AUC_{0\text{-}24h}$ values.

Variability in the pharmacokinetics of erlotinib was high, but the sponsor states that they were comparable with population-pk data for erlotinib in NSCLC patients. The sponsor refers to data

combined from four Phase II and two Phase III trials in 708 patients that gave final model estimates for erlotinib CL of 4.29L/h (40.5% CV) and V_D of 210 L (64.3% CV), with an estimated $t_{1/2}$ of 32.0 hours (76.7% CV). In addition, multiple dose data from 11 NSCLC patients given 100 mg erlotinib (study BO16411) gave median (range) values of erlotinib 1590 ng/mL (882-2420) for C_{max}, 3 hours (0.9-8.0) for t_{max} and 2060 ng.h/mL (1210-3210) for AUC_{0-24h} which were comparable with the data from study WO2004. In study WO2004, respective median values for erlotinib in the presence of pertuzumab (Cycle 2) for the 100 mg and 150 mg dose groups were 2.8 and 4.6 L/h for CL, 64.5 and 311 L for V_{ss}, and 17.2 and 55.9 hours for $t_{1/2}$. Overall, taking account of the small patient numbers exposed to erlotinib, particularly in Cycle 2, and the marked inter-subject variability in erlotinib PK parameters, study WO2004 suggests that pertuzumab is unlikely to significantly affect the pharmacokinetics of erlotinib.

3.2.10.5. Study TOC3258g

Study TOC3258g was a Phase II, randomized, placebo-controlled, double-blind study designed to evaluate the efficacy of pertuzumab in combination with gemcitabine, and the effect of tumour based HER2 activation in subjects with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer. Combination therapy of gemcitabine plus pertuzumab (n=65) was compared with gemcitabine monotherapy (n=65). Gemcitabine was administered on Days 1 and 8 of a 21-day cycle at a starting dose of 800 mg/m^2. Pertuzumab was administered as an 840 mg iv loading dose starting 30 minutes following the completion of gemcitabine administration on Day 1, and then as a 420 mg q3w maintenance iv dose in subsequent cycles. Treatment could continue for up to 17 cycles (1 year total).

The PK data in this study were limited due to sparse plasma and serum sampling following administration of gemcitabine and pertuzumab. PK plasma samples for gemcitabine and its metabolite (dFdU) were taken on Day 1, Cycle 2, pre-dose and then post-dose at 0-5 minutes, 25-30 minutes, and 120-125 minutes. PK serum samples for pertuzumab were collected in Cycles 1 and 2, pre-dose and post-dose on Day 1 and pre-dose on Day 8, and in Cycle 3, pre-dose on Day 1.

3.2.10.5.1. PK results gemcitabine

Gemcitabine AUC_{5-30} (i.e., from 5 to 30 minutes from end of infusion) was selected for analysis because the sample concentrations measure at 120 to 125 minutes post-infusion were less than reportable (LTR) for most subjects due to the rapid transformation of gemcitabine to dFdU. Gemcitabine plasma exposure (AUC_{5-30}) had a geometric mean ratio (gem+ptz:gem+pla) of 0.886 (90% CI: 0.625, 1.26). The 90% CI was outside the standard bioequivalence interval of 0.8 to 1.25, but the AUC was only estimated over 5 to 30 minutes. The authors commented that gemcitabine exposure in the presence or absence of pertuzumab was complicated by rapid plasma clearance of gemcitabine and the larger than expected inter-subject variability in AUC. The dFdU plasma exposure assessed by AUC_{all} (i.e., from 25 to 125 minutes from the end of the infusion) was better characterized because of the slower clearance of dFdU resulting in a plasma exposure that was approximately 50-fold greater and less variable than gemcitabine. The dFdU AUC_{all} geometric mean ratio (gem+ptz:gem+pla) was 0.968 (90% CI, 0.854, 1.10). The 90% CI was within the standard bioequivalence interval of 0.8 to 1.25. Overall, the data suggest that pertuzumab is unlikely to significantly affect the pharmacokinetics of gemcitabine and its dFdU metabolite.

3.2.10.5.2. PK results pertuzumab

The effect of gemcitabine on the PK of pertuzumab was not directly assessed. However, observed serum pertuzumab concentrations were similar to those from clinical studies in female subjects (e.g., studies TOC2689g and BO16934). The mean serum trough concentrations (pre-dose) for Cycle 2 and Cycle 3 were 57.1 µg/mL and 54.4 µg/mL, respectively. The mean serum peak concentrations (post-dose) for Cycle 2 and Cycle 3 were 188 µg/mL and 192 µg/mL, respectively. The concentration data showed that the pertuzumab loading dose of 840 mg

followed by 420 mg q3w attained steady-state concentrations by the second treatment cycle, and the target of 20 ≥ μg/mL for trough serum concentration was achieved in most subjects. These results for steady-state and target pertuzumab serum concentrations were consistent with those from other studies.

3.3. Immunogenicity

3.3.1. Overview

The submission included an integrated analysis of immunogenicity in the submitted studies. The immunogenicity of pertuzumab was assessed using validated bridging immunoassay methods designed to detect and confirm the presence of anti-therapeutic antibodies (ATAs) to pertuzumab. Serum samples from patients across the various clinical studies were screened, and samples that screened positive were further analyzed by competitive binding with pertuzumab to confirm the positive response in the assay. Samples that were confirmed positive were then diluted further to obtain a value in titre units. Only samples that tested positive in the confirmatory assay were considered positive for ATA to pertuzumab. The ATA assay was designed to have non-treatment rates (5% for screening and 1% for confirmatory), and, consequently, detecting positive results in untreated patients was not unexpected.

3.3.2. ATA incidence

There were 722 pertuzumab treated patients from the Phase I/II/III studies with at least one post-dose sample available for ATA analysis. In these 722 patients, 13 (1.8%) tested positive for ATA. In the pivotal Phase III study (WO20698/TOC4129g), 386 out of 407 patients had at least one post-sample ATA, and of these patients 10 tested negative at baseline, but tested positive during or after study treatment, and 1 tested positive at baseline and during study treatment, making a total of 11 patients (2.8%) with a positive ATA sample at some time during or after study treatment. There were 4 patients in this study without prior treatment with pertuzumab who were confirmed ATA-positive in the pre-treatment samples. These 4 patients had no positive ATA samples during treatment or after treatment and were deemed to be negative.

3.3.3. Impact of ATA on pertuzumab pharmacokinetics

In study TOC2572g, one patient had a follow-up/early termination sample that was determined to be ATA positive. The last PK sample from this patient taken on Day 22, prior to the Cycle 2 dose, showed a pertuzumab concentration of 2.71 mg/mL, which was markedly lower than the mean concentration of 45.8 mg/mL for samples taken at that time point. This large decrease in concentration may be a result of pertuzumab ATA.

In sub-study 2WO20698/TOC4129g, only 1 of 20 patients in the pertuzumab, trastuzumab and docetaxel arm tested positive for ATA to pertuzumab. The submission included an exploratory analysis of the peak and trough serum pertuzumab concentrations in this patient. The patient was ATA positive on only one occasion (Day 168 sample) and had a lower trough concentration (40.8 μg/mL) compared with mean Day 168 data from ATA negative patients (77.8 μg/mL, CV% = 26.7). In addition, this ATA positive patient had lower trough concentrations than average concentrations even on those occasions when this patient tested negative for ATAs. Consequently, it is possible that this patient might clear pertuzumab more rapidly than the average patient, unrelated to ATAs. Peak concentration for this ATA positive patient on Day 168 was 196 μg/mL which was consistent with the mean peak concentration in ATA negative patients of 196 μg/mL (CV% = 35.2). In addition, the ATA positive patient had trough pertuzumab concentrations greater than the target concentration of 20 μg/mL at all time points.

3.4. Evaluator's overall conclusions on pharmacokinetics

- The pharmacokinetics of pertuzumab have been reasonably well characterized in patients with a variety of malignant tumours. There were no pharmacokinetic studies with pertuzumab in healthy subjects.
- The two population-pk analyses in patients with cancer support the fixed, non-weight-based dosing regimen proposed for registration (Ng et al., 2006; and report 11-2998). In the pivotal population-pk analysis (report 11-2998), data from 440 cancer patients were pooled from eleven Phase I/II studies and one Phase III study at pertuzumab doses ranging from 2 to 25 mg/kg. This dose range covered the pertuzumab 840 mg loading followed by 420 mg q3w IV dosing regimen proposed for the treatment of mBC. The population-pk analysis demonstrated that the data were best described by a two-compartment model with first order elimination from the central compartment. The population-pk analysis showed no statistically significant difference in either clearance or volume of the central compartment between the pivotal Phase III study (WO20698/TOC4129g) and the Phase I/II studies.
- In the population-pk analysis (report 11-2998), the volume of distribution of pertuzumab was estimated to be 5.43 L (i.e., Vc 3.07 L [1.2% SE] + Vp 2.36 L [3.5% SE]). The estimated Vc (3.07 L) approximates plasma volume (3L). Both Vc and Vp increased in patients with greater lean body weight. However, sensitivity analyses for estimated steady state C_{min}, C_{max}, and AUC at the proposed pertuzumab dosing regimen of 840/420 mg showed that the effect of lean body weight on these parameters was within the estimated inter-individual variability of these parameters in the overall population.
- In the population-pk analysis (report 11-2998), the clearance of pertuzumab was estimated to be 0.239 L/day (2.1% SE), with a coefficient of variation of 34.5% (suggesting moderate inter-subject variability). Clearance decreased in patients with higher baseline serum albumin concentrations, and increased in patients with greater lean body weight. However, sensitivity analyses for estimated steady state C_{min}, C_{max}, and AUC at the proposed pertuzumab dosing regimen of 840/420 mg showed that the effects of serum albumin and lean body weight on these parameters were well within the estimated inter-individual variability of these parameters in the overall population. In the population-pk analysis (report 11-2998), the median terminal elimination half-life was 17.2 days (95% range: 7.8 to 32 days).
- There were no data in the submission investigating the metabolism of pertuzumab. However, it is expected that this large MW (~148 kDa) protein will undergo catabolism to small peptides and individual amino acids. There were no data in the submission on renal excretion of pertuzumab. However, it can be predicted that pertuzumab will not undergo renal filtration due to its large MW.
- In study BO16934, a loading dose of 840 mg achieved trough and peak concentrations with the range of those observed at steady state by the second treatment cycle in women with mBC (n=40). Over 17 treatment cycles (approximately 1 year) a mean serum concentration of 289 μg/mL was reached with the 840/420 mg regimen, and at the end of the cycles mean serum concentrations dropped to approximately 100 μg/mL (study BO16934). In study JO17076, the observed accumulation ratio (i.e., ratio = Cycle 3: Cycle 1, trough concentration) was 2.30 in Japanese patients. The population-pk analysis (report 11-2998) showed that about 92% of the population treated with the proposed pertuzumab fixed-dose regimen (840/420 mg) achieved trough serum concentrations > 20 μg/mL (target concentration) regardless of sex, weight or race (Japanese vs non-Japanese).
- There were no specific PK studies in patients with hepatic or renal impairment. However, as pertuzumab is not cleared by hepatic metabolism or renal excretion the absence of such studies is not considered to be a major issue. In the population-pk analysis (report 11-2998), median steady state trough pertuzumab concentrations were comparable in patients

with normal renal function and patients with mild and moderate renal impairment based on CrCL. However, there were only limited data on patients with severe renal impairment.

- There were no specific PK studies investigating the effects of pertuzumab in elderly patients (i.e., ≥ 65 years of age). However, the population-pk analysis (report 11-2998) showed that age did not significantly affect the pharmacokinetics of pertuzumab as regards clearance and the volumes of the central and peripheral compartments. Similarly, the population-pk analysis (report 11-2998) showed that there was no difference between male and female patients, or between Japanese and non-Japanese patients as regards clearance and volumes of the central and peripheral compartments.
- There were no specific studies investigating the PK drug-drug interactions. However, there were five clinical studies with relevant PK interaction data. In the pivotal efficacy and safety study in patients with mBC (WO20698/TOC4129g), substudy 2 showed that there are unlikely to be significant pharmacokinetic interactions when pertuzumab, trastuzumab, and docetaxel are administered at the proposed doses for the treatment of mBC. Other clinical combination studies in patients with cancer showed no significant PK interactions between pertuzumab and gemcitabine (BO17003[1], TOC3258g), pertuzumab and docetaxel (BO17021), or pertuzumab and erlotinib (WO20024).
- In the pivotal Phase III study WO20698/TOC4129g, there were 11 (2.8%) patients out of 386 with evaluable ATA data who tested positive at some time during or after treatment. There were data from two patients (one each in TOC2572g and WO20698/TOC4129g) suggesting that anti-pertuzumab antibodies might reduce pertuzumab serum concentrations. However, no definitive conclusions can be drawn from this limited data.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

The submission included one study containing pharmacodynamic data (QT interval data) in patients with mBC (WO20698/substudy 2).

4.2. QTc effects – study WO20698 (substudy 2)

The substudy was designed to enrol a total of 50 electrocardiogram (ECG) evaluable patients and at least 40 pharmacokinetic (PK) evaluable patients. The two treatment groups were the combination of pertuzumab, trastuzumab, and docetaxel (n=20) compared with the combination of placebo, trastuzumab, and docetaxel (n=17). A positive-control comparison drug (e.g., moxifloxacin) is recommended in "thorough QT/QTc studies" to validate assay sensitivity. However, in this study a positive-control was not administered as the sponsor considered that the use of such a drug would not be ethical in a metastatic cancer patient population.

The sponsor stated that the target receptor, HER2, precluded a multiple dose study in normal volunteers. Furthermore, the sponsor stated that long half-life of pertuzumab (approximately 17 days) makes the use of a cross-over design not feasible, as a long washout period in cancer patients would be unethical. Consequently, the sponsor chose to investigate the potential effect of pertuzumab on the QTc interval using a parallel design in the target population at the dosing schedule intended for marketing. Baseline demographic and other characteristics were reasonably well balanced between the two treatment groups.

[1] Sponsor clarification: study BO17003 is with pertuzumab and capecitabine; TOC3258g is with pertuzumab and gemcitabine.

The objectives of the ECG analyses were to assess the effect of pertuzumab on the change from baseline in the QTc interval, calculated using both Fridericia's correction (ΔQTcF) and Bazett's correction (ΔQTcB), and to assess the effect of pertuzumab on other ECG parameters of heart rate, QT interval, PR interval, and QRS duration. Data consisted of 12-lead ECG measurements obtained in triplicate and sent to a central core cardiology laboratory, which produced a single dataset that was analysed by Genentech following unblinding of the main study. Statistical analysis of ECG data was guided by the Statistical Analysis Plan (SAP), dated 12 July, 2011.

Triplicate ECG values for each patient at each time point were averaged. Baseline ECG was defined as the average of pre-dose observations at Cycle 1 Day 1 (15 minutes and 30 minutes prior to infusion), and this definition was carried forward throughout the substudy. The ECG dataset consisted of 347 observations from 20 patients treated with pertuzumab and 17 patients treated with placebo. The correlation between the RR interval and QTcF was assessed to evaluate the residual effect of RR interval on QTcF. There was a residual effect of RR interval on QTcF in the placebo treatment group ($p< 0.05$) and, consequently, the ΔΔQTc results may be associated with a small residual effect of RR interval due to placebo-correction rather than a true drug effect. However, as the sponsor notes, the QTcF is known to be more accurate in subjects with altered heart rate than other correction methods, and small residuals are not unexpected. The sponsor also explored the correlation between the RR interval and QTcB, and found that the QTcB was associated with a stronger bias than the QTcF.

4.2.1. Results

4.2.1.1. QTcF changes from baseline

The descriptive statistics of raw QTcF (ms) in Cycle 1 and 3 are provided in the dossier. Summary statistics of ΔQTcF (msec) for both pertuzumab and placebo, and ΔΔQTcF (msec) between the two groups in Cycle 1 and Cycle 3 are provided below in Table 17. Of note, in Cycle 3 the upper 90% CI for the point estimate of ΔΔQTcF was greater than 10 ms at all time points. The mean point estimate of 8.41 ms for ΔΔQTcF immediately post-infusion in Cycle 3 was greater than 5 ms (a threshold of potential regulatory concern in a thorough QT/QTc study). The median post-infusion pertuzumab concentration in Cycle 1 was higher than in Cycle 3 (~ 280 μg/mL vs ~ 200 μg/mL), due to the 840 mg loading dose in Cycle 1.

Table 17: Summary statistics of ΔQTcF (msec) and ΔΔQTcF (msec) in Cycle 1 (left panel) and Cycle 3 (right panel).

ΔQTcF (ms) and ΔΔQTcF (ms) in Cycle 1

Treatment	Summary Statistic	Time Points: Immediately post-infusion	Time Points: 60-75 mins post-infusion	Time Points: Day 3
ΔQTcF Pertuzumab	N	18	17	17
	Mean	2.56	0.34	-3.54
	SD	9.81	12.93	12.83
	Median	2.92	-2.17	-2.83
	Range	-16.67 : 20.17	-16.00 : 29.83	-26.83 : 16.33
ΔQTcF Placebo	N	15	15	15
	Mean	9.52	6.69	0.54
	SD	12.99	10.87	15.69
	Median	12	8.67	-1
	Range	-21.92 : 34.83	-20.58 : 18.83	-25.50 : 29.50
ΔΔQTcF	Mean	-6.96	-6.35	-4.08
	90% CI	-13.60 : -0.23	-13.57 : 0.88	-12.64 : 4.48

ΔQTcF (ms) and ΔΔQTcF (ms) in Cycle 3

Time Points: 30 mins pre-infusion	Time Points: 15 mins pre-infusion	Time Points: Immediately post-infusion	Time Points: 60-75 mins post-infusion
15	17	17	17
-3.80	-5.51	2.02	-4.45
15.29	14.31	13.17	15.19
-1.33	-8.17	-1	-7.5
-28.67 : 27.50	-24.83 : 25.50	-15.17 : 23.33	-28.83 : 25.83
15	15	15	15
-8.80	-9.46	-6.39	-4.41
21.86	17.94	21.3	21.55
-7.67	-8.83	-5.92	-6.92
-48.00 : 33.67	-40.33 : 18.00	-38.67 : 44.67	-38.00 : 46.33
5.07	3.95	8.41	-0.04
-6.14 : 16.29	-5.74 : 13.63	-2.58 : 19.39	-11.12 : 11.04

4.2.1.2. QTcF observed results

No subjects treated with pertuzumab (0/20) displayed QTcF values > 450 ms, compared with two subjects treated with placebo (12.5%; 2/16). A QTcF value > 450 ms is typically used to assess grade 1 (mild) QTc-related adverse events.

- No subject displayed new incidence QTcF values > 480 ms.

- No subject displayed new incidence QTcF values > 500 ms, a threshold commonly used to assess grade 3 (severe) QTc-related adverse events due to known relationship between drug-induced QTc interval prolongation > 500 ms and the probability of TdP.
- No subjects treated with pertuzumab (0/20) displayed a change from baseline QTcF values > 30 ms, compared with two subjects treated with placebo (11.76%; 2/17).
- No subject displayed a change from baseline of QTcF > 60 ms.

4.2.1.3. Abnormal ECG changes

- The proportion of patients having post-screening change from baseline in PR ≥ 25% resulting in a final PR > 200 ms was 10% (2/20) with pertuzumab and 5.88% (1/17) with placebo.
- The proportion of patients having new incidence of abnormal T waves was 11.11% (2/18) with pertuzumab and 25% (4/16) with placebo.
- The proportion of patients having new incidence of abnormal ECG morphology was 0% (0/20) with pertuzumab and 5.88% (1/17) with placebo.

4.2.1.4. Other ECG parameters

For the ECG parameters HR and PR interval, all 90% CIs of time-matched baseline-adjusted placebo-corrected values (ΔΔ values) included zero. For some time points, the 90% CIs for ΔΔQRS did not include zero (i.e., Cycle 1, immediately post-infusion, and 60-75 minutes post-infusion; Cycle 3, 30-minutes post-infusion). However, in these instances the ΔΔQRS point-estimate showed decrease in the pertuzumab group. Overall, the results suggest that pertuzumab did not significantly affect HR, PR interval or QRS interval.

4.2.1.5. Model building

An exposure-response model was constructed to characterize the relationship of change from baseline in QTcF (ΔQTcF) and pertuzumab serum concentration. The results of model building showed that there was no apparent relationship between ΔQTcF and pertuzumab serum concentration (the slope estimate of -0.0093 with standard error (SE) of 0.0167 was not statistically significant at $p<0.05$). However, a relationship was found for Cycle 3, but this may have been due to using pre-dose Cycle 1 as baseline for both Cycle 1 and 3. The sponsor states that "given the limited sample size, it is unclear whether this difference was simply random variability or an underlying true study-related change in the intercept between Cycles 1 and 3".

4.3. Evaluator's overall conclusions on pharmacodynamics

The submission included one pharmacodynamic study investigating the relationship between QTcF prolongation and pertuzumab serum concentration in patients with mBC (WO20698; substudy 2). During Cycle 3 of this study, the point estimate of ΔΔQTcF for the 30-minute pre-infusion time-point and the immediately post-infusion time-point were greater than 5 ms, and the upper 90% CIs of the ΔΔQTcF were greater than 10 ms for all four time-points assessed. The results from Cycle 3 would give rise to regulatory concern in a "thorough QT/QTc study" (relevant note for guidance, CHMP/ICH/2/04). However, the sponsor considers that these findings are attributable to random variability and not due to a drug effect.

The sponsor notes that the point estimates of ΔQTcF in Cycle 3 for pertuzumab were generally higher than the ΔQTcF for placebo, suggesting that the ΔΔQTcF values may have been inflated due to over-correction associated with the ΔQTcF of placebo. In addition, the sponsor comments that if post-baseline measurements of QTcF are regressed to the overall mean of about 413.3 ms, a difference would be observed in post-baseline changes between the pertuzumab (414.3 minus 410.7) and placebo groups (414.3 minus 420.0) of 9.3 ms, "lower than the value of 10 ms considered to important in thorough QTc studies. Thus it is unlikely pertuzumab causes ΔΔQTcF

prolongation larger than those of clinical interest in thorough QTc studies". The sponsor's analysis was *post hoc* and not specified in the study protocol. In addition, the TGA adopted QT/QTc interval guidance document (CHMP/ICH/2/04) makes no mention of adjusting post-baseline changes in the QTcF by regressing them to the overall global mean. Furthermore, the QT/QTc guideline states that the threshold of regulatory concern "is around 5 ms as evidenced by an upper bound of the 95% CI confidence interval around the mean effect on QTc of 10 ms". It appears that the 10 ms referred to in the sponsor's *post hoc* analysis refers to the mean difference between the two treatment arms rather than the upper bound of the 95% CI of the mean. If this is the case, then the observed mean difference of 9.3 ms is greater than the mean difference of 5 ms, which is of regulatory concern in a "thorough QT/QTc study".

Overall, despite the observed upper bound of the 90% CI being > 10 ms for each of the four ΔΔQTcF point estimates in Cycle 3, and the point-estimates being > 10 ms for the 30-minutes pre-infusion and the immediately post-infusion time points in this Cycle, no patients in the pertuzumab group (0/20) had QTcF values > 450 ms (c.f., 2/16 in the placebo group), and no patients in either group had QTcF values > 480 ms or > 500 ms. In addition, no patients in the pertuzumab group (0/20) had an increase in QTcF > 30 ms from baseline (c.f., 2/17 in the placebo group), and no subjects in either treatment group had an increase in QTcF > 60 ms from baseline. The categorical results are reassuring and suggest that clinically significant increases in the QTcF are unlikely with pertuzumab.

5. Dosage selection for the pivotal studies

The protocol of the pivotal Phase III study (CLEOPATRA) states that the dose of pertuzumab selected for investigation (i.e., 840 mg loading, 420 mg maintenance q3w) was based on PK studies demonstrating similar pharmacokinetics observed across doses ranging from 2.0 to 15.0 mg/kg (i.e., 140 mg to 1050 mg for a 70 kg patient). In addition, the protocol also states that the preliminary population-pk analysis showed that a two-compartment model adequately described the concentration-time data with a systemic serum clearance of approximately 0.24 L/day and a terminal half-life of approximately 17 days for a typical patient. Based on these data, a dosing interval of 3 weeks was recommended for the clinical studies. In the Phase II studies, a loading dose of 840 mg (followed by 420 mg q3w) was shown to be capable of attaining steady-state trough and peak concentrations by the second cycle. The preliminary population-pk analysis also showed that modelling data from Phase Ia and Phase II studies supported the use of fixed, non-weight based dosing. Additionally, there was no evidence that pertuzumab significantly affected the pharmacokinetics of co-administered chemotherapeutic agents docetaxel and capecitabine in Phase Ib studies.

Comment: The rationale for selection of the pertuzumab dosage regimen for the pivotal Phase III study is reasonable. Population-pk analysis involving data from all 12 PK studies included in the submission (report-11-2998) supported the use of fixed-dose pertuzumab identified in the smaller, preliminary, population-pk analysis (Ng et al., 2006). In addition, data from the pivotal Phase III PK substudy confirmed that significant PK interactions between agents were unlikely for the pertuzumab, trastuzumab and docetaxel combination. However, data from the two, single-agent (pertuzumab) PK dose-escalation studies in patients with advanced solid tumours showed that the maximum tolerated dose (MTD) of pertuzumab was "not reached" at doses up to 15 mg/kg (i.e., 1050 mg in a 70 kg person) in study TOC2297g and 25 mg/kg (i.e., 1750 mg in a 70 kg person) in study JO1706. Consequently, these data raise some uncertainties about whether the dose selected for the pivotal study was the most appropriate dose. However, despite these reservation, the population-pk analysis (report 11-2998) showed that about 92% of the population treated with the proposed pertuzumab fixed-dose regimen (840/420 mg) achieved trough serum concentrations > 20 μg/mL

(target concentration) regardless of sex, weight or race (Japanese vs non-Japanese).

6. Clinical efficacy

6.1. Overview of the studies with efficacy data

The sponsor's letter of application (4 April 2012) nominates the Phase III study (WO20698/CLEOPATRA) as the pivotal efficacy and safety study, with additional supportive data being provided by studies WO20697/NEOSPHERE and BO17929 and a range of Phase I and II studies in patients with cancers of various types. The sponsor's clinical overview identifies the Phase III study (WO20698/CLEOPATRA) as being pivotal, and two Phase II studies as being key supporting studies (WO20697/NEOSPHERE and BO17929). The submission included four studies in patients with breast cancer (see Table 18, below).

Table 18: Breast cancer studies.

Protocol No.	Study Design	Population	Efficacy Parameters	Drug, Dose, Duration	No. of Patients Sex (M:F)
PIVOTAL STUDY **Phase III – Combination therapy, HER2-positive breast cancer**					
WO20698/ TOC4129g (CLEOPATRA)	A Phase III randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety of: Arm A: Pla+T+D vs Arm B: Ptz+T+D	Patients with HER2-positive locally recurrent, unresectable and metastatic breast cancer (MBC) who have not received chemotherapy or biologic therapy for their advanced/metastatic disease.	IRF- assessed progression-free survival (PFS), overall survival (OS), investigator-assessed PFS, objective response rate (ORR), duration of response, time to symptom progression based on Quality of Life (QoL).	Pertuzumab: 420 mg every 3 weeks (q3w) (840 mg loading dose) or placebo q3w Trastuzumab: 6 mg/kg q3w (8mg/kg loading dose) Docetaxel: 75mg/m^2 escalating to 100mg/m^2 q3w. Treatment until progression	808 patients (2M: 806F): Pla+T+D : N= 406 Ptz+T+D: N= 402
KEY SUPPORTING STUDIES: **Phase II Studies – Combination therapy, HER2-positive breast cancer**					
WO20697 (NEOSPHERE)	A Phase II randomized, open-label, four-arm study evaluating • A. T+D • B. Ptz+T+D • C. Ptz+T • D. Ptz+D in the neoadjuvant setting.	Patients with locally advanced, inflammatory or early stage HER2-positive breast cancer scheduled to receive neoadjuvant therapy.	Neoadjuvant phase: Pathological complete response (pCR) rate, tumor response, clinical response rate, time to response, breast conserving surgery Adjuvant phase only: Disease-free survival, PFS	**Neoadjuvant (4 cycles):** Pertuzumab: 420 mg (840 mg loading dose) Trastuzumab: 6 mg/kg q3w (8mg/kg loading dose) Docetaxel: 75mg/m^2 escalating to 100mg/m^2 IV every 3 weeks	417 patients (0 M:417 F): Arm A (T+D): N=107 Arm B (Ptz+T+D): N=107 Arm C (Ptz+T): N = 107 Arm D (Ptz+D): N= 96
BO17929	An exploratory, two-stage Phase II, single-arm study of efficacy and safety of pertuzumab and trastuzumab.	HER2-positive MBC patients who have progressed on trastuzumab-based therapy.	ORR and clinical benefit response (CBR) rate, PFS, TTP, duration of response, time to response, OS.	Pertuzumab: 420 mg (840 mg loading dose) q3w Trastuzumab: 2mg/kg qw (4mg/kg loading dose or 6 mg/kg q3w (8mg/kg loading dose). Treatment until progression	95 patients (0M: 95F): Cohorts 1+2 (Ptz+T): N = 66 Cohort 3 (Ptz): N=29
Phase II Studies – Single agent, HER2-negative breast cancer					
BO16934	A Phase II, open-label, randomized, two-arm, multicenter study of efficacy and safety of two different doses of pertuzumab.	Patients with MBC with low expression of HER2, that has progressed during or after standard chemotherapy.	ORR, time to and duration of response, TTP.	Pertuzumab: 420 mg (840 mg loading dose) q3w OR 1050 mg q3w Treatment until progression	79 patients (0M : 79F) 420 mg Ptz: N=41 1050 mg Ptz N = 38

5-FU 5-fluorouracil, CBR = clinical benefit response, D = docetaxel, IRF = independent review facility, ORR = objective response rate, OS overall survival, Pla = placebo, Ptz = pertuzumab, PFS = progression-free survival, q3w = every three weeks, qw = every week, QoL = quality of life, T= trastuzumab, TTP = time to progression

In agreement with the sponsor's covering letter and clinical overview, it is considered that the submission includes one pivotal Phase III study (CLEOPATRA) supporting the application to register pertuzumab in combination with trastuzumab and docetaxel for the proposed indication. However, the two Phase II studies nominated by the sponsor as being the key supporting studies are considered to provide efficacy data of limited relevance to the submission. In these two Phase II studies in patients with breast cancer, the patient group and/or the pertuzumab treatment regimen differed from those being proposed and, consequently, the efficacy data from these two studies are not considered to be directly relevant to the application to register pertuzumab for the proposed indication. The pivotal study (CLEOPATRA) is reviewed below in Section 6.2, and in view of the importance that the sponsor places on the two studies that it considers to be key supporting studies (WO20697/NEOSPHERE and BO17929) these two studies have been reviewed below in Section 6.3.

One of the two Phase II studies (WO20697/NEOSPHERE) nominated by the sponsor as key supporting was undertaken in patients with locally advanced, inflammatory or early stage

HER2-positive breast cancer scheduled to receive neoadjuvant therapy for four cycles prior to surgery, including pertuzumab in combination with trastuzumab, and docetaxel. This study can not be considered to directly support the pivotal study as the patient population (early stage breast cancer) and the treatment regimen (neoadjuvant) both differed from that being proposed.

The other of the two Phase II studies (B017929) nominated by the sponsor as key supporting was an exploratory, single-arm study that evaluated the doublet combination of pertuzumab and trastuzumab in patients with HER2-positive metastatic breast cancer who had progressed while on trastuzumab based therapy. This study can not be considered to directly support the pivotal study as the treatment regimen differed from that being proposed for registration.

There was one Phase II study (BO16934) in patients with metastatic breast cancer with low HER2 expression that had progressed during or after standard chemotherapy that assessed two pertuzumab single-agent treatment regimens (see Table 18). However, the study can not be considered to directly support the pivotal study as the treatment regimen (single-agent pertuzumab) differed from that being proposed for registration.

In addition to the four clinical efficacy and safety studies in patients with breast cancer summarized above in Table 18, the submission included 9 other Phase I and II studies with pertuzumab efficacy and safety data for other indications. However, these studies are not considered to provide supportive efficacy data as the patient populations included cancers other than breast cancer and the pertuzumab dosage regimens did not include the triplet combination proposed for registration. In these studies, pertuzumab as monotherapy demonstrated little efficacy, while pertuzumab in combination with other chemotherapeutic agents showed variable efficacy depending on the indication.

6.2. Pivotal efficacy study (WO20698/TOC4129g)

6.2.1. Study design, objectives, locations and dates

This pivotal Phase III study (WO20698/TOC4129g), commonly known as CLEOPATRA (**Cl**inical **E**valuation **o**f **P**ertuzumab **a**nd **Tra**stuzumab), is a multinational, multicentre, randomized, double-blind, placebo-controlled, clinical trial designed to evaluate the efficacy and safety of the combination of pertuzumab, trastuzumab, and docetaxel compared with the combination of placebo, trastuzumab, and docetaxel in patients with previously untreated HER2-positive metastatic breast cancer (mBC).

The study was sponsored by F.Hoffmann-La Roche Ltd, and has been published in the New England Journal of Medicine (Baselga et al., 2012). The principal investigator is located at the Massachusetts General Hospital Cancer Center, Boston, USA. The study was undertaken at 204 centres study 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). The study was conducted from 12 February 2008 to 13 May 2011, and the CSR was dated October 2011.[2] The sponsor states that the study was conducted in accordance with the principles of Good Clinical Practice (GCP).

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

The **secondary objectives** of the study in the order presented in the protocol were:

[2] Sponsor clarification: The study was initiated on 12 Feb 2008 and is ongoing. The cut-off for the primary analysis was 13 May 2011 and the CSR was dated October 2011

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

A substudy was also designed to evaluate corrected QT (QTc) interval, pharmacokinetics (PK) and drug-drug interactions (DDI), and the results of this substudy were presented in two separate reports. These reports have been evaluated above under the relevant Pharmacokinetic and *Pharmacodynamics* sections of this CER.

An independent data monitoring committee (DMC) monitored patient safety. In addition to the DMC, an independent Cardiac Review Committee (CRC) reviewed the blinded cardiac data generated during the course of the study. The CRC reported their findings to the DMC every 6 months starting 9 months after the first patient was enrolled and at the safety interim analysis. An independent review facility (IRF) evaluated progressive disease and overall tumour response through a periodic review of all radiographic, cytologic and photographic data from all patients.

6.2.2. Inclusion and exclusion criteria

The study population included patients aged ≥ 18 years with previously untreated (in the metastatic setting) HER2-positive, metastatic or locally recurrent, unresectable breast cancer. This population included patients who had not been treated previously with chemotherapy and/or biologic therapy for their metastatic disease. Patients were allowed prior adjuvant hormonal therapy, and one line of hormonal therapy for metastatic disease. Patients with stage IV disease at initial disease presentation or progressive disease occurring ≥ 12 months after neoadjuvant or adjuvant therapy were included. Trastuzumab and/or taxanes were acceptable neoadjuvant or adjuvant treatments.

Comment: The inclusion and exclusion criteria were extensive, but characteristic of clinical trials of oncological agents involving patients with advanced metastatic cancer. Adequate bone marrow, liver, renal and cardiovascular functions were required by all patients, and patients required a baseline LVEF ≥ 50%. In addition, patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (see Appendix 1).

6.2.3. Study treatments

The study planned to include a total of 800 patients randomized 1:1 to one of two treatment arms:

- **Treatment arm A (Pla +T +D):**
  - Pertuzumab placebo: IV infusion q3w.
  - Trastuzumab: loading dose of 8 mg/kg IV, followed by 6 mg/kg IV q3w,
  - Docetaxel dose of 75 mg/m^2 IV q3w for at least six cycles.

- **Treatment arm B (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/m^2 IV q3w for at least six cycles.

Study treatment cycles were three weeks (21 days) in duration. The first dose of pertuzumab/placebo (Cycle 1, Day 1) was to be administered within three days of the date of randomization. The first dose of trastuzumab was administered 24 hours later (Cycle 1, Day 2), followed by the first dose of docetaxel. If the investigator determined that the initial infusions of all three agents were well tolerated, then in subsequent cycles all three drugs were administered on Day 1 of the cycle in the sequence pertuzumab/placebo ⟶ trastuzumab ⟶ docetaxel.

The first infusion of trastuzumab was administered over 90 minutes and blinded pertuzumab/placebo over 60 minutes. If the first infusion of trastuzumab and the first two infusions of blinded pertuzumab/placebo were tolerated without infusion associated adverse events, subsequent infusions could be delivered over 30 minutes

At the investigator's discretion, the initial docetaxel dose of 75 mg/m^2 could be increased to 100 mg/m^2 for patients who tolerated at least one cycle without significant toxicities. Docetaxel dose (mg/m^2) adjustments for changes in body weight were based on the investigative site's usual practice. The dose of trastuzumab (mg/kg) was recalculated only if the change in body weight exceeded ± 10% from baseline.

Pertuzumab was provided by the sponsor as a single-use vial formulation containing 30 mg/mL pertuzumab, and the formulation of placebo was equivalent to pertuzumab without the active agent. Commercial preparations of docetaxel were obtained locally by investigational sites. Where permitted by local regulatory requirements, commercial preparations of trastuzumab were also used by the investigational sites. Otherwise, trastuzumab was supplied by the sponsor.

6.2.3.1. Treatment duration

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. Treatment with pertuzumab/placebo and trastuzumab was to continue until investigator-assessed PD or unmanageable toxicity. Treatment with docetaxel was to continue for a minimum of six cycles, unless the patient experienced unacceptable toxicity or PD. After six cycles, continuation of docetaxel was at the discretion of the investigator.

6.2.3.2. Dose delays or modifications

If administration of any of the individual study drugs had to be delayed for a day or more, administration of the other two agents was delayed for the same time period. Administration of pertuzumab/placebo or trastuzumab could be delayed due to toxicities. If the patient missed a dose of pertuzumab/placebo or trastuzumab for ≥ 1 cycle (i.e., the doses were 6 or more weeks apart), a re-loading dose of pertuzumab (840 mg) or trastuzumab (8 mg/kg) was required. If re-loading was required, the three drugs had to be given as in Cycle 1 (i.e., pertuzumab/placebo on one day, followed by trastuzumab and docetaxel the following day). If pertuzumab/placebo or trastuzumab dosing was delayed for more than 2 cycles or had to be permanently discontinued, the patient was withdrawn from all study treatment and was monitored post-treatment. Pertuzumab/placebo and trastuzumab dose modifications were not permitted.

Administration of docetaxel could be delayed due to toxicities. If docetaxel dosing was delayed for more than 3 weeks with no recovery, the patient was withdrawn from docetaxel treatment. If docetaxel had to be permanently discontinued, the patient could continue on pertuzumab/placebo and trastuzumab treatment. The docetaxel dose could be increased at the discretion of the treating physician to 100 mg/m^2 for patients who tolerated at least 1 cycle without febrile neutropenia, NCI-CTCAE Grade 4 neutropenia for more than five days, ANC less than 100/µL for more than one day, or non-haematological toxicities of Grade > 2. Dose reductions as specified in the protocol were allowed in case of myelosuppression, hepatic dysfunction and other toxicities. Docetaxel had to be discontinued for severe hypersensitivity reactions, Grade > 3 peripheral neuropathy, severe or cumulative cutaneous reactions, and persistent/prolonged myelosuppression or liver function test abnormalities.

Comment: The use of a placebo for pertuzumab in this study is justifiable on the basis that patients randomized to the placebo treatment arm received trastuzumab plus docetaxel combination therapy. The combination of trastuzumab plus docetaxel is consistent with Australian approved recommended treatment for HER2-positive mBC in patients who have not previously received chemotherapy for metastatic disease (i.e., trastuzumab 8 mg/kg loading followed by 6 mg/kg in combination with docetaxel 100 mg/m^2 q3w).

6.2.4. Schedule of assessments

Scans, medical photography and other relevant data relating to disease assessments were sent to the IRF on an ongoing basis. When progressive disease (PD) was diagnosed by the investigator, scans, cytologic data and relevant clinical information including medical photography were sent to the IRF for expedited review. If PD was confirmed by the IRF, the investigator was notified that the patient no longer needed to undergo study tumour assessments. If PD was not confirmed, the IRF notified the investigator and requests that the patient continue to be scanned every 9 weeks, as per protocol. The investigator did not need to wait until IRF confirmation of PD before deciding what action to take and was free to initiate alternative anticancer treatment according to his/her clinical judgment. The schedule of assessment for the study period including screening (Day -28), treatment period, and follow-up for up to 3 years is summarized in the dossier.

6.2.5. Efficacy variables and outcomes

6.2.5.1. Primary efficacy parameter

The primary endpoint was PFS based on tumour assessments by an IRF. PFS was defined as the time from randomization to the first documented PD, as determined by the IRF using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, or death from any cause within 18 weeks of last tumour assessment, whichever occurred first. RECIST (Therasse et al., 2000) assessment criteria are summarized in Appendix 2 of this CER.

6.2.5.2. Secondary efficacy parameters

- Overall survival (OS), defined as the time from the date of randomization to the date of death from any cause.
- PFS based on investigator assessments, defined as the time from randomization to the first documented radiographic PD, as determined by the investigator using RECIST, or death from any cause, whichever occurred first.
- Overall response rate (ORR), defined as a complete response [CR], or partial response [PR] determined by the IRF using RECIST on two consecutive occasions ≥ 4 weeks apart (patients without measurable disease or with disease localized only to the bone were not included in the analysis of objective response).

- Duration of objective response, defined as the period from the date of initial confirmed partial or complete response until the date of PD or death from any cause (tumour responses were based on IRF evaluations using RECIST).
- Time to symptom progression, defined as the time from randomization to the first symptom progression as measured by the FACT TOI-PFB - a 24-item subscale generated using three subsections from the FACT-B questionnaire (physical well-being, functional well-being, and additional concerns); a decrease of five points was considered to be clinically meaningful and thus to be symptom progression.
- Biomarker analysis evaluating the relationship between molecular markers and efficacy outcomes (IRF-assessed PFS). The markers considered included the HER receptors, HER ligands, Fcγ-R, shed antigens (e.g., ECD/HER2), and other markers relevant for the HER family pathway. Special emphasis was placed on qRT-PCR markers (tumor gene expression profiles associated with HER2 activation) and baseline serum markers (levels of ECD/HER2 and HER ligands), both of which have been suggested as possibly being associated with clinical outcome in patients treated with pertuzumab.

6.2.6. Randomization and blinding methods

An Interactive Voice Response System (IVRS) was used to collect patient screening information and to randomize eligible patients in a 1:1 ratio to one of the two treatment arms. A complete block randomization scheme was applied to achieve balance 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). Unblinding of treatment assignment was not permitted during the study except for safety issues arising during study treatment. Approval from the sponsor's medical monitors was required prior to any unblinding of treatment code. Under no circumstances were patients who enrolled in this study permitted to be re-enrolled and randomized for a second course of treatment. According to the current protocol, patients and investigators will remain blinded until the 385 deaths required for the final analysis of OS have occurred.

6.2.7. Analysis populations

Intent-to-Treat (ITT) Population: The ITT population included all randomized patients. The efficacy analyses were based on the ITT population in patients in the treatment arm to which they had been randomized.

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.

Safety Analysis Population: Patients who received any amount of any component of study treatment were included in the safety analysis population. Safety results were summarized by the actual treatment patients received.

6.2.8. Statistical hypothesis and sample size

6.2.8.1. Statistical hypothesis

The null hypothesis was that the survival distributions of PFS in the two treatment groups are the same, and the alternate hypothesis was that the survival distributions of PFS in the treatment and control arms are different. The difference between the two treatment arms in the primary efficacy endpoint of IRF-assessed PFS was compared using a two-sided log-rank test at the 5% significance level, stratified by prior treatment status (de novo and prior adjuvant or neoadjuvant therapy) and region (Europe, North America, South America, and Asia).

6.2.8.2. Sample size

The primary analysis of PFS was planned to be undertaken 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 (i.e., 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 is planned to take place after 385 deaths have occurred, which will provide 80% power to detect a 33% improvement in OS (median OS for the control group is assumed to be 36 months).

6.2.8.3. Statistical methods

The statistical tests employed for each type of endpoint in the study are summarized below in Table 19. Efficacy analyses were based on the ITT population,

Table 19: CLEOPATRA – Statistical analyses of the efficacy endpoint.

Variable	Test	Stratification*
Primary endpoint: IRF-assessed PFS	Log-rank	prior treatment status, region
Secondary endpoints: time-to-event: investigator-assessed PFS, OS, time to symptom progression, duration of response	Cox regression	prior treatment status, region
objective response rate	Mantel–Haenszel χ^2	prior treatment status, region
	Fisher's exact	unadjusted (sensitivity)

* Strata: Prior treatment status: de novo vs prior (neo)adjuvant therapy; 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.

The **primary endpoint was IRF-assessed PFS**. The log-rank test, stratified by prior treatment status (de novo and prior adjuvant or neoadjuvant therapy) and region (Europe, North America, South America, and Asia), was used to compare PFS between the two treatment arms. The Kaplan-Meier approach was used to estimate median PFS for each treatment arm and the Cox proportional hazard model, stratified by prior treatment status and region was used to estimate the HR between the two treatment arms and its 95% confidence interval (CI). Pre-defined demographic subgroup analyses were also performed. Univariate and multivariate Cox regression analyses were also performed to investigate the association between PFS and pre-

defined stratification and baseline prognostic covariates. Six sensitivity analyses were also planned to assess the potential impact of specified factors on PFS.

The **key secondary endpoints** were analysed by the statistical methods outlined below:

a. Overall survival was assessed by the same methods as those described above for the primary endpoint.

b. PFS based on investigator assessments for patients without documented PD or who did not die within 18 weeks of the last tumor assessment were censored at the time of the last investigator tumor assessment (or, if no tumour assessments are performed after the baseline visit, at 1 day), and analysis methods were same as for the primary endpoint.

c. Objective response included only patients with IRF determined measurable disease at baseline and was based on the best overall response recorded from the start of trial treatment until IRF-assessed PD, death or first administration of next-line anti-cancer therapy, whichever occurs earliest. Patients without a post-baseline IRF-assessed tumour assessment were considered to be non-responders. An estimate of the objective response rate (ORR) and its 95% CI was calculated for each treatment arm. The Mantel-Haenszel $\chi 2$ test stratified by prior treatment status and region was used to compare the ORR between the two treatment arms. An unadjusted Fisher's exact test result was provided as a sensitivity analysis. As a sensitivity analysis, Investigator-assessed objective response was evaluated, based on patients with Investigator-determined measurable disease at baseline.

d. Duration of objective response was based on IRF assessments. No formal hypothesis testing was performed on this endpoint, as the subgroup of patients with objective response was not a randomized subset. Median duration of objective response for each treatment arm was estimated using the Kaplan-Meier approach. The hazard ratio between the two treatment arms was estimated using Cox regression. As a sensitivity analysis, duration of objective response was repeated based on Investigator assessments.

e. Time to symptom progression was evaluated using the FACT-B questionnaire with the TOI-PFB subscale. Female patients completed questionnaires every 9 weeks (within three days prior to each tumor assessment) until IRF-determined PD. complete the assessment on schedule even if study therapy was no longer being administered due to toxicity or investigator-determined PD (assessments stopped at IRF-determined PD). Analysis methods were the same as those described for the IRF determined PFS. Time to event analysis using Kaplan Meier methodology tested the hypothesis that the addition of pertuzumab to the treatment regimen does not have meaningful impact on HRQoL. The FACT-B (Version 4) questionnaire is provided in Appendix 3 of this CER.

f. At the time of protocol development, biomarker analyses were essentially exploratory and no fixed hypothesis testing was planned. The analyses of the efficacy endpoints time to response and CBR are exploratory with no formal hypothesis testing. These endpoints will not be discussed further as they are not considered to be directly relevant to accept or reject the submission because of their exploratory nature.

6.2.9. Participant flow

A total of 1196 patients were screened for the study, and 808 patients were randomized to one of two treatment arms: Pla+T+D, 406 patients; or Ptz+T+D, 402 patients. The countries contributing most patients to the study were US, Brazil and South Korea, each providing more than 90 patients. Individual centres contributed between one and 30 patients, but the majority of centers (110) recruited only one or two patients. Of the randomized patients, 2 in each of the treatment arms did not receive any study treatment; 3 had ALT and AST levels that were

greater than 2.5 x ULN (in breach of an exclusion criterion) and 1 withdrew consent prior to study drug administration. The overall disposition of patients in the study and reasons for patient withdrawal from treatment are summarized in the dossier.

The median overall time on study, including post-treatment follow-up, was 73.1 weeks (range: 0.4, 165) in the Pla+T+D arm (n=397), and 77.1 weeks (range: 0.7, 165.3) in the Ptz+T+D arm (n=407), while the median overall time on study treatment was 47.0 weeks (range: 0.3, 150.3) and 57.1 weeks (range: 0.6, 165.1), respectively.

Patients were to receive docetaxel for a minimum of 6 cycles, after which the Investigator had the option to continue or stop docetaxel while continuing with placebo/pertuzumab and trastuzumab. Docetaxel discontinuations in each treatment arm in the safety analysis (treatment received) are summarized in the dossier.

Comment: The major difference between patient disposition in the two treatment arms was the notably higher percentage of patients withdrawing from treatment in the Pla+T+D arm (70.3%, n=279) than in the Ptz+T+D arm (57.2%, n=233). The main reason for this difference was the higher incidence of withdrawal due to insufficient therapeutic response (progressive disease) in the Pla+T+D arm (57.2%, n=227) compared with the Ptz+T+D arm (44.2%, n=180). Other reasons resulting in premature were well balanced between the two treatment arms, and occurred less frequently than withdrawals for insufficient therapeutic response. Discontinuations due to safety reasons occurred in 7.8% (n=31) of patients in the Pla+T+D arm and 7.4% (n=30) of patients in the Ptz+T+D arm. At the time of clinical data cut-off, the proportion of patients still alive and on treatment was greater in the Ptz+T+D arm than in the Pla+T+D arm (42.5%, n=171 vs 29.8%, n=121). A further 166 patients (40.9%) in the Pla+T+D and 144 patients (35.8%) in the Ptz+T+D arm were alive and in the survival follow-up period. Median overall time on study was longer in the Ptz+T+D+ arm (57.1 weeks) than in the Pla+T+D arm (47.0 weeks), as was the median overall time on study including treatment follow-up (77.1 and 73.1 weeks, respectively).

Docetaxel was permanently discontinued in a greater proportion of patients in the Ptz +T+D arm (73.2%, n=298) than in the Pla+T+D arm (64.2%, n=255), while continuing treatment with pertuzumab/placebo plus trastuzumab. The main difference between the two treatment arms was the greater proportion of patients discontinuing treatment for administrative (adequate therapy) reasons in the Ptz+T+D arm (19.2%, n=78) than in the Pla+T+D arm (11.8%, n=47). The main reason for discontinuation of docetaxel in both treatment arms was administrative (standard practice) (23.8%, n=97, Ptz+T+D vs 22.%, n=90, Pla+T+D), followed by AE/intercurrent illness (24.3%, n=99 vs 25.7%, n=102, respectively).[3] The proportion of patients completing at least 6 docetaxel cycles was greater in the Ptz+T+D arm than in the Pla+T+D arm (70.0%, n=285 vs 61.7%, n=245, respectively).

6.2.10. Major protocol violations/deviations

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, and all were identified after the patient had been enrolled in the study. Protocol violations were reported frequently in both treatment arms (60.6%, n=246, Pla+T+D vs 61.2%, n=246, Ptz+T+D). The main reasons for protocol violations are summarized below in Table 20.

[3] Sponsor corrections: administrative (standard practice) (24.3%, n=99 vs 25.7%, n=102, respectively); AE/intercurrent illness (23.8%, n=97, Ptz+T+D vs 22.%, n=90, Pla+T+D)

Table 20: CLEOPATRA – Summary of protocol violations.

	Pla+T+D (n=406)	Ptz+T+D (n=402)
At least one protocol violation	246 (60.6%)	246 (61.2 %)
At least one inclusion criterion violation	50 (12.3 %)	49 (12.2 %)
At least one exclusion criterion violation	98 (24.1 %)	81 (20.1 %)
At least one on study violation	193 (47.5 %)	201 (50.0 %)

Note: Patients may have violations for more than one reason. Received no study treatment results in exclusion from safety analysis population. All other protocol deviations are deemed minor and do not lead to exclusion from any data set.

Protocol violations occurring in ≥ 5% of patients in at least one of the two treatment arms were (Pla+T+D vs Ptz+T+D): ECH0/MUGA or ECG missing or not done every 9 weeks (38.2%, n=155 vs 40.0%, n=161); tumour assessment not done every 9 weeks (20.7%, n=84 vs 26.4%, n=106); inadequate organ function confirmed ≤ 28 days before randomization (19.2%, n=78 vs 17.7%, n=71); bone scan outside allowed window (7.9%, n=32 vs 7.2%, n=29); CT/MRI outside allowed baseline window (5.2%, n=21 vs 4.7%, n=19); same method of LVEF assessment (ECHO or MUGA) not used during the study (4.9%, n=20 vs 5.0%, n=20); and pregnancy test not done during study medication (4.2%, n=17 vs 5.2%, n=21).

Of the 149 patients failing to have adequate organ function confirmed before randomization (exclusion criterion 14), the majority (57.8%, 86/149) 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). The sponsor comments that 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, the sponsored considered that, since docetaxel is routinely given in clinical practice without assessment of INR/aPPT, the violation did not compromise patient safety.

Comment: Protocol violations occurred frequently in both treatment arms, but were well balanced (60.6%, Pla+T+D vs 61.2%, Ptz+T+D). On-study protocol violations occurred more commonly than exclusion and inclusion criteria violations. The majority of on-study protocol violations were due to assessments outside the protocol defined window. The only protocol violations resulting in exclusion from the analyses were those in which patients received no study treatment and were excluded from the safety analysis (2 patients in each of the treatment arms). All other protocol deviations were considered by the sponsor to be minor and did not result in exclusion from any evaluation data set. Overall, it is considered that that inclusion of all patients with protocol violations in the efficacy analyses is unlikely to have biased the results or significantly influenced the validity of the analyses.

6.2.11. Baseline data

The two treatment arms (ITT population) were well balanced with respect to baseline demographic characteristics. The mean age in both treatment arms was 53.5 years, and over 80% of patients in both arms were aged < 65 years (83.5%, Pla+T+D vs 85.1%, Ptz+T+D). Two male patients took part in the study, both of whom were randomized to the Pla+T+D arm. The

majority of patients were categorized as either White (57.9%, Pla+T+D vs 60.9%, Ptz+T+D), or Asian (32.8% Pla+T+D vs 31.8%, Ptz+T+D). There was no sub-categorization of the Asian patients (e.g., Japanese, Chinese, Korean etc).

The two treatment arms (ITT population) were generally well balanced with respect to other baseline characteristics. The only imbalance of note was a smaller proportion of patients in the Pla+T+D arm with ECOG status 0 compared with patients in the Ptz+T+D arm (61.1% vs 68.2%, respectively).

Overall, breast cancer history was similar for the two treatment arms (ITT population). The most common breast cancer subtype was ductal (90.6%, Pla+T+D vs 91.5%, Ptz+T+D). Histological tumour grade was unknown for about 30% of patients in both treatment arms. Nearly all patients in both treatment arms had metastatic disease (98.0%, Pla+T+D vs 97.3%, Ptz+T+D). Of the 19 patients categorized as having locally recurrent disease (n=8, Pla+T+D and n=11, Ptz+T+D arm), 7 (n=2, Pla+T+D vs n=5, Ptz+T+D) had metastases noted at baseline disease assessment. The term "locally recurrent disease" was used for patients who had not had a prior surgical resection, as well as for patients who had previously had a surgical resection. HER2-positive status (FISH) was reported in all but 2 patients (1 patient in each treatment arm). ICH3+/FISH positive HER status was reported in 86.0% of patients in the Pla+T+D arm and 82.6% of patients in the Ptz+T+D arm. ER/PgR status was reported as positive in 49.0% of patients in the Pla+T+D arm and 47.0% of patients in the Ptz+T+D arm. ER/PgR status was positive if patients were ER and/or PgR positive, and ER/PgR status was negative if both ER and PgR were negative.

Visceral disease at baseline was reported in 77.8% of patients in the Pla+T+D arm and 78.1% of patients in the Ptz+T+D arm, with lung (47.0%, Pla+T+D vs 46.0%, Ptz+T+D) and liver involvement (41.1%, Pla+T+D vs 43.8%, Ptz+T+D) each being reported in just under half of all patients. The most common non-visceral sites (Pla+T+D vs Ptz+T+D) were lymph nodes (61.6% vs 64.9%), bone 43.3% vs 46.5%) and breast (36.5% vs 38.8%). Patients in both treatment arms had a median of five lesions (target and non-target) documented at baseline, and measurable disease at screening was present in 91.4% of patients in the Pla+T+D arm and 91.3% of patients in the Ptz+T+D arm.

Previous surgery had been undertaken in 70.4% of patients in the Pla+T+D arm and 70.9% of patients in the Ptz+T+D arm, and about a third of patients in both treatment arms had undergone resection of axillary nodes. At least one radiotherapy treatment had been received by 43.1% of patients in the Pla+T+D arm and 42.5% of patients in the Ptz+T+D, with the most frequent sites in both treatment arms (Pla+T+D vs Ptz+T+D) being bone (24.1% vs 21.9%)[4] and breast (21.4% vs 22.1%). Previous hormone therapy (only one prior hormone therapy allowed) had been received by 26.4% of patients in the Pla+T+D arm and 28.4% of patients in the Ptz+T+D arm, with the most frequently used agent in both treatment groups being tamoxifen. At least one previous chemotherapy or biological therapy had been received by 47.3% of patients in the Pla+T+D arm and 45.8% of patients in the Ptz+T+D arm, and about 40.4% of patients in the Pla+T+D arm and 37.3% of patients in the Ptz+T+D arm had been treated with at least one "anthracycline".

Previous trastuzumab-containing adjuvant or neoadjuvant regimen had been received by 10.1% of patients in the Pla+T+D arm and 11.7% of patients in the Ptz+T+D arm. For patients who had previously received trastuzumab, the median time from completion of trastuzumab to diagnosis of metastases was 17.0 months in the Pla+T+D arm and 19.6 months in the Ptz+T+D arm. The sponsor comments that the relatively low proportion of patients who had previously received adjuvant or neoadjuvant trastuzumab was due to the lack of widespread availability of adjuvant/neoadjuvant trastuzumab in the years prior to recruitment into the trial, and to the

[4] Sponsor clarification/correction: The rates of 24.1% & 21.9% are the rates for radiotherapy with no specific site given. Rates for radiotherapy to the bone are only 6.4% & 6.0%.

protocol requirement for patients to have at least a one year disease-free interval since prior systemic adjuvant/neoadjuvant therapy (other than hormone therapy, but including prior adjuvant/neoadjuvant trastuzumab).

The proportion of patients with previous diseases/conditions (non-active at baseline) other than breast cancer were comparable in the two treatment arms; 128 patients (31.5%) for the Pla+T+D arm and 110 patients (27.4%) for the Ptz+T+D arm. “Gastrointestinal disorders”, and “infections and infestations disorders” were the most commonly reported previous conditions, and both disorders were reported with a similar frequency in the two treatment arms. A wide variety of diseases and conditions were reported within these categories, but with < 2% of patients in either treatment arm reporting specific events. Previous “cardiac disorders”, most commonly, cardiomyopathy, myocardial infarction, coronary artery disease and myocardial ischemia were reported in 13 (3.2%) patients in the Pla+T+D arm and 16 patients (4.0%) in the Ptz+T+D arm.

According to the protocol, radiotherapy was only allowed during the treatment period for bone lesions present at baseline. The proportion of patients who had any form of concomitant radiotherapy for breast cancer during the study was balanced between the treatment arms; 12 patients (3.0%) in the Pla+T+D arm and 13 patients (3.2%) in the Ptz+T+D arm. Most of these patients received radiotherapy to the bone (6 patients, Pla+T+D vs 7 patients, Ptz+T+D), as specified in the protocol.

Comparable proportions of patients underwent medical or surgical procedures in the two treatment arms; 65 patients (16.0%) in the Pla+T+D arm vs 48 patients (11.9%) in the Ptz+T+D arm. The protocol specified that patients with locally recurrent disease must not be amenable to resection with curative intent. However, there were several patients who had a mastectomy while on study treatment (Pla+T+D vs Ptz+T+D): mastectomy (n=2, 0.5% vs 7, 1.7%); modified radical mastectomy (n=7, 1.7% vs n=2, 0.5%); simple mastectomy (n=4, 1.0% vs n=1, 0.2%); radical mastectomy (n=2, 0.5% vs n=1, 0.2%). The sponsor states that in each of these cases the patient’s breast lesions had either responded to such an extent that they were now amenable to resection or mastectomy was performed as a precautionary measure because of good response in their systemic disease. In no patient was the mastectomy performed because of suspected progression of disease.

The proportion of patients who received treatments other than for breast cancer prior to study entry was comparable between treatment arms (114 patients [28.1%], Pla+T+D vs 132 patients [32.8%], Ptz+T+D). The most common class of drug used was analgesics, received by 4% of patients in both treatment arms (17 patients, Pla+T+D vs 16 patients, Ptz+T+D). Treatment (Pla+T+D vs Ptz+T+D) with bisphosphonates had been received by 11 (2.7%) vs 10 (2.5%) patients, corticosteroids by 6 (1.5%) vs 8 (2.0%) patients, clotting and haemostatic factors by 4 (1.0%) vs no patients; blood (whole or packed cells) 2 treatments in each arm; haemopoietic stimulants no patients vs 6 (1.5%) patients. Colony stimulating factors had been received by 42 (10.3%) patients in the Pla+T+D arm and 53 (13.2%) patients in the Ptz+T+D arm, and a total of 42 and 59 treatments had been received, respectively.

The majority of patients (84% in each arm) received pre-medication prior to an infusion, with corticosteroids (77% to 78%) and 5-HT3 antagonists (59% to 60%) being the most common classes of pre-medications received. Other pre-medications used by at least 10% of patients were antihistamines (47% to 49%), histamine H2-receptor antagonists (31% to 32%) and analgesics (19% to 22%). Colony-stimulating factors were recorded as “pre-medication” by some investigators (meaning, it is thought, used as prophylaxis), and was well balanced between the two treatment arms when used in this setting; 16 patients (3.9%) in the Pla+T+D arm and 20 patients (5.0%) in the Ptz+T+D arm.

6.2.12. Results for the primary efficacy outcome

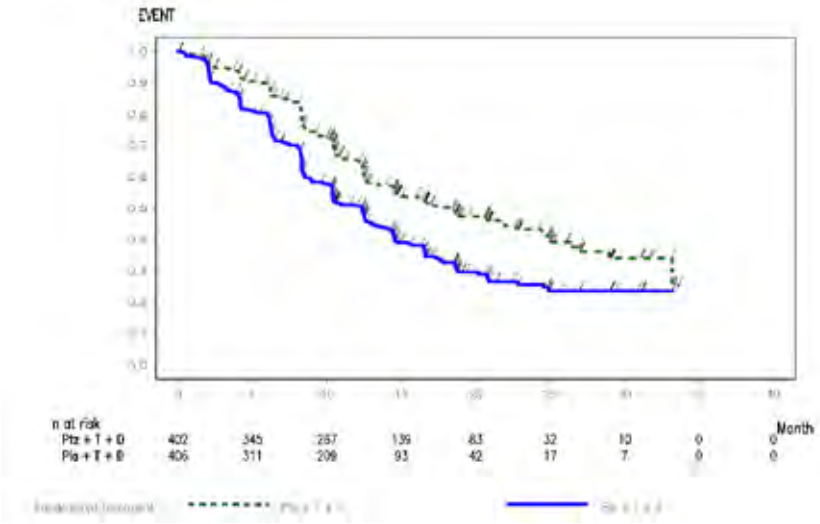
The results for the primary efficacy analysis of IRF-assessed PFS at the time of the data cut-off (13 May 2011) are summarized below in Table 21, and Kaplan-Meier curves of IRF-assessed PFS are provided below in Figure 9.

Table 21: CLEOPATRA – Summary of the IRF-assessed PFS primary efficacy endpoint analysis

	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]

Note: [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.

Figure9: CLEOPATRA - Kaplan-Meier curves of IRF-assessed progression-free survival.



In all six sensitivity analyses, PFS was significantly improved for patients receiving Ptz+T+D compared with patients receiving Pla+T+D, supporting the results of the primary analysis.

Exploratory univariate and multivariate Cox regression analyses on PFS were undertaken taking into account pre-specified prognostic factors. The results of the univariate Cox regression analysis are summarized in the dossier. The treatment effect (HR = 0.63, unstratified analysis) was not influenced by the addition of any of the pre-defined covariates, with the HR being close to 0.63 (range 0.61 to 0.63) when each individual covariate was added to the model. Significant covariate effects in the univariate analyses were identified for visceral disease status (HR = 0.63, p = 0.0004), and HER2 IHC status (HR = 1.69, p = 0.0003), with the results indicating that the

time to an IRF-PFS event was longer in patients with non-visceral disease compared with visceral disease, and in patients with IHC 3+ disease compared with IHC 2+ disease.

The impact of the imbalance in baseline ECOG status was investigated by univariate Cox regression as a post-hoc analysis after database lock. ECOG status was found to be significantly associated with IRF-PFS, with the time to an IRF-PFS event being longer in patients with ECOG 0 compared with patients with an ECOG of ≥ 1 (HR = 0.67, p < 0.0001). However, despite the significant covariate effect in the univariate analysis, the inclusion of ECOG status in the model with treatment had little influence on the treatment effect: i.e., with ECOG status HR = 0.64 (95% CI: 0.53, 0.77); without ECOG status HR = 0.62 (95% CI: 0.51, 0.75).

A further exploratory analysis was performed after database lock to investigate potential covariate by treatment interactions with each covariate tested separately (prior treatment status, region, race, age group, visceral disease status, ER/PgR status, HER2 IHC status, ECOG status). The only tested covariate demonstrating a statistically significant likelihood ratio test for interaction (0.1 significance level) was visceral disease status (p=0.0332). There was strong treatment effect in the subgroup analysis of patients with visceral disease (HR = 0.55 [95% CI: 0.45, 0.68]). Within this subgroup, the median time to IRF-PFS was estimated to be 10.4 months in the Pla+T+D arm compared with 17.2 months in the Ptz+T+D arm. In contrast, within the subgroup of patients with non-visceral disease there was no statistically significant difference between the treatment arms (median 17.3 months, Pla+T+D vs 20.8 months Ptz+T+D, HR = 0.96 [95% CI: 0.61, 1.52]).

The result for the exploratory multivariate (multiple) Cox regression analyses for IRF-assessed by PFS (without interactions) are summarized in the dossier. In these models, all covariates (baseline stratification and pre-specified prognostic factors) were included in the analysis. Two models were required, one with a cut-off age of 65 years and one with a cut-off age of 75 years, due to the covariates being highly correlated. Consistent results were observed in both analyses, with the treatment effect remaining significant when all pre-defined covariates were included in the model (HR = 0.60, p < 0.0001 in both models). In the exploratory multivariate Cox regression analyses, visceral disease status and HER2 IHC status were also identified as significant covariates, consistent with the univariate analysis.

Comment: The study met its primary endpoint. Treatment with Ptz+T+D resulted in a statistically significant improvement in IRF-assessed PFS (HR = 0.62 [95% CI: 0.51, 0.75], p < 0.0001) with an increase in median PFS of 6.1 months (median PFS of 12.4 months in the Pla+T+D arm vs 18.5 months in the Ptz+T+D arm). At the time of the clinical data cut-off for the primary analysis of PFS, 433 IRF confirmed PFS events had occurred, 242 (59.6%) in the Pla+T+D arm and 191 (47.5%) in the Ptz+T+D arm. In designing the study, median PFS for the control group was assumed to be 10.5 months in the control group improving to 14 months with the addition of pertuzumab, assuming that PFS is exponentially distributed. Consequently, it can be inferred that the minimum clinically improvement in PFS for this study is a 33% increase in median PFS following the addition of pertuzumab (i.e., from 10.5 to 14 months). The observed results showed that pertuzumab improved median PFS by 49% (i.e., from 12.4 to 18.5 months). The observed improvement in median PFS following inclusion of pertuzumab is considered to be clinically meaningful. Therefore, the primary endpoint analysis of this study is considered to have demonstrated that the improvement in PFS in the Ptz+T+D arm (relative increase 49%, absolute difference 6.1 months) is not only statistically significant but clinically meaningful. The HR indicates that the likelihood of experiencing a PFS event (i.e., disease progression or death) is 38% lower in the Ptz+T+D arm than in the Pla+T+D arm, and that this difference is statistically significant. Kaplan-Meier

curves show that improvement in PFS began to emerge in the Ptz+T+D arm relative to the Pla+T+D arm at about 2 to 3 months after initiation of treatment.

6.2.13. Results for key secondary efficacy outcomes

Time to investigator-assessed PFS was significantly improved in patients in the Ptz+T+D arm compared with the Pla+T+D arm: HR = 0.65 (0.54, 0.78), p < 0.0001). In the Ptz+T+D arm, the median time to PFS was 18.5 months compared with 12.4 months in the Pla+T+D arm, and the proportion of patients with PFS events at the time of the analysis was 50.0% (201 events) and 61.6% (250 events), respectively. The results for investigator-assessed PFS were consistent with those observed for IRF-assessed PFS.

Overall survival (OS) favoured the Ptz+T+D arm over the Pla+T+D arm (96 deaths vs 69 deaths, respectively, HR = 0.64 [96% CI: 0.47, 0.88], p = 0.0053). However, the estimated HR did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α-spending function for this interim analysis (i.e., HR ≤ 0.603, p ≤ 0.0012). Consequently, the observed OS benefit in favour of the Ptz+T+D arm relative to the Pla+T+D arm is deemed to be not statistically significant. The Kaplan-Meier curves of OS showed separation in favour of Ptz+T+D compared with Pla+T+D beginning at about 10 months. The median time to death had not been reached in either treatment arm at the time of data cut-off. The median length of follow-up of follow-up for survival was estimated to be 19.3 months in both treatment arms. The protocol estimated that approximately 50% (193) of the total required deaths (385) 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). However, only 43% (165/385) of the pre-specified number of deaths had occurred at the time of the primary analysis of the PFS.

The ORR (CR or PR) was higher in the Ptz+T+D arm than in the Pla+T+D arm (80.2% [275/343] vs 69.3% [233/336], respectively), but the majority of responders in both treatment arms were partial rather than complete. The difference in the response rates between treatments was 10.8% (95%CI: 4.2, 17.5); p=0.0011. However, the statistically significant results should be considered to be exploratory rather than confirmatory. Based on the pre-specified fixed-sequence testing hierarchy for the purposes of confirmatory statistical testing (i.e., IRF-assessed PFS ⟶ OS ⟶ ORR), statistical testing of the ORR was to proceed only if the results for the OS analysis were positive (i.e., statistically significant).

Duration of IRF-assessed objective response was assessed in the 233 patients in the Pla+T+D arm and 275 patients in the Ptz+T+D arm with a best overall response of CR or PR, as assessed by the IRF. The median duration of response in the Pla+T+D arm was 54.1 weeks (range: 5, 135 weeks) and 87.6 weeks (range: 7, 137) in the Ptz+T+D arm; HR = 0.66 (95% CI: 0.51, 0.85). Objective response was maintained for an estimated additional 33.5 weeks in patients receiving Ptz+T+D compared with Pla+T+D.

The FACT-B questionnaire showed no significant difference in female patients between the two treatment arms in time to symptom progression (i.e., 18.3 weeks [95% CI: 18, 27] Pla+T+D vs 18.4 weeks [95% CI: 18, 27] Ptz+T+D). The median time to symptom progression in the two treatment arms represented about 6 treatment cycles, with a HR of 0.97 [95% CI: 0.81, 1,16]; p=0.7161. Symptom progression according to FACT-B was defined as a decrease from baseline in the TOI-PFB score of five points or more. The TOI-PFB is a composite score derived from the physical wellbeing, functional wellbeing and additional concerns subscales.

6.2.14. Results for subgroup efficacy analyses (PFS and OS)

Subgroup analyses for IRF-assessed PFS were performed on a set of pre-specified covariates. The benefit associated with pertuzumab was seen in all of the subgroups tested, with point estimates of the HR all <1.0. In the majority of subgroups tested, the HR was comparable to the overall HR observed in the primary analysis.

Subgroup analyses of OS were performed using the same pre-specified covariates defined for PFS. The benefit associated with pertuzumab (HR < 1.0) was seen in all subgroups, apart from non-visceral disease (HR = 1.01).

6.3. Other efficacy studies

6.3.1. Study WO20697 (NEOSPHERE)

6.3.1.1. Design and methodology

Study W020697 was a Phase II, randomized, multinational (16 countries, including Australia), multicentre (59 centres), open-label study, designed to preliminarily assess the efficacy and safety of four neoadjuvant treatment regimens in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer. Patients with metastatic disease (Stage IV) or bilateral breast cancer were excluded. The study was initiated on 17 December 2007 and is ongoing. The data cut-off date for the primary analysis was 22 December 2009, and the CSR (Version 3) was dated 3 June 2011. The study was conducted in accordance with the principles of GCP.

The four treatment arms were:

- Treatment Arm A: trastuzumab and docetaxel (T+D).
- Treatment Arm B: trastuzumab, pertuzumab and docetaxel (T+P+D).
- Treatment Arm C: trastuzumab and pertuzumab (T+P).
- Treatment Arm D: pertuzumab and docetaxel (P+D).

All patients received 4 cycles q3w of the neoadjuvant therapy to which they had been randomized. At the end of 4 cycles, patients underwent physical examination, mammogram (and ultrasound if required by local practice) prior to breast surgery. The pathological specimen was evaluated for pathological complete response (pCR) at the treatment site, according to the Michelangelo Foundation Pathology Guidelines. Post surgery, patients in treatment arms A, B and D received 3 cycles of FEC therapy (see below) and patients in arm C received 4 cycles of docetaxel followed by 3 cycles of FEC. All patients received trastuzumab every 3 weeks for 1 year in total. Standard hormone treatment for estrogen-receptor positive patients and radiotherapy were to be administered following post-operative chemotherapy, as per local guidelines. Tumour response assessment (clinical breast examination) was performed at every cycle. ECHO (or MUGA) were performed every second cycle. Laboratory parameters, blood counts, ECOG status and vital signs were assessed at every cycle. AEs were monitored continuously until 28 days after last treatment dose. All patients had a tissue specimen at study entry. In addition, a sample of the resected surgical specimen was collected.

The treatment dosing regimens were:

- Pertuzumab was administered as a loading dose of 840 mg IV, followed by 420 mg IV q3w for 4 cycles.
- Trastuzumab was administered as an 8 mg/kg loading dose IV, then 6 mg/kg q3w for 4 neoadjuvant cycles and up to 1 year total post-surgery.
- Docetaxel was administered as a 75 mg/m^2 IV dose, escalating if tolerated to 100 mg/m^2 IV q3w for 4 cycles.
- The post-surgery standard of care was FEC consisting of 5-fluorouracil 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV q3w for 3 cycles. Hormone therapy in estrogen receptor-positive patients and/or radiotherapy as per local practice after post-operative chemotherapy.

Comment: This study was designated as being "key supporting" by the sponsor. However, it is considered to be not directly relevant to the proposed indication. The study population differs from that being proposed, and most notably excluded patients with metastatic breast cancer (Stage IV). In addition, treatment was administered in the neoadjuvant setting and pertuzumab was administered q3w for only 4 cycles. The study was open-label in design, which exposes the analysis to the well known biases associated with unblinded study designs.

6.3.1.2. Study population

The study population included female patients aged ≥ 18 years with locally advanced, inflammatory or early stage, unilateral and histologically confirmed invasive HER2-positive breast cancer, with the primary tumor being > 2 cm in diameter. Metastatic disease (Stage IV) or bilateral breast cancer, and previous anticancer therapy or radiotherapy for any malignancy were exclusion criteria.

6.3.1.3. Primary efficacy endpoint (definition, statistical analysis, sample size)

The primary efficacy endpoint was the post-surgery pathological complete response (pCR) rate in the breast, evaluated after patients had received 4 cycles of treatment and surgery or had withdrawn from the study, whichever occurred first. The pCR was defined as absence of invasive neoplastic cells at microscopic examination of the tumour remnants after surgery following primary systemic therapy. The pCR rate was the proportion of the intent-to-treat (ITT) population that achieved a pCR. The ITT population included all randomized patients, regardless of whether they received any study medication.

The pCR rate for arms B and C were compared with arm A separately, and arm D was compared with arm B. All 3 comparisons were of equal importance. The comparisons were made using a Cochrane Mantel-Hansel test, stratified by operable (T2-3, N0-1, M0), locally advanced (T2-3, N2 or N3, M0; T4a-c, any N, M0) and inflammatory (T4d, any N, M0) breast cancer and estrogen and/or progesterone positivity (either positive vs both negative). The three individual comparisons were tested using a two-sided Cochrane Mantel-Haenszel (CMH) test at an alpha level of 0.2.

A pCR rate of 25% was expected in arm A (trastuzumab and docetaxel) and arm D (pertuzumab and docetaxel). A pCR rate of 40% in arm B (trastuzumab, pertuzumab and docetaxel) or arm C (trastuzumab and pertuzumab) would be of clinical interest. As there were three individual comparisons, a Simes multiplicity adjustment was applied to the individual p-values obtained at the end of the study to maintain the overall false positive risk at 0.2. With a sample size of 400 patients (approximately 100 per arm), the study would have 80% power to detect an absolute percentage difference of 15% between arms for each of the three primary comparisons.

6.3.1.4. Secondary efficacy endpoints (definition and analysis)

Secondary endpoints included clinical response rate, time to clinical response, rate of breast conserving surgery (defined as quadrantectomy or lumpectomy), and evaluation of biomarkers. Only descriptive results were provided for these endpoints Disease free survival (DFS) and progression free survival (PFS) were also defined as secondary efficacy endpoints, but were not reported in the primary analysis since the data were not sufficiently mature.

6.3.1.5. Patient disposition

A total of 107, 107, 107 and 96 patients were randomized to arms A, B, C and D respectively, but the number of patients who actually received treatment according to each arm was 107, 107, 108 and 94 (respectively). The data cut date for this study report occurred at the last patient's surgery or withdrawal (22 December 2009). Therefore, patients remaining on study at this point included patients who had yet to receive, or were having ongoing adjuvant treatment, in addition to patients who had completed treatment and/or were in post-treatment follow-up. Nearly all patients (≥ 93%) received all four cycles of planned study treatment, and total doses

received were balanced across the treatment arms. Time on study was generally balanced across treatment arms, with the majority of patients completing less than one year of treatment.

6.3.1.6. Baseline characteristics

The treatment arms were generally well balanced with respect to baseline demographic factors. The median age was 49-50 years, the median weight was 62-67 kg, the majority of patients were Caucasian (71%), and the majority of patients were ECOG PS 0 (88.5%). The four treatment arms were well balanced with respect to the characteristics of the primary tumour. Overall, 7% of patients had inflammatory cancer, 32% had locally advanced cancer and 61% had operable cancer. Estrogen and progesterone receptor status was balanced across arms with the overall proportion or E and/or PgR positive patients being 47.4%. The majority of patients (approximately 90%) were HER2 receptor 3+ as assessed by IHC, or FISH and IHC combined. Breast cancer history and HER2 status for the four treatment arms are provided.

6.3.1.7. Efficacy results

6.3.1.7.1. Primary efficacy endpoint (pCR)

The results for the primary efficacy endpoint analysis (pCR) in the ITT population are summarized below in Table 22. Nearly all patients underwent surgery and data for pCR assessment were available on 103 (96.3%), 101 (94.4%), 96 (89.7%) and 92 (95.8%) patients in treatment arms A, B, C, and D, respectively. There were fewer patients in arm C who underwent surgery, as compared with arms A, B and D, primarily due patients who withdrew as a result of disease progression in this arm.

Table 22: Study WO20697 – Efficacy of neoadjuvant treatment; ITT population.

	Arm A (T+D) (N=107)	Arm B (Ptz+T+D) (N=107)	Arm C (Ptz+T) (N=107)	Arm D (Ptz+D) (N=96)
pCR assessment available	103 (96.3%)	101 (94.4%)	96 (89.7%)	92 (95.8%)
Responders *	31 (29.0%)	49 (45.8%)	18 (16.8%)	23 (24.0%)
Non-responders	76 (71.0%)	58 (54.2%)	89 (83.2%)	73 (76.0%)
95% CI for response rates	[20.6; 38.5]	[36.1; 55.7]	[10.3; 25.3]	[15.8; 33.7]
Difference in response rates^		(Arm B-Arm A) +16.8 %	(Arm C-Arm A) -12.2 %	(Arm D-Arm B) -21.8 %
95% CI for difference in response rates		[3.5; 30.1]	[-23.8; -0.5]	[-35.1; -8.5]
p-value from CMH		0.0094	0.0198	0.0010
P-value (Simes Corr. For CMH Test)		0.0141	0.0198	0.0030

*Responders were the pts who had achieved pCR. ^Treatment Arm B and C were compared to Arm A while Arm D was compared to Arm B.
Pre-defined 2-sided type 1 error level was 0.2.
CMH= Cochran-Mantel-Haenszel; D=docetaxel; Ptz=Pertuzumab; T=trastuzumab.

Comment: The combination Ptz+T+D (Arm B) significantly increased the pCR rate compared with the T+D (Arm A): 45.8% vs 29.0%; difference +16.8% (95% CI: 3.5, 30.1); p=0.0141. In addition, the pCR rate was notably higher for triplet combination Ptz+T+D (Arm A) than for each of the Ptz+T (Arm C) and Ptz+D (Arm D) doublet combinations. Overall, the results support superior efficacy of the Ptz+T+D triplet neoadjuvant regimen compared with each of the three doublet regimens (T+D, Ptz+T, and Ptz+D), based on pCR.

6.3.1.7.2. The secondary endpoints

The results for the primary and key secondary efficacy endpoints are summarized in the dossier. The study did not analyze the key secondary endpoints and only descriptive results were provided.

6.3.2. Study BO17929

6.3.2.1. Design and methodology

Study BO17927 was an exploratory Phase II, multinational (5 countries), multicentre (16 centres), single-arm, two-stage study designed to evaluate the efficacy and safety of 8 cycles of pertuzumab in combination with trastuzumab in patients with HER2-positive metastatic breast cancer whose disease had progressed on trastuzumab. The study was sponsored by F.Hoffmann-La Roche Ltd and was initiated on 10 May 2006 and is still ongoing. The data cut-off date for the report was 8 February 2008, and the report was dated 5 December 2008. The study was conducted in accordance with the principles of GCP.

For all patients, pertuzumab was given as loading dose of 840 mg IV, and then q3w at a maintenance dose of 420 mg IV. In Cohorts 1 and 2 trastuzumab was administered either weekly at 2 mg/kg IV over 30 minutes, or q3w at 6 mg/kg IV (depending on prior treatment). Patients underwent a baseline evaluation and were then treated q3w for 8 cycles. Tumour response assessments (according to RECIST) and ECHO (or MUGA) were performed every second cycle, up to cycle 8 and thereafter every 4 cycles until disease progression. Laboratory parameters, blood counts, ECOG status and vital signs were assessed at every cycle. AEs were monitored continuously until 28 days after last treatment dose, at which time a safety follow up visit was conducted. Patients who progressed or discontinued study medication are to be followed up every 4 months for survival until the last patient has died, withdrawn consent, or is lost to follow-up, or has reached 3 years after the last study dose, whichever is earlier.

The study had a Simon's two-stage design that allowed for early termination in case of lack of efficacy or safety concerns. In Cohort 1, 27 patients were to be recruited to ensure 24 evaluable patients. In this Cohort, previous trastuzumab was continued and pertuzumab was added. After all 24 evaluable patients had completed at least 2 cycles of therapy and one efficacy evaluation after the second cycle of therapy, or had withdrawn prematurely due to death or progressive disease before completing 2 cycles of therapy, recruitment stopped and an interim analysis was conducted. At the interim analysis, the predefined criteria for proceeding to the next stage (> 1 patient with ORR or ≥ 3 patients with clinical benefit response [CBR] out of 24 patients) were met, and a further 42 patients were enrolled into Cohort 2, for a total of 66 patients in the first two cohorts.

After completion of the first 2 stages, a third cohort of 27 patients (to ensure 24 evaluable patients) was to be recruited to evaluate the activity and safety associated with single agent pertuzumab. Once the disease stopped responding to pertuzumab, patients in Cohort 3 could have trastuzumab added to their pertuzumab therapy if they showed evidence of disease progression (excluding brain metastases) on single-agent pertuzumab. The efficacy and safety of combined pertuzumab plus trastuzumab following progression on either agent alone was therefore also assessed in a subset of patients in Cohort 3.

The primary clinical cut-off took place when all patients enrolled into Cohorts 1 and 2 had completed 8 cycles (approximately 24 weeks) of combination pertuzumab and trastuzumab treatment, or had withdrawn for any reason prior to that time. The submitted clinical study report was based on analysis of these data, with a cut off date of 8 February 2008, and all data collected after the clinical cut-off, including data on the 3rd cohort, are to be reported in an addendum to the report.

Comment: The sponsor nominated this study as a "key supporting" study. However, this study is considered not to be directly relevant to the submission to register pertuzumab for the proposed indication. The study used a doublet combination (P+T) rather than the proposed triplet combination (Ptz+T+D) proposed for approval. The study has no randomized, controlled arm (either double-blind or open-label). Consequently, it is subject to the well known biases associated with

non-randomized, uncontrolled studies, and limits clinically meaningful interpretation of the data.

6.3.2.2. Study population

The study population included patients aged ≥ 18 years with histologically confirmed, HER2-positive metastatic breast cancer whose disease had progressed on trastuzumab as last treatment for the disease. Patients were required to have at least one measurable lesion according to RECIST. The inclusion and exclusion criteria are provided in the dossier.

6.3.2.3. Primary efficacy endpoints (definition, statistical analysis, sample size)

The primary efficacy endpoints were the objective response rate (ORR) and the clinical benefit response (CBR) rate. Both were based on evaluations of target and non-target lesions according to RECIST to ascertain the overall best response status of each patient by the end of the trial. An ORR by tumour measurement according to RECIST occurred if there was a documented and confirmed Complete Response (CR) or Partial Response (PR). CBR included patients who met the criteria for ORR at any time and for any duration (at least 4 weeks), and patients whose best response was stable disease (SD) defined according to RECIST that lasted at least 6 months (or 8 cycles of therapy).

The ORR and CBR rate were calculated at the second stage of the study. Two-sided 80% confidence intervals (CI) were calculated around the ORR and around the CBR rate, using Pearson-Clopper method, and the CIs were not adjusted for the two-stage design or multiplicity of testing. The efficacy analysis was based on the all treated population, defined as all patients who received any amount of the study medication.

An ORR of no clinical interest was defined to be 7% or less and a CBR rate of no clinical interest was defined to be 15% or less. At the end of the second stage, with a total of 58 patients enrolled for the final analysis and ≥ 8 patients with response or ≥ 14 patients with CBR, the trial would have power of approximately 67% to reject the null hypothesis when the ORR was ≥ 13% or CBR rate was ≥ 25%, at a one-sided alpha level of ≤ 0.100. With 62 patients and ≥ 8 patients with ORR or ≥ 15 patients with CBR, the trial would have had a power of approximately 70% to reject the null hypothesis, at a one-sided alpha level of ≤ 0.100.

6.3.2.4. Secondary efficacy endpoints

The secondary efficacy endpoints included duration of response, time to response, time to progression, progression-free survival, overall survival, and tumour response. These endpoints were to be analyzed using standard statistical methodology.

6.3.2.5. Patient disposition

A total of 99 patients with metastatic breast cancer were screened for Cohorts 1 and 2, of whom 66 were recruited. Twenty-four (24) patients were recruited into Cohort 1 and were assessed for safety and efficacy after they had all completed 2 cycles of therapy, or had withdrawn or died. Based on this assessment, the study was continued and a further 42 patients were recruited. All patients received at least one cycle of pertuzumab and trastuzumab, and 23 patients were recorded as ongoing in the study at the time of data cut off.

6.3.2.6. Baseline demographics and disease characteristics

The all treated population (n=66) included women with a median age of 54.9 years (range: 25, 85), a median weight of 71.4 kg (range: 39, 122), a median height of 158 cm (range: 141, 178) and who were predominantly Caucasian (91%). The majority of women (80%) had an ECOG PS score of 0 at screening, with 19% having a score of 1.

The majority of women (n=60, 91%) had ductal breast cancer at baseline, and 50% (n=33) had histologically determined poorly differentiated tumours. Nearly all patients (n=63, 96%) had experienced at least a first progression of metastatic disease, and 41% (n=27) had also

experienced a second progression of metastatic disease. Two (2) patients entered the study without progression on trastuzumab in the metastatic setting, and consequently were protocol violators. Half of the patients (n=33) were estrogen receptor positive, and 19 (29%) were progesterone receptor positive. There were 12 (18%) patients who were HER2 2+ and 52 (79%) patients who were HER2 3+, while HER2 status was unknown for 2 patients.

Patients had a median of 4 target and non-target lesions (range: 1, 14), and most had either 1 (46%) or 2 (26%) organs involved. The most common sites for target lesions were visceral (74%) consisting of liver (52%), lung (30%), and lymph (30%), and "other" (24%) consisting of breast, skin and mediastinum. Target lesions had a median measurable tumor burden of 63 mm (range: 11, 588). Thirty-one patients (47%) had non-target lesions in the viscera, primarily liver (20 patients, 30%) and lung (15 patients, 23%). Other common sites for non-target lesions were bone (19 patients, 29%), lymph (13 patients, 20%) and "other" (11 patients, 17%, comprising skin, breast, mediastinum and colon).

As per the protocol, all patients had received trastuzumab prior to the study. Nearly all patients (92%) had undergone at least one surgical procedure; 71% had received prior taxane therapy (docetaxel and/or paclitaxel) therapy; and anti-metabolites, cytotoxic antibiotics (anthracyclines), and cyclophosphamide had each been used by 70% of patients. Aromatase inhibitors, anti-estrogens and antineoplastic agents were also commonly prescribed (> 25% of patients). Neoadjuvant therapy had been received by 26% of patients, and adjuvant therapy by 46% of patients. Palliative chemotherapy for metastases had been received by 85% of patients, with the majority receiving 1 (50%) or 2 (30%) lines of treatment prior to study entry.

6.3.2.7. Efficacy results

6.3.2.7.1. Primary efficacy endpoints (ORR and CBR)

The ORR (primary efficacy endpoint) in the all treated population at the time of the data cut for primary analysis was 24.2% (80% CI: 174, 32.3), with 5 (7.6%) patients achieving a CR and 11 (16.7%) patients achieving a PR. The CBR (primary efficacy endpoint) in the all treated population was 50% (80% CI: 42, 59). The ORR and CBR results are summarized below in Table 23.

Table 23: Study BO17929 – Primary efficacy endpoints ORR (left panel) and CBR (right panel); all treated population.

ORR; all treated patients

	PERTUZUMAB+HERCEPTIN (N=66)
Responders [1]	16 (24.2 %)
Non-Responders [2]	50 (75.8 %)
80% CI for Response Rates*	[17.4; 32.3]
Complete Response (CR)	5 (7.6 %)
80% CI for CR Rates*	[3.7; 13.6]
Partial Response (PR)	11 (16.7 %)
80% CI for PR Rates*	[10.9; 24.1]
Stable Disease (SD)	17 (25.8 %)
80% CI for SD Rates*	[18.8; 33.9]
Progressive Disease (PD)	33 (50.0 %)
80% CI for PD Rates*	[41.5; 58.5]
Missing (No Response Assessment)	0 (0.0 %)

[1]Responder=CR + PR = Objective Response
[2]Non-Responder= SD or PD
*80% CI for sample binomial using Pearson-Clopper method

CBR; all treated patients

	PERTUZUMAB+HERCEPTIN (N=66)
Responders [3]	33 (50.0 %)
Non-Responders [4]	33 (50.0 %)
80% CI for Response Rates*	[41.5; 58.5]
Complete Response (CR)	5 (7.6 %)
80% CI for CR Rates*	[3.7; 13.6]
Partial Response (PR)	11 (16.7 %)
80% CI for PR Rates*	[10.9; 24.1]
Stable Disease (SD) ‡	17 (25.8 %)
80% CI for SD Rates*	[18.8; 33.9]
Progressive Disease (PD)	33 (50.0 %)
80% CI for PD Rates*	[41.5; 58.5]
Missing (No Response Assessment)	0 (0.0 %)

‡ SD lasting at least 6 cycles of therapy
[3]Responder=CR + PR + SD>= 6 cycles = Clinical Benefit Response
[4]Non-Responder= SD< 6 cycles or PD
*80% CI for sample binomial using Pearson-Clopper method

Comment: In the all treated population (Cohort 1 + 2), the ORR was 24.2% (16/66) and the CBR was 50% (33/66). Consequently, both the ORR and the CBR rate were

clinically meaningful as defined by the protocol (i.e., pre-specified criteria ORR ≥ 13%, and CBR ≥ 25%).

6.3.2.7.2. Secondary efficacy endpoints

The median duration of response assessed in 16 (24.2%) patients with an objective response was 25.1 weeks (range: 12.4, 66.6), and 29.1 weeks (range: 12.4, 74.0) in 33 (50%) patients with a clinical benefit response.

The median time to response assessed in 16 (24.2%) patients with an objective response was 11.1 weeks (range: 4.9, 37.3).

The median time to progression in 45 patients with an event was 24.0 weeks (range: 4, 74). Since the one patient who died was recorded with progression prior to death, the analysis population for PFS was the same for that of TTP. The median PFS time (Kaplan Meier analysis) was therefore 24 weeks in the all treated population (80% CI: 18, 31).

6.4. Evaluator's conclusions on clinical efficacy for mBC

The submitted data included four studies with efficacy data for pertuzumab in patients with breast cancer, and nine additional studies with efficacy data for pertuzumab in patients with other cancers. Of the four breast cancer studies, it is considered that one of the studies includes pivotal efficacy data (CLEOPATRA), while the other three studies are considered not to provide direct supportive efficacy data because the indication and/or the pertuzumab dosing regimens differ from those being proposed for approval. The nine studies in patients with indications other than breast cancer are considered not to include supportive efficacy data.

The pivotal phase III study (CLEOPATRA) is considered to have satisfactorily demonstrated that the combination of Ptz+T+D for the treatment of the proposed patient population results in a clinically meaningful increase in PFS compared with the combination of Pla+T+D. In this study, both the primary efficacy endpoint (PFS) and the secondary endpoint (OS) are consistent with the endpoints recommended in the TGA adopted guideline on the evaluation of anticancer medicinal products (CPMP/EWP/205/95/Rev.3/Corr). The study showed that the median duration of the IRF-assessed PFS (primary efficacy endpoint) was 6.1 months longer in the Ptz+T+D arm (18.5 months) than in the T+D arm (12.4 months), and that the risk of a PFS event (disease progression or death) was reduced 38% in the Ptz+T+D arm relative to the Pla+T+D arm (HR = 0.62 [95% CI: 0.51, 0.75], p<0.0001). The Kaplan-Meier analysis showed that the IRF-assessed PFS curves began to separate in favour of the Ptz+T+D arm at about 2 to 3 months following initiation of treatment, with separation being maintained throughout the remainder of the observation period. The difference in IRF-assessed PFS was not only statistically significant, but is also considered to be clinically meaningful. The observed improvement in the observed median duration of the IRF-assessed PFS in the Ptz+T+D arm compared with the Pla+T+D (relative increase 49%, absolute increase 6.1 months) was greater than the estimated increase used to power the study (relative increase 33%, absolute difference 3.5 months). The robustness of the observed result in favour of the Ptz+T+D arm compared with the Pla+T+D arm was supported by the six sensitivity analyses of PFS, the univariate and multivariate Cox regression analyses of the PFS, and the subgroup PFS analyses. Furthermore, the result of the secondary efficacy endpoint analysis of investigator-assessed PFS was consistent with the results of the primary efficacy endpoint analysis of IRF-assessed PFS.

In addition to investigator-assessed PFS, other key secondary efficacy endpoint analyses also supported the efficacy of the Ptz+T+D combination compared with the Pla+T+D combination. The analysis of overall survival favoured the Ptz+T+D arm over the Pla+T+D arm (96 deaths vs 69 deaths, respectively, HR = 0.64 [96% CI: 0.47, 0.88], p = 0.0053), but the estimated HR did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α-spending function for this interim analysis (HR ≤ 0.603, p ≤ 0.0012). Consequently, the observed survival benefit in

favour of the Ptz+T+D arm relative to the Pla+T+D arm was deemed to be not statistically significant. However, the Kaplan-Meier analysis showed that the survival curves began to separate in favour of the Ptz+T+D arm at about 10 months. The median length of follow-up for survival was estimated to be 19.3 months in both treatment arms, but the median time to death had not been reached in either treatment arm at the time of data cut-off. Furthermore, at the time of the analysis only 43% (165/385) the prespecified number of deaths had occurred.

The ORR was higher in the Ptz+T+D arm than in the Pla+T+D arm (80.2% vs 69.3%, respectively), but the observed statistically significant difference between the two arms (10.8% [95% CI: 4.2, 17.5]; p=0.0011) was deemed to be exploratory rather than confirmatory due to the pre-specified fixed-sequence testing hierarchy. This hierarchy (IRF-assessed PFS ⟶ OS ⟶ ORR) specified that confirmatory testing should stop if the statistical the analysis of the OS was found to be negative.

The duration of the IRF-assessed objective response was assessed in the 233 patients in the Pla+T+D arm and 275 patients in the Ptz+T+D arm and showed that objective response was maintained for an estimated additional 33.5 weeks in patients receiving Ptz+T+D compared with Pla+T+D. The median duration of response in the Pla+T+D arm was 54.1 weeks (range: 5, 135 weeks) and 87.6 weeks (range: 7, 137) in the Ptz+T+D arm; HR = 0.66 (95% CI: 0.51, 0.85). The FACT-B analysis showed that time to symptom progression in both treatment arms was similar and represented about 6 treatment cycles (18.3 weeks, Pla+T+D vs 18.4 weeks, Ptz+T+D).

The two breast cancer studies identified by the sponsor as providing key supporting efficacy data were WO20697/NEOSPHERE and BO17929. However, as discussed previously neither of these two studies are considered to provide direct supportive efficacy data as the indication and/or the pertuzumab dosing regimen differed from those being proposed.

In WO20697/NEOSPHERE, the efficacy of a triplet combination including pertuzumab, trastuzumab, and docetaxel as neoadjuvant therapy (four cycles) was compared with three doublet combinations for the treatment of female patients with locally advanced, inflammatory or early stage, HER2-positive breast cancer. The study showed that the proportion of patients with pCR was significantly greater in patients treated with pertuzumab, trastuzumab, and docetaxel (n=107) compared with trastuzumab plus docetaxel (n=107): 45.8% vs 29.0%, respectively; difference 16.8% (95% CI: 3.5, 30.1); p=0.0141. In addition, the pCR in the pertuzumab and docetaxel arm (n=96) was significantly lower than in the pertuzumab, trastuzumab, and docetaxel arm (n=107): 24.0% vs 45.8%, respectively; difference -21.8% (95% CI: -35.1, -8.5); p=0.0030.

In study B017929, a doublet combination of pertuzumab plus trastuzumab (n=66) showed ORR (24.2%) and CBR (50.0%) results defined by the sponsor to be clinically meaningful in patients with trastuzumab insensitive advanced metastatic HER2-positive breast cancer.

In study BO16934, single-agent pertuzumab therapy (840/420 mg or 1050 mg) in women with metastatic breast cancer with low expression of HER2 resulted in only 2 out of 41 patients (4.9%) in the 840/420 mg arm achieving a partial response and no patients out of 37 achieving a partial response in the 1050 mg arm.

In summary, it is considered that the submission to register pertuzumab for the proposed indication and the proposed dosage regimen is supported by only one pivotal Phase III study (CLEOPATRA). However, there is a relevant TGA adopted guidance document indicating that submissions can be supported by only one pivotal study provided that the study is particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality and internal consistency. Overall, it is considered that the pivotal Phase III study (CLEOPATRA) meets the required criteria for submissions supported by one pivotal study and supports the registration of the proposed pertuzumab treatment regimen for the proposed indication.

7. Clinical safety

7.1. Studies providing evaluable safety data

The key safety data in the submission comes from the pivotal Phase III efficacy and safety study (CLEOPATRA). This study included 407 patients treated with Ptz+T+D for the proposed indication compared with 397 patients exposed to Pla+T+D. The safety data from CLEOPATRA has been evaluated below in Section 7.2.

Supportive safety data comes from an integrated summary from a total of 1412 patients exposed to pertuzumab. These 1412 patients included:

- 514 patients exposed to pertuzumab, trastuzumab and docetaxel (Ptz+T+D) in patients with mBC from the pivotal Phase III study (CLEOPATRA; n=407), and in patient with early stage breast cancer from the neoadjuvant treatment Phase II study (WO20697; n=107);
- 191 patients exposed to pertuzumab and trastuzumab (Ptz+T) in patients with breast cancer from Phase II study WO20697 (n=108) and Phase II study BO17929 (n=83);
- 386 patients exposed to pertuzumab monotherapy in Phase II studies using fixed-dose regimens of 420/840 mg or 1050 mg; and
- 321 patients exposed to pertuzumab in Phase I dose escalation studies.

An overview of the key safety from the integrated database is summarized below in Table 24. Overall, adverse events associated with the pertuzumab, trastuzumab, and docetaxel (Ptz+T+D) combination arm in the pivotal Phase III study (CLEOPATRA) occurred more frequently than with pertuzumab in the remainder of the safety database. However, exposure to pertuzumab was greater in the Ptz+T+D arm of CLEOPATRA than in the other studies, and this might account for the differences between this study and the Phase I/II studies. The safety profile of the Ptz+T+D combination from the Phase II study WO20697 was consistent with the safety profile of this combination from CLEOPATRA. The safety data from the all pertuzumab treated patient population (n=1412) have been reviewed, as have the safety data from the integrated data base relating to adverse events of particular interest. Interpretation of the integrated pertuzumab safety database is complicated by the fact that in this database pertuzumab has been either combined with various chemotherapeutic agents (primarily in doublet regimens) or administered as a single-agent.

Table 24: Summary of 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 AE	98.5%	99.9%	98.1%	98.1%	72.2%	98.9%	95.2%	94.3%	95.8%
Grade ≥ 3	72.8%	74.2%	72.9%	62.6%	6.5%	70.2%	18.1%	40.2%	53.3%
Related AE	96.2%	97.3%	97.2%	96.3%	67.6%	97.9%	79.5%	76.2%	86.9%
AE→disc	27.7%	29.2%	0	0.9%	1.9%	2.1%	3.6%	7.3%	12.9%
AE→int/mod	53.1%	60.0%	34.6%	32.7%	14.8%	43.6%	15.7%	11.9%	33.9%
AE→Rx	92.9%	95.6%	86.9%	79.4%	52.8%	84.0%	78.3%	81.1%	85.2%
SAE	26.2%	34.4%	16.8%	10.3%	3.7%	17.0%	14.5%	26.9%	25.7%
AE→death	2.5%	2.0%	0	0.9%	0	0	1.2%	1.3%	1.6%
Death on Trt	3.0%	2.5%	0	0.9%	0	0	2.4%	7.8%	4.5%
Death, PD	0.8%	0.2%	0	0	0	0	0	7.0%	2.9%
Death, other	2.3%	2.2%	0	0.9%	0	0	2.4%	0.8%	1.6%

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; AE→disc = any AE leading to

discontinuation of one or more study drugs; AE→int/mod = any AE leading to dose interruption/ modification; AE→Rx = any AE requiring treatment; AE→death = AE with outcome, death (i.e., Grade 5 AE; Death on Trt = all deaths within 42 days of last treatment; Death, PD = deaths due to progressive disease (a subset of deaths within 42 days of last treatment); Death, other = deaths due to causes other than progressive disease (a subset of deaths within 42 days of last treatment).

7.2. Pivotal phase III study (CLEOPATRA)

7.2.1. Overview

Patients who received any amount of any component of study treatment were included in the safety analysis population. A total of 804 patients (out of 808 randomized) started study treatment (397 in the Pla+T+D arm and 407 in the Ptz+T+D arm), and were included in the safety analysis population. The safety analyses included the following:

- **Incidence and severity of AEs and serious adverse events (SAEs).**

An AE was defined as any unfavourable and unintended sign (including an abnormal clinical or laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to treatment. Pre-existing conditions that worsened during the study were also considered to be AEs. Progression of underlying malignancy was not reported as an AE if it was clearly consistent with the suspected progression of the cancer as defined by RECIST or other pre-determined criteria. All AEs were graded for severity (Grade 1-5) according to the NCI-CTCAE (V3). Adverse events not listed in the CTCAE were graded as mild, moderate, severe, life-threatening, or fatal. The causal relationship of any of the three study drugs to the AE was assessed by the investigator as either Yes or No.

For all patients who received at least one dose of study medication, all non-cardiac, non-serious AEs (related and unrelated) were collected during the treatment period up to and including the treatment discontinuation visit, which was scheduled 28 to 42 days after the last dose of study medication. SAEs, defined per ICH criteria, underwent expedited reporting (within one working day of the investigator becoming aware of the event).

- **Incidence of symptomatic LVSD (CHF) and asymptomatic LVSD events**

Investigators were instructed to record symptomatic declines in left ventricular ejection fraction (LVEF) as symptomatic left ventricular systolic dysfunction (LVSD), and the term congestive heart failure (CHF) was not to be used in this study. Symptomatic LVSD was also to be reported as a single diagnosis and not as individual signs and symptoms. Patients with symptomatic LVSD were to be withdrawn from study treatment. Each case of LVSD was also to be reported as an SAE and graded according to NCI-CTCAE (V3) and NYHA classifications. NCI-CTCAE ≥ Grade 3 symptomatic LVSD was to be reported for up to 3 years after discontinuation of study treatment and followed until either resolution/stabilization/death, confirmation from the investigator that no further improvement could be expected, or completion of survival follow-up.

An asymptomatic decline in LVEF was to be reported as an AE only if this decline was at least 10 percentage points from baseline, and below 50%, or if it required treatment or led to discontinuation of study medication. An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment was to be reported in an expedited manner by using the SAE form, classifying the event as a Non-Serious Event of Special Interest. In both cases, investigators were requested to use the AE term LVSD and to grade the event according to NCI-CTCAE (V3).

The algorithm for continuation and discontinuation of pertuzumab/placebo and trastuzumab based on LVEF assessment is summarized in the dossier.

- **Cardiac events – adjudication by the cardiac review committee (CRC)**

Patients with potential cardiac events were identified by the sponsor for review by the CRC. These events included patients with symptomatic LVSD, patients who died on study due to peripheral oedema or myocardial infarction (other than progressive disease AEs), and patients initiating new cardiac medication. The CRC assigned potential cardiac events to the following categories: symptomatic LVSD (non-death); symptomatic LVSD (death); other cardiac non-death event; non-LVSD cardiac death; non-cardiac cardiovascular death; non cardiovascular death; probable cardiac death; and not evaluable.

- **Laboratory test abnormalities**

Treatment-emergent abnormal laboratory results which were clinically significant were to be reported as an AE. AEs were considered clinically significant if they accompanied clinical symptoms, resulted in a change in study medication, or required a change in concomitant therapy.

- **Events to monitor**

The study also assessed selected "adverse events to monitor" prospectively defined to address specific safety topics. These events were based on clinical and nonclinical data for pertuzumab, and the safety profile established for trastuzumab, monoclonal antibodies in general and potential effects associated with HER receptor inhibition. The database search was based on SMQs, as far as available, or prospectively defined Roche-standardized adverse event grouped terms (AEGTs).

- **Terminology**

For classification purposes, preferred terms (PTs) were assigned by the sponsor to the original terms entered on the eCRF, using the Medical Dictionary for Regulatory Activities (MedDRA [V4]) for AEs and diseases, and the International Non-proprietary Name (INN) drug terms and procedures dictionary for treatments and surgical and medical procedures.

7.2.2. Exposure

Patients were to receive study medication (Pla+T+D or Ptz+T+D) q3w until progressive disease (PD) or unacceptable toxicity. Patients could continue placebo/pertuzumab plus trastuzumab if docetaxel was discontinued due to unacceptable toxicity. However, if placebo/pertuzumab and/or trastuzumab were discontinued for toxicity all three study medications had to be stopped and the patient was withdrawn from the treatment phase of the study. In Cycle 1, placebo/pertuzumab was given on Day 1 followed by trastuzumab plus docetaxel on Day 2. In subsequent cycles, all three drugs were scheduled for the same day. It was recommended that docetaxel be given for at least 6 cycles.

A total of 804 patients started at least one cycle of study treatment; 397, Pla+T+D and 407, Ptz+T+D. By Cycle 16, a smaller proportion of patients in the Pla+T+D arm were still receiving treatment compared with the Ptz+T+D arm (n=188, 47% vs n=252, 62%, respectively). At the time of the data cut-off for the primary analysis, the median number of administered placebo/pertuzumab cycles was 15 (range: 1, 50) in the Pla+T+D arm, and 18 (range: 1, 56) in the Ptz+T+D arm, and the respective mean±SD number of administered cycles were 16.2±10.19 and 19.9±11.60. The difference between the arms was due to a greater number of early withdrawals from study treatment in the Pla+T+D arm, mainly due to the higher incidence of patients with PD. Post-hoc Kaplan-Meier analysis of the length of time on treatment in relation to disease progression as assessed by the Investigator showed that patients were treated up to the time of a PFS event for a median of 11.8 months in the Pla+T+D arm and 18.1 months in the Ptz+T+D arm.

7.2.2.1. Pertuzumab/placebo

The median total dose of pertuzumab in the Ptz+T+D arm was 7980 mg (range: 840, 23940 mg) compared with a median total dose of 6720 mg (range: 840, 21840) of placebo in the Pla+T+D

arm. Most of the pertuzumab or placebo infusions were administered without the need for delay, slowing down, interruption, or discontinuation (92.7%, Pla+T+D vs 93.0%, Ptz+T+D), and the proportion of these occurrences due to AEs was similar in the two treatment arms (3.3%, Pla+T+D vs 2.7%, Ptz+T+D). The number of cycles requiring a delay (defined as greater than 24 days between cycles based on the protocol-defined window) was similar in the two treatment arms (6.3%, Pla+T+D vs 5.8%, Ptz+T+D arm), and delays in both treatment arms were mostly less than 14 days. Pertuzumab/placebo infusions delayed, slowed down, interrupted or discontinued are summarized in the dossier.

7.2.2.2. Trastuzumab

Exposure to trastuzumab was similar to that of pertuzumab. This was to be expected since the protocol did not allow treatment to continue with only of the two medicines. A median of 15 cycles (range:1, 50) of trastuzumab was administered in the Pla+T+D arm (median total dose of 5814 mg; range 438 to 22100) compared with a median of 18 cycles (range: 1, 56) of trastuzumab in the Ptz+T+D arm (median total dose of 7714 mg; range 448 to 28916). The median dose of trastuzumab per cycle was similar in both treatment arms (403.9 mg [range: 242, 886], Pla+T+D vs 399.5 mg [range: 242, 769], Ptz+T+D). As for placebo/pertuzumab, from Cycle 10 onwards the proportion of patients receiving trastuzumab was notably higher in the Ptz+T+D arm than in the Pla+T+D arm. As for placebo/pertuzumab, nearly all trastuzumab infusions were administered without the need for delay, slowing down, interruption, or discontinuation (92.2%, Pla+T+D vs 92.9%, Ptz+T+D), and the majority of dose delays were less than 14 days. The proportion of cycles delayed, slowed down, interrupted or discontinued due to AEs was similar in the two treatment arms (3.6%, Pla+T+D vs 3.1%, Ptz+T+D). Trastuzumab infusions delayed, slowed down, interrupted or discontinued are summarized in the dossier.

7.2.2.3. Docetaxel

The initial docetaxel dose was 75 mg/m^2 for all patients and at the investigator's discretion could be escalated to 100 mg/m^2 after Cycle 1 in patients who tolerated the first infusion. A minimum of 6 cycles of docetaxel was recommended and no upper limit was specified. In both treatment arms, patients received a median of 8 cycles, ranging from 1 to 41 cycles in the Pla+T+D arm and from 1 to 35 cycles in the Ptz+T+D arm. The median dose of docetaxel per cycle was similar in the two treatment arms, 125 mg (range: 20, 307) in the Pla+T+D arm and 123 mg (range: 64, 244) in the Ptz+T+D arm. The median dose intensity was also similar in the two treatment arms, 24.8 mg/m^2/week (range: 4, 34) in the Pla+T+D arm and 24.6 mg/m^2/week (range: 12, 33) in the Ptz+T+D arm.

From Cycle 2 onwards, the majority of patients (> 85%) in both treatment arms were not escalated to the higher dose, due mainly to investigator discretion and standard clinical practice rather than toxicity. A higher proportion of patients in the Pla+T+D arm received 100 mg/m^2 at any cycle compared with patients in the Ptz+T+D arm (n=61, 15.4% vs n=48, 11.8%, respectively). The proportion of patients who received a dose of docetaxel lower than 75 mg/m^2 was 22.4% (n=89) in the Pla+T+D arm and 25.6% (n=104) in the Ptz+T+D arm. Overall, the majority of cycles of docetaxel administered in both treatment arms did not require delay, slowing down, interruption or discontinuation (88%, Pla+T+D vs 87.3%, Ptz+T+D), and the proportion of these occurrences due to AEs was similar in the two treatment arms (5.9%, Pla+T+D vs 5.0%, Ptz+T+D). Docetaxel infusions delayed, slowed down, interrupted or discontinued are summarized in the dossier.

7.2.3. Adverse events

7.2.3.1. Overview of adverse events

AEs were reported separately for the treatment period and the post-treatment follow-up period. The treatment period was defined as starting on Study Day 1 and ending 42 days after the last dose of study treatment. According to the protocol, only specific AEs were collected during the post-treatment phase, defined as starting more than 42 days after discontinuation of all study

medication. The overall incidence of AEs occurring in patients during the treatment period was balanced between the treatment arms (98.5%, Pla+T+D vs 99.8%, Ptz+T+D), although the total number of AEs reported in the Ptz+T+D arm was higher than in the Pla+T+D arm (6048 vs 5300).

7.2.3.2. Commonly occurring adverse events by body system (SOC)

The SOCs in which the most common AEs (≥ 10% of patients in either treatment arm) were reported (Pla+T+D vs Ptz+T+D) included:

- General Disorders and Administration Site Conditions (81.9% vs 83.3%): most frequently fatigue (36.8% vs 37.6%), asthenia (30.2% vs 26.0%), peripheral oedema (30.0% vs 23.1%), mucosal inflammation (19.9% vs 27.8%), pyrexia (17.9% vs 18.7%) and oedema (12.6% vs 11.3%).
- Skin and Subcutaneous Tissue Disorders (78.6% vs 83.3%): most frequently alopecia (60.5% vs 60.9%), rash (24.2% vs 33.7%), nail disorder (22.9% vs 22.9%), pruritus (10.1% vs 14.0%) and dry skin (4.3% vs 10.6%).
- Gastrointestinal Disorders (76.1% vs 84.0%): most frequently diarrhoea (46.3% vs 66.8%), nausea (41.6% vs 42.3%), vomiting (23.9% vs 24.1%), constipation (24.9% vs 15.0%), stomatitis (15.4% vs 18.9%), abdominal pain (12.3% vs 14.0%) and dyspepsia (12.1% vs 12.0%).
- Blood and Lymphatic System Disorder (62.7% vs 69.0%): most frequently neutropenia (49.6% vs 52.8%), anaemia (18.9% vs 23.1%), leukopenia (20.4% vs 18.2%) and febrile neutropenia (7.6% vs 13.8%).
- Nervous System Disorders (61.2% vs 65.6%): most frequently peripheral neuropathy (20.2% vs 21.1%), headache (16.9% vs 20.9%), dysgeusia (15.6% vs 18.4%), peripheral sensory neuropathy (14.1% vs 12.0%), dizziness (12.1% vs 12.5%) and paraesthesia (10.1% vs 9.1%).
- Musculoskeletal and Connective Tissue Disorders (61.2% vs 59.5%): most frequently myalgia (23.9% vs 22.9%), arthralgia (16.1% vs 15.5%), pain in extremity (11.8% vs 15.2%) and back pain (11.6% vs 13.5%).
- Infections and Infestations (56.2% vs 61.7%): most frequently upper respiratory tract infection (13.4% vs 16.7%) and nasopharyngitis (12.8% vs 11.8%).
- Respiratory, Thoracic and Mediastinal Disorders (48.1% vs 48.6%): most frequently cough (18.6% vs 21.4%) and dyspnoea (15.6% vs 14.0%).
- Metabolism and Nutrition Disorders (38.0% vs 40.0%): most frequently decreased appetite (26.4% vs 29.2%).
- Eye Disorders (23.7% vs 32.2%): most frequently increased lacrimation (13.9% vs 14.0%).

Cardiac disorders (SOC) occurred marginally more frequently in patients in the Pla+T+D arm (16.4%) than in the Ptz+T+D arm (14.5%). The most common cardiac disorder AEs (Pla+T+D vs Ptz+T+D) were LVD (8.3% vs 4.4%), tachycardia (3.0% vs 2.5%), palpitations (2.5 vs 2.7%), and pericardial effusion (1.5% vs 1.2%). None of the other cardiac disorder AEs occurred in more than 1% of patients in either of the two treatment arms.

Renal and urinary disorders (SOC) occurred more frequently in patients in the Ptz+T+D arm (10.6%) than in the Pla+T+D arm (7.6%), primarily due to the increased incidence of dysuria (5.4% vs 2.3%, respectively). None of the other renal and urinary disorder AEs occurred in more than 1% of patients in either of the two treatment arms. There was no difference between the two arms in the proportion of patients with increased “blood creatinine” (1.5%, Ptz+T+D vs 0.7%, Pla+T+D).

Hepatobiliary disorders (SOC) occurred in a similar proportion of patients in both treatment arms (2.3%, Pla+T+D vs 2.5%, Ptz+T+D), and no hepatobiliary AEs occurred with an incidence of more than 1% in patients in either of the two treatment arms. Increases in hepatic transaminase AEs occurred with similar frequencies in both treatment arms.

7.2.3.3. Commonly occurring adverse events by preferred terms

AEs with an incidence rate of at least 5% in patients in either treatment arm are summarized in the dossier. AEs occurring in at least 5% of patients in either treatment arm, and at least 5% more frequently in the Ptz+T+D arm compared with the Pla+T+D arm were: diarrhoea (66.8% vs 46.3%); rash (33.7% vs 24.2%); mucosal inflammation (27.8% vs 19.9%); febrile neutropenia (13.8% vs 7.6%); and dry skin (10.6% vs 4.3%). AEs occurring in at least 5% of patients in either treatment arms, and at least 5% more frequently in the Pla+T+D arm compared with the Ptz+T+D arm were peripheral oedema (30.0% vs 23.1%) and constipation (24.9% vs 15.0%). The percentage differences (≥ 2%) between the two treatment arms in the incidence of AEs (PT) are summarized. The majority of commonly reported AEs occurred in ≥ 2% patients in the Ptz+T+D arm than in the Pla+T+D arm. Approximately 88% of AEs in both treatment arms were Grade 1 or 2 in severity; 4640/5300 AEs (87.5%), Pla+T+D vs 5298/6048 AEs (87.6%) Ptz+T+D.

7.2.3.4. Grade ≥ 3 adverse events

The proportion of patients with at least one Grade ≥ 3 AE (i.e., 3, 4, or 5) was similar in the two treatment arms: 72.8% (289 patients), 576 events, Pla+T+D vs 74.2% (302 patients), 637 events, Ptz+T+D. The majority of these AEs were in the SOC "blood and lymphatic system disorders". Grade ≥ 3 AEs occurring in at least 1% of patients in either treatment arm are summarized in in the dossier and Grade ≥ 3 AEs occurring in at least 5% in either treatment arm are summarized below in Table 25.

Table 25: CLEOPATRA - Summary of Grade 3, 4 or 5 AEs with an incidence rate of at least 5% in at least one of the treatment arms; safety analysis.

Adverse Event	Placebo + Trastuzumab + Docetaxel N = 397 No. (%)	Pertuzumab + Trastuzumab + Docetaxel N = 407 No. (%)
NEUTROPENIA	182 (45.8)	199 (48.9)
LEUKOPENIA	58 (14.6)	50 (12.3)
FEBRILE NEUTROPENIA	30 (7.6)	56 (13.8)
DIARRHOEA	20 (5.0)	32 (7.9)

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.

The incidence of the following Grade ≥ 3 AEs was higher in patients in the Ptz+T+D arm compared with the Pla+T+D arm (≥ 2% difference): neutropenia (48.9% vs 45.8%); febrile neutropenia (13.8% vs 7.6%); and diarrhoea (7.9% vs 5.0%). However, the incidence of Grade ≥ 3 leukopenia was higher in the Pla+T+D arm (14.6%) than in the Ptz+T+D arm (12.3%). Despite the greater incidence of Grade ≥ 3 AEs of neutropenia and febrile neutropenia in the Ptz+T+D arm compared with the Pla+T+D arm, the incidence of Grade ≥ 3 infections and infestations was similar in the treatment arms (11.1% vs 10.1%, respectively).

The proportion of patients experiencing Grade ≥ 3 cardiac disorders (SOC) was higher in the Pla+T+D arm (3.8%, n=15) than in the Ptz+T+D arm (1.5%, n=6), and LVD was the most commonly reported cardiac Grade ≥ 3 AE (2.8%, n=11 vs 1.2%, n=5, respectively). Despite the increased incidence (all grades) in the Ptz+T+D arm (vs Pla+T+D) of mucosal inflammation (27.8% vs 19.9%) and rash (33.7% vs 24.2%), Grade ≥ 3 AEs were reported infrequently and with similar frequencies in the two treatment arms for both mucosal inflammation (1.5%, n=6, Ptz+T+D vs 1.0%, n=4, Pla+T+D) and rash (0.7%, n=3, Ptz+T+D vs 0.8%, n=3, Pla+T+D). Grade ≥

3 interstitial lung disease was reported in 2 (0.5%) patients in the Ptz+T+D arm and no patients in the Pla+T+D arm.

7.2.3.5. Treatment-related adverse events

The majority of patients in both treatment arms experienced at least one AE considered by the investigator to be related to treatment (96.2%, 382 patients, 3248 events, Pla+T+D vs 97.3%, 396 patients, 3822 events, Ptz+T+D). The most commonly reported AEs occurring in at least 20% of patients in either arm and considered by the investigator to be treatment-related (Pla+T+D vs Ptz+T+D) were: alopecia (54.7%, n=217 vs 57.0%, n=232); diarrhoea (38.3%, n=152 vs 57.7%, n=235); nausea (36.0%, n=143 vs 36.6%, n=149); neutropenia (47.4%, n=188 vs 50.1%, n=204); fatigue (30.7%, n=122 vs 31.0%, n=126); rash (19.1%, n=76 vs 27.0%, n=110); asthenia (25.9%, n=103 vs 23.1%, n=94); mucosal inflammation (17.6%, n=70 vs 25.6%, n=104); decreased appetite (23.2%, n=92 vs 25.6%, n=104); nail disorder (20.7%, n=82 vs 21.4%, n=87); and myalgia (20.4%, n=81 vs 19.2%, n=78).

The proportion of patients who experienced Grade ≥ 3 AEs considered by the investigator to be treatment-related was higher in the Ptz+T+D arm (67.6%, 275 patients, 489 events) than in the Pla+T+D arm (64.7%, 257 patients, 425 events). The majority of these AEs were "blood and lymphatic system disorders" (51.4%, n=204, Pla+T+D vs 57.0%, n=232, Ptz+T+D arm), particularly neutropenia (43.3%, n=172, Pla+T+D vs 46.4%, n=189, Ptz+T+D). Other common Grade ≥ 3 AEs considered related to trial treatment (Pla+T+D vs Ptz+T+D) by the investigator were leukopenia (13.1%, n=52 vs 10.8%, n=44), febrile neutropenia (7.3%, n=29 vs 13.8%, n=56), diarrhoea (3.5%, n=14 vs 6.1%, n=25), and anaemia (2.5%, n=10 vs 2.2%, n=9).

7.2.3.6. Adverse events reported in the post-treatment period

The post-treatment period was defined as starting more than 42 days after discontinuation of study medication. According to the protocol, the following AEs were to be reported during this period: cardiac events (regardless of causality or seriousness) up to one year; treatment-related SAEs up to one year; and symptomatic LVD (regardless of causality) up to three years. In the post-treatment period at the time of the clinical cut-off date, 8 (2.0%) patients in the Pla+T+D arm had experienced 10 AEs compared with 9 (2.2%) patients in the Ptz+T+D arm who had experienced 15 AEs. There were no notable differences between the two treatment arms as regards AEs reported in the post-treatment period.

7.2.3.7. Infusion reactions (adverse events)

Infusion reactions occurred more commonly in the first treatment cycle than in any of the other treatment cycles. AEs starting during a placebo/pertuzumab infusion give the most accurate assessment of acute infusion reactions related to infusions and avoid including events that are associated with trastuzumab and docetaxel infusions when these are given on the same day as placebo/pertuzumab (all cycles except Cycle 1). However, AEs assessed during the infusion will miss events that occur soon after cessation of an infusion and might result in underestimating the incidence of infusion related reactions. AEs starting during a placebo/pertuzumab infusion occurred more frequently in the pertuzumab arm than in the placebo, and were predominantly Grade 1 or 2 events.

In the first cycle, infusion reactions were reported **during the placebo/pertuzumab infusion** in 2.0% of patients in the Pla+T+D arm and 3.9% of patients in the Ptz+T+D arm. During the first placebo infusion, 8 patients experienced 10 events including nausea, asthenia, chills, dysgeusia, hypersensitivity, hypertension, peripheral motor neuropathy, peripheral sensory neuropathy, and pyrexia. During the first pertuzumab infusion, 16 patients experienced 19 events including chills, dyspnoea, erythema, hypersensitivity, chest pain, dizziness, drug hypersensitivity, flushing, infusion-related reaction, metastases to skin (this was reported by the Investigator as itching of skin metastases), nausea, pyrexia, restlessness, throat irritation and visual impairment

In the first cycle, infusion reactions reported **on the day of the placebo/perfusion infusion** were reported in 14.6% of patients in the Pla+T+D arm and 19.2% of patients in the Ptz+T+D arm. The most frequently reported AEs (≥ 1% of patients) on the day of the placebo/pertuzumab infusion in Cycle 1 were nausea, myalgia, fatigue, insomnia, constipation and decreased appetite in the Pla+T+D arm, and nausea, pyrexia, diarrhoea, chills, fatigue, headaches, asthenia, hypersensitivity and vomiting in the Ptz+T+D arm. Of these, only pyrexia was reported more frequently (≥ 2% difference) in the Ptz+T+D arm (2.7% vs 0.5%).

7.2.4. Deaths and other serious adverse events

7.2.4.1. Deaths

By the clinical data cut-off date, 163 deaths had been reported in the study (see Table 26, below). There were more deaths in the Pla+T+D arm (n=94, 23.7%) than in the Ptz+T+D arm (n=69, 17.0%). The most frequent cause of death was PD, and this was notably higher in the Pla+T+D arm (n=81, 20.4%) than in Ptz+T+D arm (n=57, 14.0%). Deaths due to causes other than PD were generally well balanced between the two treatment arms.

Table 26: CLEOPATRA – Summary of deaths.

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)	-

Deaths due to AEs were reported in a similar proportion of patients in the Pla+T+D arm (n=10, 2.5%) and the Ptz+T+D arm (n=8, 2.0%), with 17 of the 18 deaths (19 AEs) being reported in the treatment period and the remaining death being reported in the post-treatment period. The majority of AEs leading to death were either cardiovascular events or infection and/or febrile neutropenia. The incidence of death due to infection and/or febrile neutropenia was similar in both treatment arms (3 patients, 4 events, Pla+T+D vs 5 patients, 5 events, Ptz+T+D). There were three cardiovascular related deaths, all in the Pla+T+D arm (2 x myocardial infarctions and 1 x cerebrovascular accident). There were 12 AEs in 11 patients considered related to treatment by the investigator (6 patients, 7 AEs, Pla+T+D vs 5 patients, 5 AEs, Ptz+T+D). In addition to the 18 deaths due to AEs, there were an additional 7 deaths for which no cause was reported.

7.2.4.2. Other serious adverse events

SAEs occurred more frequently in patients in the Ptz+T+D arm (34.4%, n=140) than in the Pla+T+D arm (26.2%, n=104). Blood and lymphatic system disorders were the most frequently reported SAEs in both treatment arms and these occurred more frequently in patients in the Ptz+T+D arm (16.0%, n=65) than in the Pla+T+D arm (10.6%, n=42). The difference between the two treatment arms was mainly due to a higher incidence of febrile neutropenia in patients in the Ptz+T+D arm (11.3%, n=46) than in the Pla+T+D arm (5.0%, n=20). Except for one case of febrile neutropenia in the Pla+T+D arm (considered related to a wound infection), all SAEs of febrile neutropenia were assessed by the investigator as treatment-related. Following blood and

lymphatic system disorders, the next most frequently reported group of SAEs was infections and infestations and these were also reported more commonly in the Ptz+T+D arm (10.8%, n=44) than in the Pla+T+D arm (7.3%, n=29). However, no single SAE accounted for the difference in incidence between the two arms and single SAEs involved no more than 2% of patients in either arm.

Gastrointestinal SAEs occurred in a similar proportion of patients in the Pla+T+D arm (4.3%, n=17) and the Ptz+T+D arm (4.4%, n=18), and the most frequently reported SAE in both arms was diarrhoea which was reported more commonly in the Ptz+T+D arm (2.7%, n=11) than in the Pla+T+D arm (1.3%, n=5). General and administration site SAEs were more frequently reported in the Ptz+T+D arm (3.4%. n=14) than in the Pla+T+D arm (2.0%, n=8), as were respiratory, thoracic and mediastinal SAEs (3.2%, n=13, Ptz+T+D vs 2.0%, n=8, Pla+T+D).

The proportion of patients who experienced cardiac SAEs was higher in the Pla+T+D arm (3.3%, 13 patients, 13 events) than in the Ptz+T+D arm (1.2%, 5 patients, 5 events). There were two SAEs of mucosal inflammation (one in each arm) and two SAEs of interstitial lung disease (ILD), both in the Ptz+T+D arm.

7.2.5. Adverse events and laboratory abnormalities leading to withdrawal

According to the protocol, patients could continue placebo/pertuzumab plus trastuzumab if docetaxel was discontinued due to unacceptable toxicity. However, if placebo/pertuzumab and/or trastuzumab were discontinued for toxicity, all three study medications were stopped and the patient was withdrawn from the treatment phase of the study. AEs leading to discontinuation of one or more of the study drugs were reported in a similar proportion of patients in both treatment arms (27.7%, n=110, Pla+T+D vs 29.2%, n=119, Ptz+T+D).

7.2.5.1. Discontinuations of all three study medications

AEs leading to discontinuation of all three study medication, excluding events leading to discontinuation of docetaxel only, were reported in a similar proportion of patients in the Pla+T+D arm (5.3%, 21 patients, 22 events) and the Ptz+T+D arm (6.1%, 25 patients, 26 events). The majority of the 48 events (total) were cardiac disorders (2.5%, 10 patients, 10 events, Ptz+T+D vs 2.0%, 8 patients, 8 events, Pla+T+D). The most commonly reported AE in patients leading to discontinuation of all three study medications, excluding events leading to discontinuation of docetaxel only, was LVD (2.0%, n=8, Pla+T+D vs 1.5%, n=6). No other AEs occurred in ≥ 2% of patients in either treatment arm. Of the total 48 events, all were considered to be treatment-related with the exception of 6 events (postoperative wound infection, fluid retention, sepsis, haematoma, cerebrovascular accident, and rash). AEs leading to discontinuation of study medication (excluding events leading to discontinuation of docetaxel only) are summarized in the dossier.

7.2.5.2. Discontinuation of docetaxel alone

AEs leading to discontinuation of docetaxel were reported more frequently than AEs leading to discontinuation of all three study medications. AEs leading to discontinuation of docetaxel only were reported with a similar frequency in the two treatment arms (23.2%, 92 patients, 98 events, Pla+T+D vs 23.6%, 96 patients, 111 events). AEs leading to discontinuation of docetaxel only and reported in ≥ 1 % of patients in any arm (Pla+T+D vs Ptz+T+D) in decreasing order of frequency in the Ptz+T+D arm were: peripheral neuropathy (2.5%, n=10 vs 3.4%, n=14); oedema (3.0%, n=12 vs 3.2%, n=13); fatigue (2.0%, n=8 vs 2.2%, n=9); neutropenia (1.8%, n=7 vs 1.7%, n=7); peripheral sensory neuropathy (1.0%, n=4 vs 1.5%, n=6); nail disorder (0.8%, n=3 vs 1.5%, n=6); peripheral oedema (2.5%, n=10 vs 1.0%, n=4); febrile neutropenia (0% vs 1.0%, n=4); diarrhoea (0.3%, n=1 vs 1.0%, n=4); and pleural effusion (1.5%, n=6 vs 0.5%, n=2). The majority of events reported as leading to discontinuation of docetaxel (alone) were assessed by the investigator to be treatment-related (19.1%, 76 patients, 81 events, Pla+T+D vs 21.9%, 89 patients, 104 events). The most frequently occurring of these events were oedema

(2.8% [n=11], Pla+T+D vs 3.2% [n=13], Ptz+T+D), and peripheral neuropathy (2.3% [n=9], Pla+T+D vs 3.2% [n=13], Ptz+T+D arm).

7.2.6. Adverse events after discontinuing docetaxel treatment

The cut-off period for AEs starting after discontinuation of docetaxel was defined as starting at the date of the next placebo/pertuzumab or trastuzumab infusion after the last dose of docetaxel. In both treatment arms, the proportion of patients with AEs starting after discontinuation of docetaxel was lower than AEs occurring on triplet therapy. The proportion of patients with AEs starting after discontinuation of docetaxel was marginally higher in the Ptz+T+D arm than in the Pla+T+D arm (83.6%, 249 patients, 1462 events vs 79.2%, 202 patients, 1005 events). However, more patients remained on treatment in the Ptz+T+D arm (n=298) than in the Pla+T+D (n=255) arm. Events reported after discontinuation of docetaxel were mainly of Grade 1 or 2 severity. The incidence of Grade ≥ 3 events was balanced in the two treatment arms, and none occurred in ≥ 2% of patients in the Ptz+T+D arm.

AEs occurring in ≥ 5% of patients in either arm (Pla+T+D vs Ptz+T+D) and with decreasing order of frequency in the Ptz+T+D arm were: diarrhoea (9.0% vs 19.1%); upper respiratory infection (9.0% vs 12.8%); rash (6.3% vs 11.7%); headache (9.8% vs 11.4%); fatigue (8.6% vs 11.1%); pain in extremity (5.9% vs 10.1%); asthenia (7.8% vs 9.7%); cough (9.4% vs 9.7%); nasopharyngitis (9.8% vs 9.4%); back pain (7.5% vs 9.4%); pruritus (5.9% vs 8.7%); oedema peripheral (10.2% vs 7.4%); nausea (9.8% vs 7.4%); dizziness (6.7% vs 6.7%); arthralgia (6.3% vs 6.4%); decreased appetite (2.7% vs 6.4%); vomiting (5.5% vs 6.0%); hypertension (3.9% vs 5.7%); neuropathy peripheral (3.1% vs 5.4%); abdominal pain (3.9% vs 5.0%); insomnia (5.5% vs 5.0%); myalgia (4.7% vs 5.0%); dyspnoea (5.9% vs 4.4%); LVD (6.7% vs 4.0%); constipation (5.9% vs 3.7%); and musculoskeletal pain (5.1% vs 3.7%).

7.2.7. Adverse events leading to dose interruptions/modifications

Dose interruption or modification was the term used to describe slowing down, temporary interruption or discontinuation of the current infusion, or reduction or delay of the subsequent dose (dose reductions were only allowed for docetaxel). AEs leading to dose interruption or modification of any of the three study medications were reported more frequently in patients in the Ptz+T+D arm (60.0%, n=244) than in the Pla+T+D arm (53.1%, n=211). AEs reported in ≥ 2% of patients in either treatment arm and more commonly in the Ptz+T+D arm (vs Pla+T+D) were: febrile neutropenia (7.6%, n=31 vs 5.0%, n=20); diarrhoea (5.4%, n=22 vs 1.8%, n=7); and hypersensitivity (4.4%, n=18 vs 2.3%, n=9). AEs leading to dose interruptions/modifications and occurring in ≥ 2% of patients in either treatment arm are summarized in the dossier. The proportion of patients experiencing SAEs that resulted in dose interruption/modification was higher in the Ptz+T+D arm (16.2%) than in the Pla+T+D arm (12.1%), and the most common event was febrile neutropenia (6.1% vs 3.3%, respectively). Other SAEs occurred in less than 2% of patients (i.e., less than 6 patients) in either arm.

7.2.8. AEs of special interest including "adverse events to monitor".

7.2.8.1. Cardiac toxicity

7.2.8.1.1. Cardiac disorders (SOC)

The proportion of patients with cardiac disorders (SOC) reported during study treatment was similar in the two treatment arms (16.4%, n=65, Pla+T+D vs 14.5%, n=59, Ptz+T+D). Cardiac AEs occurring in ≥ 2% of patients in either of the two treatment arms (Pla+T+D vs Ptz+T+D) were: LVD (8.3%, n=33 vs 4.4%, n=18); tachycardia (3.0%, n=12 vs 2.5%, n=10); and palpitations (2.5%, n=10 vs 2.7%, n=11). The proportion of patients experiencing cardiac disorder Grade ≥ 3 events was higher in the Pla+T+D arm (3.8%) than in the Ptz+T+D arm (1.5%), and LVD Grade ≥ 3 was reported more frequently in the Pla+T+D arm (2.8%) than in the Ptz +T+D arm (1.2%).

7.2.8.1.2. Left ventricular dysfunction

The terms left ventricular systolic dysfunction (LVSD) and left ventricular dysfunction (LVD) were used interchangeably in the CSR, and the MedDRA codes LVSD events to LVD. Symptomatic LVSD assessed by the investigator was identified as cardiac failure SAE ("AE to monitor") based on the SMQ cardiac failure [wide]). The CRC also adjudicated on LVSD. The distribution of patients with symptomatic LVSD adjudicated by the CRC and assessed by the investigator), LVD (AEs preferred term), and SAEs suggestive of CHF ("AE event to monitor") are summarized below in Table 27.

Table 27: CLEOPATRA –LVD, and SAEs suggestive of CHF ("AE to monitor")

	Total (N=804)	Placebo + Trastuzumab + Docetaxel (N=397)	Pertuzumab + Trastuzumab + Docetaxel (N=407)
Number of Patients with Events to Monitor			
Symptomatic LVSD adjudicated by the CRC	8 (1.0%)	4 (1.0%)	4 (1.0%)
NYHA class III/IV	3 (0.4%)	0 (0.0%)	3 (0.7%)
Symptomatic LVSD assessed by the Investigator	11 (1.4%)	7 (1.8%)	4 (1.0%)
NYHA class III/IV	7 (0.9%)	4 (1.0%)	3 (0.7%)
Left Ventricular Dysfunction[1]	51 (6.3%)	33 (8.3%)	18 (4.4%)
NCI-CTCAE grade >= 3	16 (2.0%)	11 (2.8%)	5 (1.2%)
SAE suggestive of CHF[2]	11 (1.4%)	7 (1.8%)	4 (1.0%)

[1] Left ventricular Dysfunction AEs identified by selecting the PT "Left Ventricular Dysfunction"
[2] AEs identified using the appropriate AEGT or SMQ - see glossary L_UD09_AEGT for a more detailed description

The incidence of all grade LVD (AE, PT) was higher in the Pla+T+D arm (8.3%) than in the Ptz arm (4.4%), as was the incidence of Grade ≥ 3 LVD (AE, PT) (2.8% vs 1.2%, respectively). Asymptomatic LVD AEs were reported more frequently in the Pla+T+D arm (5.5%, n=22) than in the Ptz+T+D arm (3.2%, n=13), as were reports of asymptomatic LVD requiring treatment (n=9, 2.3% vs n=7, 1.7%, respectively). Asymptomatic LVD leading to study discontinuation were reported in 2 patients in each treatment arm. None of the reported LVD events had a fatal outcome.

SAEs suggestive of CHF ("AE to monitor") were reported in 1.8% of patients in the Pla+T+D arm and 1.0% of patients in the Ptz+T+D arm, all events were considered by the investigators to be treatment related. At the time of the clinical data cut-off, the events had resolved in 5 out of 7 patients in the Pla+T+D arm, and in 3 out of 4 patients in the Ptz+T+D arm.

The CRC adjudicated LVSD to have occurred in 1.0% of patients in each of the two treatment arms, and identified NYHA class III/IV disease in 0.7% of patients in the Ptz+T+D arm and no patients in the Pla+T+D arm.

The study included an assessment of pre-defined baseline characteristics considered to be possible risk factors for LVSD in the 11 patients who developed symptomatic LVSD (i.e., prior anthracycline, trastuzumab or radiation exposure, age, smoking status, diabetes mellitus, hypertension and other cardiac conditions or medication). All of the patients who developed symptomatic LVSD had at least one of these potential risk factors. Most patients had received prior anthracyclines or radiotherapy or both, and only 2 patients had not received such treatments. Overall, patients who developed symptomatic LVSD had similar baseline characteristics to the overall study population, apart from a notably higher incidence of previous anthracycline therapy and radiotherapy to the thoracic area. Eight (8) of the 11 patients (72.7%) who developed symptomatic LVSD had been previously treated with anthracyclines and 8 (72.7%) had been previously treated with radiotherapy to the thoracic area, compared with 38.9% (anthracyclines) and 47% (radiotherapy) of patients in the overall study population.

7.2.8.1.3. Left ventricular ejection fraction (LVEF)

In order to enter the study, patients required a LVEF of at least 50%. The mean LVEF at baseline was 65.6% in the Pla+T+D arm (n=394) and 64.8% in the Ptz+T+D arm (n=405) (range 50% to 88%; both arms). The mean worst on treatment change from baseline in the Pla+T+D arm (n=376) was -6.8% (range: -32, 26) in the Pla+T+D arm and -6.2% (range: -39, 14) in the Ptz+T+D arm (n=391); p=0.3015. The worst on treatment LVEF < 40% was reported in 3 (0.8%) patients in the Pla+T+D arm and 3 (0.7%) patients in the Ptz+T+D arm. The proportion of patients with worst on treatment LVEF < 50% and a reduction from baseline of ≥ 10% points was 6.6% (n=25) in the Pla+T+D arm and 3.8% (n=15) in the Ptz+T+D arm. Changes in LVEF from baseline over time are summarized in the dossier.

7.2.8.1.4. Review of cardiac data by the CRC

Data from 329 patients (82.9%) in the Pla+T+D arm and 320 patients (78.6%) in the Ptz+T+D arm were reviewed by the CRC. Symptomatic LVSD was identified by 1.0% (n=4) of patients in each treatment arm. At the time of the clinical data cut-off date, CRC adjudicated symptomatic LVSD had resolved in 3 of the 8 patients reported to have experienced this event (2/4, Pla+T+D vs 1/4, Ptz+T+D), and none of the events had a fatal outcome. CRC assessments of symptomatic LVSD did not coincide with investigator assessments. The CRC agreed with the investigator for 2 patients in the Pla+T+D arm and for all 4 patients in the Ptz+T+D arm. However, the investigator assessed 5 additional patients in the Pla+T+D arm as experiencing symptomatic LVSD, and the CRC assessed 2 additional patients in the Pla+T+D arm as experiencing symptomatic LVSD. According to the CRC, there were more cases of NYHA Class III/IV dysfunction in the Ptz+T+D arm (3 patients; 0.7%) than in the Pla+T+D arm (no patients). The CRC considered that there were 3 probable cardiac deaths in the Pla+T+D arm and 2 in the Ptz+T+D arm. All cardiac events determine by the CRC are summarized in the dossier.

7.2.8.1.5. QT prolongation events ("AE to monitor")

QT prolongation ("AE to monitor") events included SMQ (wide) "Torsade de pointes / QT prolongation". The incidence of QT prolongation ("AE to monitor") was comparable in the two treatment arms (1.3%, Pla+T+D vs 2.0%, Ptz+T+D) (see Table 28, below). Of the 13 events, 2 were SAEs (1 case of syncope and 1 case of ventricular fibrillation resulting in discontinuation of study treatment). After adjusting for the higher exposure in the patients receiving pertuzumab, QT prolongation ("AE to monitor") events per patient-year were estimated to be 0.01 in the Pla+T+D arm and 0.02 in the Ptz+T+D arm.

Table 28: CLEOPATRA – QT prolongation (SMQ) AEs; safety analysis.

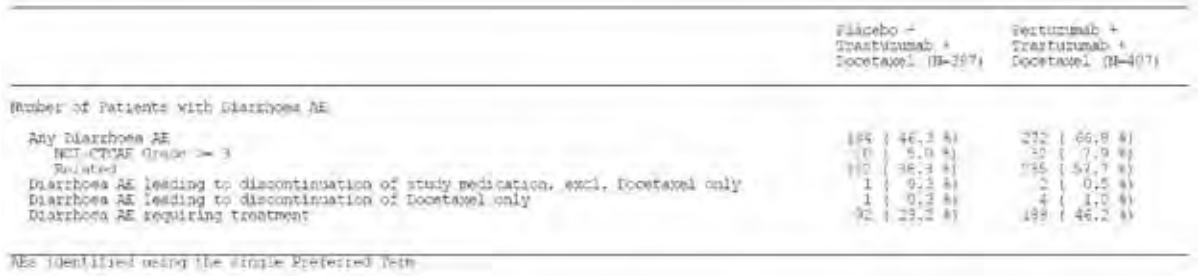
Body System/ Adverse Event	Placebo + Trastuzumab + Docetaxel N = 391 No. (%)	Pertuzumab + Trastuzumab + Docetaxel N = 407 No. (%)
ALL BODY SYSTEMS		
Total Pts With at Least one AE	5 (1.3)	8 (2.0)
Total Number of AEs	5	8
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	4 (1.0)	4 (1.0)
SYNCOPE	4 (1.0)	4 (1.0)
Total Number of AEs	4	4
INVESTIGATIONS		
Total Pts With at Least one AE	1 (0.3)	2 (0.5)
ELECTROCARDIOGRAM QT PROLONGED	1 (0.3)	2 (0.5)
Total Number of AEs	1	2
CARDIAC DISORDERS		
Total Pts With at Least one AE	-	2 (0.5)
VENTRICULAR ARRHYTHMIA	-	1 (0.2)
VENTRICULAR FIBRILLATION	-	1 (0.2)
Total Number of AEs	-	2

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. QT prolongation AEs identified using the SMQ (wide) 'Torsade de pointes/QT prolongation'.

7.2.8.2. Diarrhoea ("AE to monitor")

Diarrhoea as an "AE to monitor" (i.e., PT diarrhoea) is summarized below in Table 29. Diarrhoea occurred more frequently in patients in the Ptz+T+D arm (66.8%, n=272) than in the Pla+T+D arm (46.3%, n=184). During the study treatment period, 389 episodes of diarrhoea were reported in patients in the Pla+T+D arm and 817 episodes in patients in the Ptz+T+D arm (mean episodes per patient 2.1 vs 3.0, respectively; median 2.0 episodes per patient in both arms). The majority of episodes occurred in the first three treatment cycles, and < 10% of patients in either treatment arm experienced diarrhoea from Cycle 7 onwards and < 5% of patients from Cycle 10 onwards. The median time to first episode was shorter in the Ptz+T+D arm (7 days) than in Pla+T+D arm (22 days). Most of the episodes were Grade 1 or 2 in severity, but more Grade ≥ 3 episodes were recorded in the Ptz+T+D arm (32 episodes) than in the Pla+T+D arm (20 episodes). On average, episodes of diarrhoea lasted longer in the Ptz+T+D arm than in the Pla+T+D arm, with the median duration of the longest episode being 8 days in the Pla+T+D arm and 17 days in the Ptz+T+D arm. About twice as many patients in the Ptz+T+D arm (46.2%) required treatment for diarrhoea than patients in the Pla+T+D arm (23.2%).

Table 29: CLEOPATRA - Diarrhoea as an AE to monitors (single PT of diarrhoea).



	Placebo + Trastuzumab + Docetaxel (N=397)	Pertuzumab + Trastuzumab + Docetaxel (N=407)
Number of Patients with Diarrhoea AE		
Any Diarrhoea AE	184 (46.3 %)	272 (66.8 %)
NCI-CTCAE Grade >= 3	20 (5.0 %)	32 (7.9 %)
Related	153 (38.5 %)	235 (57.7 %)
Diarrhoea AE leading to discontinuation of study medication, excl. Docetaxel only	1 (0.3 %)	2 (0.5 %)
Diarrhoea AE leading to discontinuation of Docetaxel only	1 (0.3 %)	4 (1.0 %)
Diarrhoea AE requiring treatment	92 (23.2 %)	189 (46.2 %)

AEs identified using the Single Preferred Term

7.2.8.3. Rash ("AE to monitor")

Rash "AE to monitor" identified by a ROCHE AEGT for EGFR-association rash is summarized below in Table 30. Rash (AEGT) occurred more frequently in patients in the Ptz+T+D arm (45.2%, n=184) than in patients in the Pla+T+D arm (36.0%, n=143), and "rash" was the most frequently reported event (33.7% vs 24.2%, respectively) followed by erythema (5.4% vs 4.8%, respectively) and acne (2.5% vs 2.3%, respectively). Infectious rash (PT coded in the SOC "Infections and infestations") also occurred more commonly in patients in the Ptz+T+D arm (5.7%, n=23) than in the Pla+T+D arm (1.5%, n=6). AEs of Rash occurred most commonly during the first two treatment cycles and decreased in number with subsequent cycles. By Cycle 10, < 2% of patients in either treatment arm experienced any form of rash. The majority of AEs were of Grade 1 or 2 severity, and only 5 (1.3%) patients in the Pla+T+D arm and 11 (2.7%) patients in the Ptz+T+D arm experienced Grade 3 events. The median number of episodes per patient was 1.0 for the Pla+T+D arm and 2.0 for the Ptz+T+D arm, with a median duration of 48 days and 64 days, respectively, for all episodes.

Table 30: CLEOPATRA - Rash (identified by a Roche AEGT for EGFR-associated rash).

	Placebo + Trastuzumab + Docetaxel (N=397)	Pertuzumab + Trastuzumab + Docetaxel (N=407)
Number of Patients with Rash AE		
Any Rash AE	143 (36.0 %)	184 (45.2 %)
NCI-CTCAE Grade >= 3	5 (1.3 %)	11 (2.7 %)
Related	114 (28.7 %)	153 (37.6 %)
Rash AE leading to discontinuation of study medication, excl. Docetaxel only	1 (0.3 %)	3 (0.7 %)
Rash AE leading to discontinuation of Docetaxel only	0 (0.0 %)	8 (2.0 %)
Rash AE requiring treatment	80 (20.2 %)	119 (29.2 %)

Rash identified by a Roche AEGT for EGFR Associated Rash

7.2.8.4. Leukopenia ("AE to monitor")

Leukopenia ("AE to monitor") was defined using the SMQ [narrow] "Hematopoietic leukopenia" (includes the PT febrile neutropenia) and is summarized below in Table 31. At least one leukopenic ("AE to monitor") event was experienced by the majority of patients in both treatment arms, and these events occurred more frequently in patients in the Ptz+T+D arm (62.4%, n=254) than in the Pla+T+D arm (58.2%, n=231). The proportion of patients requiring dose modifications for leukopenia ("AE to monitor") was marginally higher in the Ptz+T+D arm (19.4%) than in the Pla+T+D arm (17.1%), and just over a third of all patients received treatment for these events.

The higher incidence of leukopenia ("AE to monitor") events in patients in the Ptz+T+D arm compared with the Pla+T+D arm was mainly driven by a higher incidence of febrile neutropenia (13.8%, n=56 vs 7.6%, n=30; respectively). The AE rate per patient year for Grade ≥ 3 febrile neutropenia was estimated to be approximately 0.09 in the Pla+T+D arm and 0.12 in the Ptz+T+D arm. In both treatment arms, the majority of the febrile neutropenic events started in the first cycle. Neutropenia reported in the first cycle resolved in a median of 14 days (corresponding to the time of the next scheduled infusion) in both arms. There was no difference in dose delays or interruptions between the two treatment arms due to neutropenia.

Table 31: CLEOPATRA – Leukopenia ("AE to monitor").

	Placebo + Trastuzumab + Docetaxel (N=397)	Pertuzumab + Trastuzumab + Docetaxel (N=407)
Number of Patients with Leukopenia AE		
Any Leukopenia AE	231 (58.2 %)	254 (62.4 %)
NCI-CTCAE Grade >= 3	211 (53.1 %)	237 (58.2 %)
Related	222 (55.9 %)	246 (60.4 %)
Leukopenia AE leading to discontinuation of study medication, excl. Docetaxel only	0 (0.0 %)	1 (0.2 %)
Leukopenia AE leading to discontinuation of Docetaxel only	8 (2.0 %)	12 (2.9 %)
Leukopenia AE leading to interruption/modification of study medication	68 (17.1 %)	79 (19.4 %)
Leukopenia AE resulting in death	1 (0.3 %)	3 (0.7 %)
Leukopenia AE requiring treatment	132 (33.2 %)	154 (37.8 %)
Febrile Neutropenia[1]	30 (7.6 %)	56 (13.8 %)
NCI-CTCAE Grade >= 3	30 (7.6 %)	56 (13.8 %)
Leukopenic Infection[2]	38 (9.6 %)	51 (12.5 %)
NCI-CTCAE Grade >= 3	3 (0.8 %)	14 (3.4 %)
Febrile Neutropenic Infection[2]	3 (0.8 %)	14 (3.4 %)
NCI-CTCAE Grade >= 3	1 (0.3 %)	6 (1.5 %)

Leukopenia identified by any AE in the SMQ haematopoietic leukopenia (narrow)
[1] AEs identified using single Preferred Term
[2] Leukopenic infection/febrile neutropenic infection events identified as any event in the Infections/infestations SOC with a start date <=14 days after the start date of an event of CTCAE grade >=3 in the SMQ (narrow) 'Leukopenia'/febrile neutropenia PT respectively

Febrile neutropenic infection events were defined as infections/infestations occurring ≤ 14 days after a Grade ≥ 3 febrile neutropenic event. The incidence of such events was higher in patients in the Ptz+T+D arm (3.4%, 14 patients, 17 events) than in the Pla+T+D arm (0.8%, 3 patients, 3 events). A diverse range of febrile neutropenic infections were reported, mostly in the Ptz+T+D arm, and were generally Grade 1 or 2 in severity. There were 6 febrile neutropenic infections Grade ≥ 3 events reported in the Ptz+T+D arm, and 1 in the Pla+T+D arm. Of these events, 3 were SAEs all in the Ptz+T+D arm (pneumonia, cellulitis, urinary tract infection). Pneumonia with concurrent febrile neutropenia resulted in death, and was considered by the investigator to be related to docetaxel treatment. The AE rate per patient year for febrile neutropenic infections Grade ≥ 3 was < 1 AE in both treatment arms (0.01, Pla+T+D vs 0.04, Ptz+T+D).

7.2.8.5. Interstitial lung disease ("AE to monitor")

Interstitial lung disease (ILD) ("AE to monitor") was defined as SMQ (narrow) ILD and is summarized below in Table 32. The incidence of ILD ("AE to monitor") was similar in patients in the Ptz+T+D arm (2.2%, n=9) and the Pla+T+D arm (1.5%, n=6). The most common ILD ("AE to monitor") in patients in both treatment arms was pneumonitis (1.0%, n=4, Ptz+T+D vs 0.5%, n=2, Pla+T+D). The ILD ("AE to monitor") rate per 100 patient years was 1.5 in the Pla+T+D arm and 1.9 in the Ptz+T+D.

Table 32: CLEOPATRA – Interstitial lung disease (and AE in the SMQ ILD [narrow]).

	Placebo + Trastuzumab + Docetaxel (N=397)	Pertuzumab + Trastuzumab + Docetaxel (N=407)
Number of Patients with Interstitial Lung Disease (ILD) AE		
Any ILD AE	6 (1.5 %)	9 (2.2 %)
NCI-CTCAE Grade >= 3	2 (0.5 %)	3 (0.7 %)
Related	3 (0.8 %)	5 (1.2 %)
ILD AE leading to discontinuation of study medication, excl. Docetaxel only	0 (0.0 %)	1 (0.2 %)
ILD AE leading to discontinuation of Docetaxel only	0 (0.0 %)	2 (0.5 %)
ILD AE requiring treatment	6 (1.5 %)	7 (1.7 %)

Interstitial Lung Disease is any AE in the SMQ Interstitial Lung Disease (narrow)

7.2.8.6. Hypersensitivity/anaphylaxis ("AE to monitor")

Hypersensitivity/anaphylaxis ("AEs to monitor") were defined as Roche standard AEGT "Anaphylaxis and hypersensitivity" containing the MedDRA SMQ (narrow) "Anaphylactic reaction" plus all MedDRA PTs containing "hypersensitivity". Hypersensitivity/anaphylaxis ("AEs to monitor") were reported in 9.1% (n=36) of patients in the Pla+T+D arm (37 events) and 10.8% (n=44) of patients in the Ptz+T+D arm (48 events). The most common event reported (Pla+T+D vs Ptz+T+D) was hypersensitivity (5.0%, n=20 vs 6.4%, n=26), followed by drug hypersensitivity (3.8%, n=15 vs 4.4%, n=18) and anaphylactic reaction (0.5%, n=2 vs 1.0%, n=4).

Three (3) patients in each treatment arm experienced SAEs of drug hypersensitivity. In the Pla+T+D arm all study medications were stopped in 1 patient and docetaxel was stopped in 2 patients, while in the Ptz+T+D arm, 1 patient had trastuzumab and pertuzumab doses modified[5], 1 patient had trastuzumab dose modified and 1 patient had docetaxel dose modified. Drug hypersensitivity SAEs were mainly Grade ≥ 3 in severity (5/6 events) occurring on Day 2 (Cycle1) and all events resolved with treatment. Two (2) other patients with drug hypersensitivity events, not reported as SAEs, discontinued one or all components of study treatment. There were 3 patients in the Ptz+T+D with SAEs of hypersensitivity that resolved with treatment. There were 2 other patients (1 in each arm) with non-serious hypersensitivity events who discontinued one or all three components of the study treatment. Six (6) patients experienced anaphylactic reactions; SAEs in 2 patients (1 in each treatment arm) of Grade 3 (Pla+T+D) and Grade 4 (Ptz+T+D) severity. Almost all patients experiencing an AE of hypersensitivity or anaphylaxis continued study medication in spite of the event, and some experienced these reactions on more than one occasion. The modifications made to study medication in response to these reactions are summarized below in Table 33.

[5] sponsor correction: the patient had trastuzumab and docetaxel doses modified, not trastuzumab & pertuzumab

Table 33: CLEOPATRA – Study drug adjustments following anaphylaxis and hypersensitivity events.

Treatment modification	Pla+T+D arm No. events (% of total events)	Ptz+T+D arm No. events (% of total events)
None	14 (29%)	18 (29%)
Docetaxel modified	24 (50%)	17 (27%)
Docetaxel discontinued	4 (8%)	0
Trastuzumab modified	1 (2%)	12 (19%)
Trastuzumab + docetaxel modified	1 (2%)	2 (3%)
Placebo/pertuzumab modified	2 (4%)	9 (14%)
All modified	0	1 (2%)
All discontinued *	2 (4%)	4 (6%)
Total events evaluated	**48**	**63**

Discontinuation of placebo/pertuzumab or trastuzumab required all treatments to be discontinued

7.2.8.7. Mucositis ("AE to monitor")

Mucositis "AE to monitor" was defined as Roche Standard AEGT "Mucositis of gastrointestinal tract", and was reported more frequently in patients in the Ptz+T+D arm (48.6%, n=198, 256 events) than in patients in the Pla+T+D arm (37.0%, n=147, 181 events). The most commonly reported event in patients in both treatment arms was mucosal inflammation (19.9%, Pla+T+D vs 27.8%, Ptz+T+D) followed by stomatitis (15.4%, Pla+T+D vs 18.9%, Ptz+T+D). All other AEs occurred in < 5.0% of patients in both treatment arms. There were a total of 9 SAEs (2, Pla+T+D vs 7, Ptz+T+D).

7.2.8.8. Hepatic disorders

7.2.8.8.1. Hepatic disorders ("AE to monitor"); drug related

Hepatic disorders ("AE to monitor") were defined as SMQ (wide) "Drug related hepatic disorders" –comprehensive search, and comprised eight individual SMQs. The proportion of patients with drug related hepatic disorders ("AE to monitor") was 10.1% (n=40) in the Pla+T+D arm (50 events) and 9.6% (n=39) in the Ptz+T+D arm (see Table 34 below). The most common SOG in both arms was "Investigations" (6.8%, Pla+T+D vs 6.4%, Ptz+T+D), and the most common AE (PT) in this group was ALT increased (3.0%, Pla+T+D vs 3.7%, Ptz+T+D). Apart from ALT increased, no other AEs (PT) were reported in ≥ 2% of patients in either treatment arm. There were 3 patients in the Ptz+T+D arm with drug related hepatic disorders resulting in discontinuation of docetaxel, compared with no patients in the Pla+T+D arm.

Table 34: CLEOPATRA – Drug related hepatic disorders ("AE to monitor").

	Placebo + Trastuzumab + Docetaxel (N=397)	Pertuzumab + Trastuzumab + Docetaxel (N=407)
Number of Patients with Drug Related Hepatic Disorder (DRHD) AE		
Any DRHD AE	40 (10.1 %)	39 (9.6 %)
NCI-CTCAE Grade 3+ 3	5 (1.3 %)	7 (1.7 %)
Related	23 (5.8 %)	30 (7.4 %)
DRHD AE leading to discontinuation of Docetaxel only	0 (0.0 %)	3 (0.7 %)
DRHD AE leading to interruption/modification of study medication	13 (3.3 %)	14 (3.4 %)
DRHD AE resulting in death	1 (0.3 %)	0 (0.0 %)
DRHD AE requiring treatment	13 (3.3 %)	15 (3.7 %)

Drug related Hepatic Disorder is identified in the SMQ Drug Related Hepatic Disorder - Comprehensive Search

7.2.8.8.2. Abnormal liver function tests (laboratory data)

LFT results for patients with ALT/AST levels ≥ 5 x ULN and ≥ 10 x ULN or total bilirubin ≥ 2 x ULN are summarized in the dossier. The results showed that LFT abnormalities meeting these categories were infrequent in both treatment arms, but were more common in the Ptz+T+D arm than in the Pla+T+D arm. The incidence of an increase in patients in LFTs (defined as AST > 5 x

ULN or ALT > 5 x ULN or total bilirubin > 2 x ULN) was 3.7% (n=15) in the Ptz+T+D arm and 2.0% (n=8) in the Pla+T+D arm. When time to first increase in LFTs (defined as AST ≥ 5 x ULN, ALT ≥ 5 x ULN or total bilirubin ≥ 2 x ULN) was assessed in the small number of patients meeting the criteria, the hazard ratio (HR = 1.66 [95% CI: 0.70, 3.91]) favoured the Pla+T+D arm, although the 95% CI included 1.

7.2.8.8.3. Hy's law

In this study, Hy's law for detecting drug-induced liver injury was defined as AST and/or ALT > 3 x ULN and total bilirubin > 2 x ULN, with alkaline phosphatase < 2 x ULN. In order to meet the Hy's Law criteria for drug-induced liver injury fully, there should be no alternative cause for hepatic dysfunction such as coexistent liver disease or confounding factors such as administration of a known hepatotoxic agent. No patients in either arm of the study completely met Hy's law for drug-induced liver injury. However, one Pla+T+D treated patient fulfilled the liver enzyme criteria, but possible contributing factors included raised baseline enzyme levels pre-dating the observed abnormalities, obesity and paracetamol.

7.2.8.9. "AEs to monitor" leading to treatment modification/discontinuation

Overall, "AEs to monitor" resulted in a higher incidence of dose interruption/modification than discontinuations of study medication, and both dose amendment categories occurred more frequently in patients in the Ptz+T+D arm than in the Pla+T+D arm.

7.2.9. Laboratory data

Throughout the study the majority of patients had laboratory values within the normal range or Grade 1-2 abnormalities. The exceptions were WBC (leukopenia) and neutrophil count (neutropenia) in which the majority of patients had Grade 3 or 4 events. Grade 3 or 4 leukopenia was observed in 60.6% (238/393) of patients in the Pla+T+D arm and 64.5% (260/403) of patients in the Ptz+T+D arm, and Grade 3 or 4 neutropenia was observed in 86.6% (318/367) of patients in the Pla+T+D arm and 86.0% (331/385) of patients in the Ptz+T+D arm. Overall, laboratory abnormalities, including Grade 3 or 4 events, were reasonably well balanced between the two treatment arms.

At baseline, the majority of laboratory values were Grade 0 for all laboratory parameters tested (as required by the protocol). Shifts from baseline were most common for haematological parameters, in particular, WBC and neutrophils. Generally, shift patterns were comparable between the two treatment arms. Shifts from to Grade 3 or 4 in haematological parameters were similar for the two treatment arms (see Table 35, below). For lymphocytes and platelets, shifts were generally to worst values Grade 1 or 2.

Table 35: CLEOPATRA – Newly occurring Grade 3 or 4 haematology values during treatment.

	Pla+T+D N = 397		Ptz+T+D N = 407	
	Grade 3 n (%)	Grade 4* n (%)	Grade 3 n (%)	Grade 4 n (%)
↓ Hemoglobin	15 (3.8%)	5 (1.3%)	14 (3.4%)	2 (< 1%)
↓ White Blood Cells	186 (46.9%)	52 (13.1%)	209 (51.4%)	50 (12.3%)
↓ Platelets	2 (< 1%)	-	2 (< 1%)	1 (< 1%)
↓ lymphocytes	27 (6.8%)	12 (3.0%)	31 (7.6%)	11 (2.7%)
↓ Neutrophils	48 (12.1%)	117 (29.5%)	52 (12.8%)	114 (28.0%)

Data source: t_lb22_wo, page 4079 ; *Excluding one shift from Grade 3 to Grade 4 in lymphocyte count

Biochemistry parameters shifts to Grade 3 or 4 events occurred in less than 5% of patients in both treatment arms for all events, apart from uric acid. Shift patterns for all parameters were similar in the two arms with the following exceptions: increased ALT (Grade 3), 3 (< 1%) patients, Pla+T+D vs 11 patients (2.7%), Ptz+T+D; decreased sodium (Grade 3), 17 patients (4.3%), Pla+T+D vs 9 patients (2.2%), Ptz+T+D; increased magnesium (Grade 3), 18 patients

(4.5%) Pla+T+D vs 12 patients (2.9%) Ptz+T+D arm; increased uric acid (Grade 3), 66 patients (16.6%) Pla+T+D vs 49 patients (12.0%) Ptz+T+D arm and 2 patients in the Ptz+T+D arm had Grade 4 shifts.

7.2.10. Vital signs

- ECG abnormalities are summarized in the dossier. These summaries were based on investigator assessments of ECG abnormalities, which were collected as free text in the eCRF. Measurements of ECG parameters such as QT interval duration were not requested and were only available if the investigator reported them. Overall, there were a total of 35 ECG abnormalities in 397 patients in the Pla+T+D arm (9.0%) and 43 abnormalities in 407 patients in the Ptz+T+D arm (10.6%). The abnormality patterns were generally similar in the two treatment arms. Only two of the EGG abnormalities were reported as AEs. There were 8 patients with QT prolongation ("AE to monitor"); 4 in each treatment arm. The ECG findings based on Holter monitoring of patients in the QT substudy have been discussed previously in the *Pharmacodynamics* section of this CER above.
- ECOG scores remained unchanged in the majority of patients during treatment. The proportion of patients whose ECOG status worsened at any time point was similar in the Pla+T+D arm (39.0%, n=155) and the Ptz+T+D arm (41.5%, n=169).
- No clinically meaningful differences between the treatment arms were noted in temperature, supine diastolic and systolic blood pressure or pulse rate.

7.2.11. Special groups

7.2.11.1. Age

The safety profiles of patients aged < 65 years and aged ≥ 65 years for the two treatment arms are summarized in the dossier. The total number of patients aged > 75 years (n=19) is considered too small to provide meaningful comparisons with other age groups. There was a marked imbalance in patient numbers between the < 65 years age group (n=678, total) and the ≥ 65 year age group (n=126, total), and differences between the safety profiles of these two age groups should be interpreted conservatively. The proportion of patients with at least one AE was similar in both age groups and in both treatment arms and ranged from 98.5% to 100%.

The main differences between the two age groups were:

in the older age group, greater incidence of SAEs in the Ptz+T+D arm (44.3% vs 32.7%) and the Pla+T+D arm (32.3% vs 25.0%);

- in the older age group, greater incidence of total deaths on treatment in the Ptz+T+D arm (8.2% vs 1.4%) and the Pla+T+D arm (4.6% vs 2.7%), and deaths due to other causes apart from PD on-treatment in the Ptz+T+D arm (8.2% vs 1.2%) and the Pla+T+D arm (4.6% vs 1.8%);
- in the older age group, greater incidence of Grade ≥ 3 infusion associated reactions (IARs) defined as any AE occurring during, on the day of or the day after an infusion in the Ptz+T+D arm (31.1% vs 13.9%) and the Pla+T+D arm (23.1% vs 13.3%);
- in the older age group, greater incidence of diarrhoea all grades in the Ptz+T+D arm (70.5% vs 66.2%) and the Pla+T+D arm (53.8% vs 44.9%), and diarrhoea grade ≥ 3 in the Ptz+T+D arm (14.8% vs 6.6%) and the Pla+T+D arm (6.2% vs 4.8%);
- in the younger age group, greater incidence of febrile neutropenia all grades in the Ptz+T+D arm (14.7% vs 8.2%) and Pla+T+D arm (7.8% vs 6.2%), and rash all grades in the Ptz+T+D arm (47.1% vs 34.4%).

- in the older age group, greater incidence of CHF and LVEF decline in the Pla+T+D arm (10.8% vs 6.6%), and lower incidence of CHF and LVEF decline in the Ptz+T+D arm (3.3% vs 4.3%).

7.2.11.2. Race

In this study, patients were categorized by race as follows:

- White, 227 patients (57.2%) in the Pla+T+D arm and 249 patients (61.2%) in the Ptz+T+D arm;
- Asian, 133 patients (33.5%) in the Pla+T+D arm and 128 patients (31.4%) in the Ptz+T+D arm;
- Black, 20 patients (5.0%) in the Pla+T+D arm and 10 patients (2.5%) in the Ptz+T+D arm;
- Other, 17 patients (4.3%) in the Pla+T+D arm and 20 patients (4.9%) in the Ptz+T+D arm.

The safety profiles based on race for the two treatment arms are summarized in the dossier. The total number of Black patients (n=30) and Other patients (n=35) are considered to be too small to provide meaningful comparisons with the two other racial groups. Overall, the safety profile of the Ptz+T+D combination appeared to be inferior in Asian patients than in White patients.

The most notable differences between Asian and White patients as regards treatment with Ptz+T+D were increased incidences in Asians compared with Whites of: Grade ≥ 3 AEs (81.3% vs 71.1%); SAEs (46.1% vs 28.1%); treatment discontinuation (42.2% vs 23.3%); AEs leading to dose interruption/modification (75.8% vs 53.0%); any IAR (96.9% vs 83.5%); leukopenia (71.9% vs 58.2%); leukopenia Grade ≥ 3 (69.5% vs 53.0%); febrile neutropenia (25.8% vs 8.0%); febrile neutropenia Grade ≥ 3 (25.8% vs 8.0%); diarrhoea (73.4% vs 61.0%); and rash (51.6% vs 41.8%). Similar differences between Asians and Whites were also observed in patients treated with the Pla+T+D combination.

7.3. Integrated safety database

7.3.1. Exposure (all pertuzumab treated patients)

Overall, a total of 1412 patients received at least one infusion of pertuzumab in the 14 studies included in the integrated safety database. The median total dose of pertuzumab received was 2100 mg (range: 58, 26460), the mean±SD total dose was 4737.5±4391.29 mg, the median number of treatment cycles was 4 (mean 9.7 cycles), and the median duration of exposure was 3 months (mean 6.9 months). Of the 1412 patients, 86.5% (n=1222) were treated with pertuzumab 840 mg loading followed by 420 mg q3w.

7.3.2. Demographics and baseline characteristics (all pertuzumab treated patients)

In the all-pertuzumab treated patients (n=1412), the majority were female (88%) and White (79%), with a mean age of 55.4 years (range: 18, 85), and 77.3% were aged < 65 years. The most common indication was MBC (41%), followed by EBC (22%) and ovarian cancer (21%). At baseline, patients had already been treated for cancer with one or more of the following: chemotherapy (57%), anthracyclines (30%), trastuzumab (10%), radiotherapy (31%), surgery (62%), other anticancer therapy (29%).

7.3.3. Adverse events (all pertuzumab treated patients)

7.3.3.1. Safety profile

The safety profile of all-pertuzumab treated patients (n=1412) is summarized in the dossier. The overall safety profile in all-treated pertuzumab treated patients is consistent with the overall safety profile in CLEOPATRA, and does not give rise to concerns relating to additional safety signals. However, the incidences of AEs in the various categories characterizing the

overall safety profile of the two populations were greater in patients in the Ptz+T+D arm of CLEOPATRA than in all pertuzumab treated patients. This difference is most likely to be due to longer patient exposure in CLEOPATRA than in the all-pertuzumab treated population.

7.3.3.2. All grades adverse events

In all-pertuzumab treated patients (n=1412), AEs reported in ≥ 20% of patients were diarrhoea (58.1%), nausea (38.5%), fatigue (34.8%), alopecia (29.8%), neutropenia (28.3%), rash (25.5%), decreased appetite (22.9%) and vomiting (22.7%).

7.3.3.3. Grade 3-4 adverse events (NCI-CTCAE)

In all-pertuzumab treated patients (n=1412), Grade 3 or 4 AEs were reported in 53.0% (749 patients, 1559 events), and in the Ptz+T+D arm of the pivotal Phase III study Grade 3 or 4 events were reported in 73.5% (299 patients, 629 events). The most common Grade 3 or 4 event in all-pertuzumab treated patients was neutropenia, which was reported in 24.7% (n=349) compared with 48.9% (n=199) of patients CLEOPATRA.

7.3.3.4. Treatment related adverse events

In all-pertuzumab treated patients (n=1412), treatment-related AEs occurred in 86.9% (1227 patients, 8111 events). Treatment related AEs occurring in ≥ 10% of patients were: diarrhoea (48.7%); nausea (28.7%); alopecia (28.1%); neutropenia (25.6%); fatigue (24.2%); rash (21.2%); decreased appetite (15.1%); mucosal inflammation (14.0%); vomiting (13.6%); asthenia (12.2%); stomatitis (10.6%); and myalgia (10.0%).

7.3.4. Deaths (all pertuzumab treated patients)

In all-pertuzumab treated patients (n=1412) there were 352 (24.9%) total deaths reported. Disease progression accounted for the majority of these deaths (88.6%, 312/352), while the rest were due to AEs or "other" causes. There were 63 (4.5%) deaths reported during the study period (i.e., within 42 days after last treatment), and 41 (2.9%) of these deaths were considered to be due to disease progression.

7.3.5. Other serious adverse events (all pertuzumab treated patients)

In all-pertuzumab treated patients (n=1412), SAEs were reported in 25.6% (362 patients, 526 events). SAEs occurring in ≥ 1% of patients were: febrile neutropenia (4.2%); neutropenia (2.0%); diarrhoea (1.4%); pneumonia (1.3%); small intestinal obstruction (1.1%); and pleural effusion (1.1%).

7.3.6. Withdrawal due to adverse events (all pertuzumab treated patients)

In all-pertuzumab treated patients (n=1412), AEs leading to discontinuation of study medication were reported in 12.8% (181 patient, 215 events). AEs resulting in discontinuation and occurring in ≥ 1% of patients were: peripheral neuropathy (1.1%); fatigue (1.0%); and oedema (1.0%). There were a number of other AEs leading to discontinuation in this patient population and all occurred in < 1% of patients.

7.3.7. Adverse events leading to dose interruption/modification (all pertuzumab treated patients)

In the all pertuzumab treated population (n=1412), AEs leading to dose interruption/modification occurred in 33.9% of patients (478 patients, 878 events). AEs resulting in dose interruption/modification and occurring in ≥ 1% of patients were: neutropenia (6.5%); diarrhoea (3.6%); febrile neutropenia (3.0%); drug hypersensitivity (2.5%); chills (1.7%); infusion reaction (1.5%); hypersensitivity (1.3%); pyrexia (1.2%); fatigue (1.1%); nausea (1.1%); rash (1.1%); and dyspnoea (1.1%).

7.3.8. "AEs to monitor" and other events of interest (total database)

7.3.8.1. Cardiac safety

The key cardiac safety data from the integrated safety database are summarized below in Table 36.

Table 36: Integrated safety database – key cardiac safety data.

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.

7.3.8.2. Leucopenia ("AE to monitor")

The incidence of leukopenia ("AE to monitor") in patients in the integrated safety database is summarized below in Table 37. The results show that leukopenia ("AE to monitor") occurred very commonly in association with pertuzumab in all components of the database.

Table 37: Integrated safety database – leukopenia adverse events.

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; FN = febrile neutropenia.

7.3.8.3. Hypersensitivity/anaphylaxis ("AE to monitor")

The incidence of hypersensitivity/anaphylaxis ("AE to monitor") events in patients in the integrated safety database is summarized below in Table 38. The incidence of these events (all grades) was highest in the two treatment arms in CLEOPATRA, and occurred in a similar proportion of patients in the two arms in this study. In CLEOPATRA, these events were mostly assessed as secondary to docetaxel infusions. Overall, hypersensitivity/anaphylaxis ("AE to monitor") events occurred less frequently with single-agent pertuzumab compared with double and triplet combination pertuzumab regimens.

Table 38: Integrated safety database – hypersensitivity/anaphylaxis

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.

7.3.8.4. Diarrhoea ("AE to monitor)

The incidence of diarrhoea ("AE to monitor") in patients in the integrated safety database is summarized below in Table 39.

Table 39: Integrated safety database – diarrhoea AEs.

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.

The incidence of diarrhoea ("AE to monitor") was high in all patients in all treatment groups, and was most marked in the Ptz+T+D arm of CLEOPATRA. Overall, the results suggest that diarrhoea is a very common adverse event observed with pertuzumab as a single agent, and that the incidence of the condition increases when the drug is combined with trastuzumab and docetaxel.

7.3.8.5. Mucositis ("AE to monitor")

The incidence of mucositis ("AE to monitor") in patients in the integrated safety database is summarized below in Table 40. Mucositis ("AE to monitor") was reported less frequently in patients treated with pertuzumab as a single agent compared with pertuzumab combined with docetaxel in doublet or triplet therapy regimens. There appears to be an additive effect for mucositis when Ptz+T+D are combined.

Table 40: Integrated safety database – mucositis.

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/column.

7.3.8.6. Rash ("AE to monitor")

The incidence of rash ("AE to monitor") in patients in the integrated safety database is summarized below in Table 41. Rash occurred most frequently when pertuzumab was combined with trastuzumab and docetaxel.

Table 41: Integrated safety database – Rash.

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.

7.3.9. Laboratory data

No integrated analyses of laboratory data were carried out.

7.3.10. Vital signs

The relevant data relate to CLEOPATRA and have been discussed previously.

7.3.11. Special groups

The relevant data relate to CLEOPATRA and have been discussed previously.

7.4. Evaluator's overall conclusions on clinical safety

The pivotal safety data in this submission are from the pivotal Phase III efficacy and safety study (CLEOPATRA). In this study, safety data from 407 patients treated with pertuzumab in combination with trastuzumab and docetaxel (Ptz+T+D) were compared with 397 patients treated with placebo in combination with trastuzumab and docetaxel (Pla+T+D). Overall, the data are considered to show that the safety profile of the Ptz+T+D combination is inferior to that of the Pla+T+D combination. However, despite the difference in the safety profile of the two treatment combinations the data are considered to have satisfactorily established the safety of Ptz+T+D for the proposed indication.

In addition to the pivotal safety data from CLEOPATRA, the submission also included an integrated safety database containing supportive safety data on 1412 patients with various types of cancer treated with pertuzumab as a single agent and in doublet and triplet combinations. Overall, the safety profile of pertuzumab from the integrated database is considered to be consistent with the safety profile of pertuzumab observed in CLEOPATRA. Therefore, the following conclusions on the clinical safety of pertuzumab will focus on the data from CLEOPATRA unless otherwise stated.

In CLEOPATRA, exposure to pertuzumab is considered sufficient to adequately characterize the safety of the Ptz+T+D combination for the proposed indication. The median number of cycles was 18 (range: 1, 56) for the Ptz+T+D arm compared with 15 (range: 1, 50) for the Pla+T+D arm. By cycle 16, 62% (252/407) of patients who had commenced treatment with Ptz+T+D were still receiving treatment compared with 47% (188/397) of patients who had commenced treatment with Pla+T+D. The difference between the two arms was due to a greater number of early withdrawals from study treatment in the Pla+T+D arm, primarily resulting from a higher

incidence of patients with progressive disease in the Pla+T+D arm. Post-hoc Kaplan-Meier analysis showed that median time on treatment to a PFS event was 18.1 months in the Ptz+T+D arm and 11.8 months in the Pla+T+D arm.

The overall incidence of AEs occurring during the treatment period was balanced between the treatment arms (98.5% of patients in the Pla+T+D arm vs 99.8% of patients in the Ptz+T+D arm), although the total number of AEs reported in the Ptz+T+D arm (6048 AEs) was higher than in the Pla+T+D arm (5300 AEs). The most commonly occurring AEs (all grades) reported with an incidence of ≥ 20% in the Ptz+T+D arm (vs Pla+T+D arm) were diarrhoea (66.8% vs 46.3%), alopecia (60.9% vs 60.5%), neutropenia (52.8% vs 49.6%), nausea (42.3% vs 41.6%), fatigue (37.6% vs 36.8%), rash (33.7% vs 24.2%), decreased appetite (29.2% vs 26.4%), mucosal inflammation (27.8% vs 19.9%), asthenia (26.0% vs 30.2%), vomiting (24.1% vs 23.9%), peripheral oedema (23.1% vs 30.0%), anaemia (23.1% vs 18.9%), myalgia (22.9% vs 23.9%), nail disorder (22.9% vs 22.9%), cough (21.4% vs 18.6%), and peripheral neuropathy (21.1% vs 20.2%).

Nearly all commonly occurring AEs (all grades) occurred more frequently in the Ptz+T+D arm than in the Pla+T+D arm. AEs occurring in at least 5% of patients in either arm, and at least 5% more frequently in the Ptz+T+D arm compared with the Pla+T+D arm were diarrhoea (66.8% vs 46.3%), rash (33.7% vs 24.2%), mucosal inflammation (27.8% vs 19.9%), febrile neutropenia (13.8% vs 7.6%), and dry skin (10.6% vs 4.3%). AEs occurring in at least 5% of patients in either arm and at least 5% more frequently in the Pla+T+D arm compared with the Ptz+T+D arm were peripheral oedema (30.0% vs 23.1%), and constipation (24.9% vs 15.0%).

Grade ≥ 3 AEs (i.e., grades 3, 4, or 5) were reported in a similar proportion of patients in the Ptz+T+D arm (74.2%) and the Pla+T+D arm (72.8%) The most frequently reported Grade ≥ 3 AEs were "blood and lymphatic tissue disorders" (59.0% of patients in the Ptz+T+D arm vs 54.2% of patients in the Pla+T+D arm). The difference was predominantly due to the higher incidence in patients in the Ptz+T+D arm (vs Pla+T+D arm) of neutropenia (48.9% vs 45.8%) and febrile neutropenia (13.8% vs 7.6%), but leukopenia occurred more frequently in the Pla+T+D arm than in the Ptz+T+D arm (14.6% vs 12.3%). The incidence of Grade ≥ 3 "infections and infestations" AEs was similar in patients in the Ptz+T+D arm (11.1%) and in the Pla+T+D arm (10.1%). The only other Grade ≥ 3 AE that occurred in greater than 2% more patients in the Ptz+T+D arm than in the Pla+T+D arm was diarrhoea (7.9% vs 5.0%, respectively). The notable increases in all grade rash, mucosal inflammation and dry skin in patients in the Ptz+T+D arm compared with the Pla+T+D arm were not seen for the corresponding Grade ≥ 3 events, with similar frequencies in these three events being reported in both treatment arms.

The total number of deaths reported at the study cut-off date was greater in the Pla+T+D arm (n=94, 23.7%) than in the Ptz+T+D arm (n=69, 17.0%). The most frequent cause of death was progressive disease, and this occurred notably more frequently in the Pla+T+D arm (n=81, 20.4%) than in Ptz+T+D arm (n=57, 14.0%). Deaths due to AEs were reported in a similar proportion of patients in the Pla+T+D arm (n=10, 2.5%) and the Ptz+T+D arm (n=8, 2.0%), with 17 of the 18 deaths (19 AEs) being reported in the treatment period and the remaining death being reported in the post-treatment period. The majority of deaths due to AEs were associated with cardiovascular events or febrile neutropenia.

Serious adverse events (SAEs) occurred more frequently in the Ptz+T+D arm (34.4%) than in the Pla+T+D arm (26.2%). The most frequently reported SAEs were SOC "blood and lymphatic system" disorders (16.0% of patients in the Ptz+T+D arm vs 10.6% of patients in the Pla+T+D arm), mainly due to a higher incidence of febrile neutropenia in the Ptz+T+D arm (11.3%) than in the Pla+T+D arm (5.0%). Following SOC "blood and lymphatic system disorders", the next most frequently reported SAEs were SOC "infections and infestations (10.8% of patients in the Ptz+T+D arm vs 7.3% of patients in the Pla+T+D arm). However, no particular SOC "infection and infestations" event accounted for the difference in incidence between the two arms, and individual events involved no more than 2% of patients in either arm. The proportion of

patients in both treatment arms with SAEs was generally comparable for all other SOCs, and no other SOC included more than 5% of patients with SAEs in either treatment arm.

According to the CLEOPATRA protocol, patients could continue placebo/pertuzumab plus trastuzumab if docetaxel was discontinued due to unacceptable toxicity. However, if placebo/pertuzumab and/or trastuzumab were discontinued for toxicity all three study medications (including docetaxel) had to be stopped and the patient was withdrawn from the treatment phase of study.

AEs resulting in discontinuation of pertuzumab and trastuzumab treatment (excluding events that led to discontinuation of docetaxel only) occurred in a similar proportion of patients in the two treatment arms (5.3%, Pla+T+D vs 6.1%, Ptz+T+D). These AEs were predominantly cardiac disorders (2.5%, Pla+T+D vs 2.0%, Ptz+T+D), consisting primarily of left ventricular dysfunction (2.0%, Pla+T+D vs 1.5%, Ptz+T+D). No other AEs resulted in discontinuation of pertuzumab and trastuzumab treatment (excluding events that led to discontinuation of docetaxel only) in ≥ 2% of patients in either arm. The proportion of patients who experienced AEs resulting in discontinuation of docetaxel only was similar in the two treatment arms (23.2%, Pla+T+D vs 23.6%, Ptz+T+D), and the most common AEs (> 2% in either arm, Pla+T+D vs Ptz+T+D) were oedema (3.0% vs 3.2%), peripheral neuropathy (2.5% vs 3.4%), fatigue (2.0% vs 2.2%), and peripheral oedema (2.5% vs 1.0%).

Dose interruption or modification was the term used to describe slowing down, temporary interruption or discontinuation of the current infusion, or reduction or delay of the subsequent dose (dose reductions were only allowed for docetaxel). AEs that resulted in interruption or dose modification of any of the three study medications were reported more frequently in patients in the Ptz+T+D arm (60.0%) than in the Pla+T+D arm (53.1%). AEs reported in ≥ 2% of patients in either treatment arm and more commonly in the Ptz+T+D arm (vs Pla+T+D) were febrile neutropenia (7.6% vs 5.0%), diarrhoea (5.4% vs 1.8%), and hypersensitivity (4.4% vs 2.3%). The proportion of patients experiencing SAEs that resulted in interruption/modification was higher in the Ptz+T+D arm (16.2%) than in the Pla+T+D arm (12.1%), and the most common event was febrile neutropenia (6.1%, Ptz+T+D vs 3.3%, Pla+T+D). Other SAEs occurred in less than 2% of patients in either arm.

CLEOPATRA included assessments of adverse events of particular interest, termed “Adverse Events to Monitor”, based on Standardized MedDRA queries (SMQs) or if no SMQs were available, selected MedDRA Adverse Event Grouped Terms (AEGTs). The “AEs to monitor” included cardiac disorders, drug related hepatic disorders, liver function test abnormalities, diarrhoea, rash, leukopenia, mucositis, hypersensitivity/anaphylaxis, interstitial lung disease, and infusion reactions. In addition, cardiac disorders were also assessed by an independent CRC, and LVEF was assessed throughout the study.

SAEs suggestive of cardiac failure (“AE event to monitor”) were infrequent in both treatment arms (1.8%, Pla+T+D vs 1.0%, Ptz+T+D), and the proportion of patients considered by the independent CRC to have experienced symptomatic LVSD was 1.0% in both treatment arms. The proportion of patients with worst on treatment LVEF of < 50% and a reduction from baseline of ≥ 10% points was higher in the Pla+T+D arm (6.6%) than in the Ptz+T+D arm (3.8%). In CLEOPATRA, the QT substudy suggests that clinically significant increases in the QT interval with Ptz+T+D compared with Pla+T+D are unlikely. No significant differences in various other ECG abnormalities were observed between the two treatment arms. QT prolongation (“AE event to monitor”) was reported in 2.0% of patients in Ptz+T+D arm and 1.3% of patients in the Pla+T+D arm. However, ECG changes were not systematically assessed in all patients in CLEOPATRA.

The proportion of patients who experienced drug related hepatic disorders (“AE to monitor”) was similar in the two treatment arms (10.1%, Pla+T+D vs 9.6%, Ptz+T+D). The incidence of increased LFTs (defined as AST > 5 x ULN or ALT > 5 x ULN or total bilirubin > 2 x ULN) was

3.7% in the Ptz+T+D arm and 2.0% in the Pla+T+D arm. There were no definite cases of drug induced hepatotoxicity meeting Hy's law criteria in either treatment arm.

The proportion of patients experiencing diarrhoea ("AE to monitor") was higher in the Ptz+T+D arm (66.8%) than in the Pla+T+D arm (46.3%), and the majority of events in both treatment arms occurred in the first treatment cycle. However, diarrhoea resulted in very few discontinuations of pertuzumab and trastuzumab (excluding events leading to discontinuation of docetaxel only) in patients in both the Pla+T+D arm (0.3%) and the Ptz+T+D arm (0.5%). The proportion of patients requiring dose interruptions/modifications due to diarrhoea were also relatively low in both treatment arms compared with the overall frequency of the event, but higher in the Ptz+T+D arm (5.4%) than in the Pla+T+D arm (1.8%). It should be noted that the "AE to monitor" for diarrhoea was based on the single preferred term (PT) of "diarrhoea", rather than grouped terms based on the SMQ or AEGT.

The proportion of patients experiencing rash ("AE to monitor") was higher in the Ptz+T+D arm (45.2%) than in the Pla+T+D arm (36.0%), and rash (PT) was the most frequently reported event in the two treatment arms (33.7%, Ptz+T+D vs 24.2%, Pla+T+D). However, the SOC of "skin and subcutaneous tissue disorders" resulted in very few discontinuations of pertuzumab and trastuzumab (excluding events leading to discontinuation of docetaxel only) in patients in both the Pla+T+D arm (0.3%) and the Ptz+T+D arm (0.7%), with rash (PT) accounting for 0% and 0.5% of patients, respectively. No dose interruptions/modifications appeared to be required in either treatment arm due to SOC "skin and subcutaneous tissue disorders".[6]

The proportion of patients experiencing leukopenia ("AE to monitor") was higher in the Ptz+T+D arm (62.4%) than in the Pla+T+D arm (58.2%). A similar proportion of patients in each treatment arm required dose modification for leukopenic events (17.1%, Pla+T+D vs 19.4%, Ptz+T+D), and just over a third of patients received treatment for these events. The majority of patients requiring treatment for leukopenic events received colony-stimulating factors (26.4%, Pla+T+D vs 28.1%, Ptz+T+D).

The proportion of patients experiencing mucositis ("AE to monitor") was higher in the Ptz+T+D arm (48.6%) than in the Pla+T+D arm (37.0%). No discontinuations of trastuzumab or pertuzumab (excluding events leading to discontinuation of docetaxel only) or dose interruptions/modifications appeared to be required in either treatment arm due to mucositis.[7]

Infusion reaction AEs were specifically assessed in CLEOPATRA. In the first treatment cycle, the proportion of patients experiencing an infusion reaction during the pertuzumab infusion was 3.9% compared with 2.0% during the placebo infusion. The incidence of hypersensitivity/anaphylaxis ("AEs to monitor") reactions (all grades) was similar in patients in the Ptz+T+D (10.8%) and the Pla+T+D (9.1%) arms, as was the incidence of Grade ≥ 3 events (2.0%, Ptz+T+D vs 2.5%, Pla+T+D).

Throughout the study the majority of patients had laboratory values within the normal range or with Grade 1-2 abnormalities. The exceptions were leukopenia and neutropenia where the majority of patients had Grade 3 or 4 events. Grade 3 or 4 leukopenia was observed in 60.6% (238/393) of patients in the Pla+T+D arm and 64.5% (260/403) of patients in the Ptz+T+D arm, and Grade 3 or 4 neutropenia was observed in 86.6% (318/367) of patients in the Pla+T+D arm and 86.0% (331/385) of patients in the Ptz+T+D arm. Biochemistry parameter shifts to Grade 3 or 4 events occurred in less than 5% of patients in both treatment arms for all events, apart from uric acid.

[6] Sponsor clarification: Dose interruptions/modifications due to SOC skin & subcutaneous tissue disorders were 3.5% & 5.2%, respectively, in the Pla+T+D arm and the Ptz+T+D arm.
[7] Sponsor clarification: Dose interruptions/modifications due to mucositis were 0.5% & 1.7%, respectively, in the Pla+T+D arm and the Ptz+T+D arm.

The AE profile of Ptz+T+D in patients aged ≥ 65 years differs from that in patients aged < 65 years. The main differences were: greater incidence of SAEs in the older age group; greater incidence of total deaths and deaths due to other causes (i.e., other than progressive disease) occurring 42 days after last treatment in the older age group; greater incidence of Grade ≥ 3 infusion associated reactions (IARs) in the older age group; greater incidence of diarrhoea (all grades and grade ≥ 3) in the older age group; greater incidence of febrile neutropenia and rash in the younger age group in the Ptz+T+D arm; and greater incidence of CHF and LVEF decline in the older age group in the Pla+T+D arm, and lowest incidence of CHF and LVEF decline in the older age group in the Ptz+T+D arm.

The AE profile was notably inferior in Asian patients treated with Ptz+T+D than White patients treated with this combination, and the AE profile in Asian patients treated with Pla+T+D was also inferior to that of White patients treated with this combination. There was no investigation of AEs in the Asian population based on region of origin (e.g., Chinese, Japanese, and Korean).

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The pivotal Phase III study (CLEOPATRA) has satisfactorily demonstrated that treatment of the proposed patient population with pertuzumab in combination with trastuzumab and docetaxel results in a statistically significant and clinically meaningful improvement in the duration of IRF-assessed PFS of 6.1 months compared with placebo in combination with trastuzumab and docetaxel (median IRF-PFS 18.5 and 12.4 months, respectively). The risk of experiencing a PFS event (disease progression or death) was reduced by 38% in patients treated with Ptz+T+D compared with Pla+T+D (HR = 0.62 [95% CI: 0.51, 0.75], p<0.0001). The Kaplan-Meier analysis showed that the IRF-assessed PFS curves began to separate in favour of the Ptz+T+D arm at about 2 to 3 months after initiation of treatment, with separation being maintained throughout the remainder of the observation period. The IRF-assessed PFS was the primary efficacy endpoint in CLEOPATRA, and the treatment benefit of Ptz+T+D compared with Pla+T+D seen in this analysis was also observed in the secondary efficacy endpoint analysis of investigator assessed PFS.

In addition to investigator-assessed PFS, other key secondary efficacy endpoint analyses also supported the benefit of the Ptz+T+D combination compared with the Pla+T+D combination for the treatment of the proposed patient population. There was an OS benefit in favour of the Ptz+T+D combination compared with the Pla+T+D combination (69 vs 96 deaths, respectively; HR = 0.64 [96% CI: 0.47, 0.88], p = 0.0053). However, the estimated HR did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α-spending function for the interim OS analysis (HR ≤ 0.603, p ≤ 0.0012). Consequently, the observed OS benefit in favour of Ptz+T+D relative to Pla+T+D was deemed to be not statistically significant. The Kaplan-Meier analysis showed that the survival curves began to separate in favour of the Ptz+T+D arm at about 10 months. The median length of follow-up for survival was estimated to be 19.3 months in both treatment arms, but the median time to death had not been reached in either treatment arm at the time of data cut-off. Furthermore, at the time of the OS analysis only 43% (165/385) the prespecified number of deaths had occurred.

The ORR analysis showed a benefit for patients treated with the Ptz+T+D combination compared with the Pla+T+D combination (80.2% vs 69.3%, respectively; difference = 10.8% [95% CI: 4.2, 17.5]; p=0.0011). However, the statistically significant result must be considered to be exploratory rather than confirmatory, as the interim analysis of OS (preceding analysis in the pre-specified testing hierarchy of IRF-assessed PFS ⟶ OS ⟶ ORR) was deemed not statistically significant.

The duration of the IRF-assessed objective response was assessed in the 233 patients in the Pla+T+D arm and 275 patients in the Ptz+T+D arm and showed that objective response was maintained for an estimated additional 33.5 weeks in patients receiving Ptz+T+D compared with Pla+T+D. The median duration of response in the Pla+T+D arm was 54.1 weeks (range: 5, 135 weeks) and 87.6 weeks (range: 7, 137) in the Ptz+T+D arm; HR = 0.66 (95% CI: 0.51, 0.85). The FACT-B analysis showed that time to symptom progression in both treatment arms was similar and represented about 6 treatment cycles (18.3, Pla+T+D vs 18.4 weeks, Ptz+T+D).

8.2. First round assessment of risks

The risks of treatment with pertuzumab in combination with trastuzumab and docetaxel for the proposed indication are considered to be greater than those with placebo in combination with trastuzumab and docetaxel. However, despite the increased risks with the triplet combination it is considered that the submission has satisfactorily established the safety of the regimen for treatment of the proposed indication. The risks of treatment described below relate to those identified in the pivotal Phase III study (CLEOPATRA), unless otherwise stated.

In CLEOPATRA, nearly all patients treated with Ptz+T+D (99.8%) experienced at least one AE (all grades), as did patients treated with Pla+T+D (98.5%). The most commonly occurring AEs (all grades) reported with an incidence of ≥ 20% in the Ptz+T+D arm (vs Pla+T+D arm) were diarrhoea (66.8% vs 46.3%), alopecia (60.9% vs 60.5%), neutropenia (52.8% vs 49.6%), nausea (42.3% vs 41.6%), fatigue (37.6% vs 36.8%), rash (33.7% vs 24.2%), decreased appetite (29.2% vs 26.4%), mucosal inflammation (27.8% vs 19.9%), asthenia (26.0% vs 30.2%), vomiting (24.1% vs 23.9%), peripheral oedema (23.1% vs 30.0%), anaemia (23.1% vs 18.9%), myalgia (22.9% vs 23.9%), nail disorder (22.9% vs 22.9%), cough (21.4% vs 18.6%), and peripheral neuropathy (21.1% vs 20.2%).

While AEs occurred commonly in both treatment arms, they appeared to be manageable by dose interruptions/modifications rather than discontinuation of treatment with pertuzumab and trastuzumab. In addition, AEs also appeared to have been frequently managed by standard symptomatic and/or supportive treatments: e.g., diarrhoea ("AE to monitor") requiring treatment (46.2%, Ptz+T+D vs 23.2%, Pla+T+D); rash ("AE to monitor") requiring treatment (29.2%, Ptz+T+D vs 20.2%, Pla+T+D); leukopenia ("AE to monitor") requiring treatment (37.8%, Ptz+T+D vs 33.2%, Pla+T+D).

[According to the protocol], if pertuzumab/placebo or trastuzumab were discontinued due to toxicity then all three study drugs had to be discontinued and the patient was withdrawn from the study. AEs resulting in discontinuation of pertuzumab and trastuzumab treatment (excluding events that led to discontinuation of docetaxel only) occurred in a similar proportion of patients in the two treatment arms (5.3%, Pla+T+D vs 6.1%, Ptz+T+D). Dose interruption or modification was the term used to describe slowing down, temporary interruption or discontinuation of the current infusion, or reduction or delay of the subsequent dose (dose reductions were only allowed for docetaxel). AEs resulting in dose interruption or modification were reported more frequently in patients in the Ptz+T+D arm (60.0%) than in the Pla+T+D arm (53.1%).

AEs (all grades) occurring in at least 5% of patients in either treatment arm and at least 5% more frequently in the Ptz+T+D arm (vs the Pla+T+D arm) were diarrhoea (66.8% vs 46.3%), rash (33.7% vs 24.2%), mucosal inflammation (27.8% vs 19.9%), febrile neutropenia (13.8% vs 7.6%), and dry skin (10.6% vs 4.3%). However, treatment discontinuations of pertuzumab and trastuzumab due to these events (excluding discontinuations of docetaxel only for these events) occurred in less than 1% of patients in either treatment arm. Dose interruptions/modifications (Pla+T+D vs Ptz+T+D) for diarrhoea were 1.8% vs 5.4%, and for febrile neutropenia were 5.0% vs 7.6%. The proportion of patients in the Ptz+T+D arm was ≥ 2% to < 5% higher for a large number of AEs, with the majority of these events being Grade 1 or 2 in severity.

Grade ≥ 3 AEs (i.e., grades 3, 4, or 5) were reported in a similar proportion of patients in the Ptz+T+D arm (74.2%) and in the Pla+T+D arm (72.8%). The most frequently reported Grade ≥ 3 AEs were SOC "blood and lymphatic tissue disorders" (59.0%, Ptz+T+D vs 54.2%, Pla+T+D arm). The difference was predominantly due to the higher incidence in patients in the Ptz+T+D arm (vs Pla+T+D arm) of neutropenia (48.9% vs 45.8%) and febrile neutropenia (13.8% vs 7.6%), while leukopenia occurred more frequently in the Pla+T+D arm than in the Ptz+T+D arm (14.6% vs 12.3%).

There was no increased risk of death during treatment due to AEs in the Ptz+T+D arm compared with the Pla+T+D arm. However, the risk of other SAEs was greater in the Ptz+T+D arm (34.4%) than in the Pla+T+D arm (26.2%). The most frequently reported SAEs were SOC "blood and lymphatic system" disorders (16.0%, Ptz+T+D vs 10.6%, Pla+T+D arm), mainly due to a higher incidence of febrile neutropenia in the Ptz+T+D arm (11.3%) than in the Pla+T+D arm (5.0%). Following SOC "blood and lymphatic system disorders", the next most frequently reported SAEs were SOC "infections and infestations" (10.8%, Ptz+T+D vs 7.3%, Pla+T+D). However, no particular SOC "infection and infestations" SAE accounted for the difference in incidence between the two arms, and individual SAEs accounted for no more than 2% of patients in either arm.

Patients in the Ptz+T+D arm did not have an increased risk of experiencing SOC "cardiac disorders" compared with patients in Pla+T+D arm (14.5% vs 16.4%, respectively), and the incidence of LVD was similar in the two arms (1.0% vs 1.8%, respectively). However, the inclusion criteria for CLEOPATRA required patients to have a LVEF of ≥ 50% and the exclusion criteria excluded patients with prior history of congestive heart failure (any NYHA grading), symptomatic decreases in LVEF to < 50% during prior trastuzumab treatment, conditions that could impair left ventricular function, clinically significant cardiovascular disease, or cumulative prior anthracycline exposures to > 360 mg/m^2 of doxorubicin (or equivalent). There were no marked differences in ECG abnormalities (included QT prolongation) between the two treatment arms.

The risk of drug related hepatic disorders ("AE to monitor") was similar in patients in the two treatment arms (9.6%, Ptz+T+D vs 10.1%, Pla+T+D). The risk of LFT abnormalities (defined as AST > 5 x ULN or ALT > 5 x ULN or total bilirubin > 2 x ULN) was low in patients in both treatment arms (3.7%, Ptz+T+D vs 2.0%, Pla+T+D). There were no definite cases of drug induced hepatotoxicity meeting Hy's law criteria in either treatment arm. SOC "hepatobiliary disorders" occurred in a similar proportion of patients in both treatment arms (2.5%, Ptz+T+D vs 2.3%, Pla+T+D vs), and no AEs (PT) occurred with an incidence of more than 1% in patients in either of the two arms. However, CLEOPATRA excluded patients with impaired liver function[8] (TBL > 1.5 x ULN; ALT or AST > 2.5 x ULN or > 5x ULN in patients with liver metastases), and there are no safety data in patients with hepatic impairment. SOC "renal and urinary disorders" occurred more commonly in patients in the Ptz+T+D arm (10.6%) than in the Pla+T+D arm (7.6%), due to the increased incidence of dysuria (5.4% vs 2.3%). However, increases in creatinine levels were reported infrequently in both treatment arms (about 1.5% of patients in each of the arms), but CLEOPATRA excluded patients with serum creatinine > 2 mg/dL.

In the first treatment cycle (day 1), when placebo and pertuzumab were administered alone, 19.2% of patients given pertuzumab experienced an AE on the day of the infusion compared with 14.6% of patients given placebo, while reactions during the infusion occurred in 3.9% and 2.0% of patients, respectively. The majority of patients (84% in each arm) received pre-medication prior to an infusion, with corticosteroids (77% to 78%) and 5-HT3 antagonists

[8] Sponsor clarification and correction: Exclusion criteria in the context of liver disorder: TBL > ULN (unless the patient had documented Gilbert's syndrome), AST or ALT > 2.5 × ULN, AST or ALT > 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 and ALT < 1.5 × ULN, Serum creatinine > 2.0 mg/dL or 177µmol/L, INR and aPTT or PTT > 1.5 × ULN (unless on therapeutic coagulation).

(59% to 60%) being the most common classes of pre-medications received. Other pre-medications used by at least 10% of patients were antihistamines (47% to 49%), histamine H2-receptor antagonists (31% to 32%) and analgesics (19% to 22%). Colony stimulating factor was also used pre-infusion in 3.9% of patients in the Pla+T+D arm and 5.0% of patients in the Ptz+T+D arm.

The risk of hypersensitivity/anaphylaxis ("AE to monitor"), all grades, was similar in patients in the Ptz+T+D (10.8%) and Pla+T+D (9.1%) arms, as was the incidence of Grade ≥ 3 events (2.0%, Ptz+T+D vs 2.5%, Pla+T+D). The proportion of patients positive for pertuzumab anti-therapeutic antibodies post-baseline was lower in the Ptz+T+D arm (2.8%, 11/386) than in the Pla+T+D arm (6.2%, 23/372).

Overall, the risks of Ptz+T+D treatment are greater in patients aged ≥ 65 years compared with patients < 65 years, and in Asian patients compared with "White" patients.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of pertuzumab in combination with trastuzumab and docetaxel, given the proposed usage, is favourable. In CLEOPATRA, the pertuzumab, trastuzumab and docetaxel combination resulted in a statistically significant and clinically meaningful increase in time to progression free events (disease progression or death due to any cause) of 6.1 months compared with the placebo, trastuzumab, and docetaxel combination. Based on the hazard ratio, the pertuzumab, trastuzumab and docetaxel combination reduced the risk of a PFS event by 28%[9] (95% CI: 25%, 49%), relative to the placebo, trastuzumab, and docetaxel combination. The risk of experiencing a PFS event was 47.5% with the pertuzumab, trastuzumab and docetaxel combination compared with 59.6% with the placebo, trastuzumab, and docetaxel combination. The risks of experiencing commonly occurring adverse events (all grades), adverse events (Grade ≥ 3), and serious adverse events were greater with the pertuzumab, trastuzumab and docetaxel combination than with the placebo, trastuzumab, and docetaxel combination. However, the observed toxicities were not unexpected, and were manageable using standard methods employed in oncological clinical practice (e.g., dose interruptions/modifications; symptomatic and/or supportive treatment).

9. First round recommendation regarding authorisation

It is recommended that pertuzumab in combination with trastuzumab and docetaxel at the proposed dosage be approved for the treatment of patients with HER2-positive metastatic (Stage IV) or unresectable locally recurrent breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy.

10. Clinical questions

10.1. Pharmacokinetics

No questions.

10.2. Pharmacodynamics

Question 1: In the QTc substudy of the pivotal trial, in discussing the results of the analysis involving regression to the mean it is stated that the observed value of 9.3 ms for the difference

[9] Sponsor comment: the correct % for reduced risk of PFS is 38%

between the QTcF post-baseline values of pertuzumab and placebo after being regressed to the global mean was "lower than the value of 10 ms considered to be important in thorough QTc studies. Thus it is unlikely pertuzumab causes ΔΔQTcF prolongation larger than those of clinical interest in thorough QTc studies". However, the TGA adopted QT/QTc interval guidance document (CHMP/ICH/2/04) makes no mention of adjusting post-baseline changes in the QTcF by regressing them to the overall global mean. Furthermore, the relevant QT/QTc guideline states that the threshold of regulatory concern "is around 5 ms as evidenced by an upper bound of the 95% CI confidence interval around the mean effect on QTc of 10 ms". It appears that the 10 ms difference referred to in the sponsor's regression to the overall mean analysis refers to the mean difference between the two treatment arms rather than the upper bound of the 95% CI of the mean. If this is the case, then the observed mean difference of 9.3 ms is greater than the mean difference of 5 ms which is of regulatory concern in a "thorough QT/QTc study". Please clarify the matter.

10.3. Efficacy

No questions.

10.4. Safety

No questions.

10.5. Indication

The proposed indication is *"Perjeta is indicated in combination with Herceptin and docetaxel for patients with HER2-positive metastatic (Stage IV) or unresectable locally recurrent breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant therapy"*.

It is recommended that the trade name Herceptin be changed to the generic name trastuzumab.

Since PERJETA is an orphan-designated drug with approval in the USA, it is open to the delegate to register the drug without referral to the Advisory Committee on Prescription Medicines (ACPM). However, the US indication is more restrictive than that proposed since it does not include unresectable locally recurrent breast cancer.

The sponsor is asked to justify the proposed indication with reference to the populations in the trials, numbers of subjects and outcomes in the metastatic breast cancer and unresectable locally recurrent breast cancer subgroups. What is the role of radiotherapy in unresectable locally recurrent breast cancer?

[Note: the Clinical Evaluator's requested revisions to product literature (the Product Information and Consumer Medicine Information) are not included in this Extract from the CER.]

11. Second round evaluation of clinical data submitted in response to questions

11.1.1 Background

In a document dated 29 November 2012, the sponsor provided a "Response to Consolidated Section 31 Request for Information (Milestone 4)" from the TGA dated 31 October 2012. The s31 consolidated response included responses to clinical (Module 5) questions arising following the first round evaluation of the submission. The clinical evaluator reviewing and commenting on the sponsor's response to the Module 5 questions is the same evaluator who undertook the

first round evaluation of the submission. The key clinical aspects of the full responses from the sponsor have been included in this review, and only minor editorial changes to the responses have been made.

11.1.2 Question on pharmacodynamics

11.1.2.1 Sponsor's response

Roche will address the response to the requested clarification by:

- Providing a clarification of the interpretation of the calculation using the regression to the mean and discuss other QTc data provided in the study report which provide additional clarity on the differences in baseline between the two arms of the study and their significance in the interpretation of the findings
- Reviewing key findings from the study, which support the lack of clinically relevant QTc and other ECG effects of this molecule, despite the inability to perform a "thorough" QT study due to the characteristic long half-life of pertuzumab and inability to use normal volunteers for this HER2-targeted agent

Clarification of the baseline calculation between the two arms: Roche acknowledges the calculation using the global mean QTcF values may be confusing and agree that this calculation is not part of the methodologies outlined in the ICH E14 guidance document. However, we would like to clarify that the 9.3 ms is not a difference between the post-baseline QTc values of pertuzumab and placebo but it is the pre-treatment baseline difference between the pertuzumab and placebo arms.

[CLEOPATRA] was a parallel group design study and differences were observed in the baseline QTcF values for the patients randomized to the pertuzumab and placebo arms. The mean baseline QTcF (defined as the mean of the raw QTcF values in Cycle 1 at 30-minute pre-infusion and 15-minute pre-infusion time points) for the pertuzumab group was 410.7 ms and 420.0 ms for the placebo group. Due to this difference in baseline of 9.3 ms, the point estimates of ΔQTcF for the placebo arm in Cycle 3 were generally lower than those observed for the ΔQTcF for the pertuzumab arm. As a result, ΔΔQTcF values may have been inflated due to the over-correction associated with the ΔQTcF of placebo.

The threshold level of regulatory concern, which is around 5 ms or as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms, is more applicable for a "thorough QT/QTc study". In a "thorough QT/QTc study", dedicated assessments of the effect of drug on cardiac repolarization with adequate controls are conducted. As noted by the evaluator, it was not a thorough QTc substudy as defined in standard guidelines (ICH14) for the reasons outlined by Liu *et al., J Clin Oncol* 26: 2008 (May 20 suppl; abstr 2554)].

Key findings in the CLEOPATRA QTc study: Key findings in this QTc substudy of pertuzumab support the lack of clinically relevant QTc and other ECG effects of this molecule, despite the inability to perform a "thorough" QT study:

1. At Cycle 3 of treatment, mean QTcF measurements immediately post-infusion for the pertuzumab and placebo treatment were 413.2 and 415.2 ms, respectively, with upper ranges not exceeding 451.7 ms. These values are below the thresholds of clinical concern as outlined in the ICH E14 guidance document, where a QTc prolongation of >500 ms or a QTc interval increase from baseline of >60 ms is noted to be of clinical concern [Ref: E14 guidance].
2. The Cycle 3 mean QTcF measured immediately post-infusion for the pertuzumab and placebo treatment patients of 413.2 and 415.2 ms, respectively, are also below the Grade 1 criteria (>450-470 ms) for mild QTc-related adverse events as outlined by the Common

Terminology Criteria for Adverse Events (CTCAE version 3) standard [Ref: Rock EP et al, Am Heart J. 2009; 157(5):827-836].

3. Following the Cycle 1 dose, at which time pertuzumab concentrations were the highest during the study period as a result of the loading dose, the upper range of ΔQTcF for the pertuzumab group was less than 30 ms at all post-infusion time points, with point estimates of ΔΔQTcF in Cycle 1 all lower than 5 ms and with the upper 90% CIs lower than 10 ms.
4. Categorical analysis of ECG data showed no pertuzumab-treated patients experienced a QTcF value of >450 ms, >480 ms, >500 ms or a change from baseline QTcF of >60 ms.
5. Concentration-QTcF modeling showed no relationship between pertuzumab concentrations and ΔQTcF.
6. Statistical analysis of other ECG parameters, such as HR, PR interval, and QRS duration, showed pertuzumab had no impact on these parameters.

Overall, based on statistical analysis of ΔQTcF and ΔΔQTcF parameters, as well as concentration-QTc modelling, results from the current substudy indicate that pertuzumab does not have a clinically relevant effect on QTcF and other ECG parameters in patients with HER2-positive MBC when combined with trastuzumab and docetaxel.

11.1.2.2 Evaluator's comments

The sponsor states that the ΔΔQTcF of 9.3 ms referred to in the pharmacodynamics question was not a difference between the post-baseline QTc values of pertuzumab and placebo but was the pre-treatment baseline difference between the pertuzumab and placebo arms. However, this is not at all clear from the following sentence in WO206968B/substudy 2, page 26 – "[f]urther, if post-BL measurements of QTcF regressed to the global overall mean of about 414.3 ms, a difference would be observed in post-BL changes (i.e., a ΔΔQTcF would be observed) between the pertuzumab and placebo groups of about (414.3-410.7) - (414.3-420.0) = 9.3 ms". This sentence appears to suggest that a post-baseline difference between pertuzumab and placebo would be 9.3 ms "if post-BL measurements of QTcF regressed to the overall mean of 413.3 ms". The origin of the 9.3 ms value remains confusing. Consequently, It would appear to be prudent to discard the reference to the 9.3 ms value based on calculation by the method defined by the sponsor as "regressed to the overall mean". However, the data from WO206968B/substudy 2 gave rise to concern as it showed that in Cycle 3 the ΔΔQTcF immediately post-infusion was 8.41 ms (90% CI: -2.58, 19.39) greater in the pertuzumab arm than in the placebo arm, with the upper 90% CI for both post infusion doses being > 10 ms (see Table 17 of this CER). It is agreed that the data from Cycle 1 showed that the ΔΔQTcF was < 5 ms and the upper 90% CI was < 10 ms.

In order to clarify the clinical relevance of the QT data the sponsor summarized the key results of WO206968B/substudy 2 and concluded that pertuzumab does not have a clinically relevant effect on QTcF and other ECG parameters in patients with HER2-positive metastatic breast cancer when combined with trastuzumab and docetaxel. The evaluator agrees with the sponsor and considers that review of the totality of the ECG data suggests that clinically significant increases in QTcF are unlikely with the proposed triplet combination in patients with metastatic breast cancer. The first round evaluation of WO206968B/substudy 2 is found in Section 4 of this CER and is consistent with the sponsor's conclusions.

Sponsor's Response to clinical question relating to the proposed indication.

11.1.3 Question on indications

11.1.3.1 Sponsors response

Roche agrees to change 'Herceptin' to 'trastuzumab' throughout the product information.

Roche acknowledges that the number of patients with unresectable, locally recurrent disease included in the pivotal WO20698/TOC4129g (CLEOPATRA) study was very low. This is because investigators were discouraged from including any patient in the study with potentially curable disease. It was considered more appropriate for such patients to receive standard loco-regional and systemic therapy, including neoadjuvant therapy if appropriate. Since high response rates were anticipated with trastuzumab and docetaxel (with or without pertuzumab), only patients with locally recurrent disease that was considered unlikely to become resectable after systemic treatment were encouraged to enter the study.

Roche acknowledges that there is an important role for radiotherapy in patients with unresectable, locally recurrent disease. However, many patients with unresectable, locally recurrent disease have already received radical radiotherapy as part of their primary treatment. Moreover, radiotherapy cannot control occult systemic disease which may be present.

Roche considers that there is no biological reason to believe that patients with locally recurrent, inoperable disease will respond differently to pertuzumab, compared to patients with metastatic disease. In general, treatments that are effective for patients with metastatic breast cancer are also effective in patients with locally recurrent, unresectable disease, and treatment guidelines may group these patients together, along with patients with locally advanced breast cancer (see for example, Cardoso et al, 2011; Cardoso et al, 2012; Carlson et al, 2012). Moreover, the WO20697 (NEOSPHERE) study indicates clearly that pertuzumab improves the efficacy (pathological complete response [pCR] rate) of trastuzumab and docetaxel in patients with locally advanced (i.e., non-metastatic) disease. A substantial and statistically significant improvement in efficacy was seen in these patients (pCR rate for Ptz+T+D = 45.8% vs. 29.0% for T+D; difference between arms = 16.8%; CI: 3.5-30.1%; p=0.0141). This is in line with the improvement in efficacy seen in the WO20698/TOC429g (CLEOPATRA) study overall (HR = 0.62 for IRF-assessed PFS; CI 0.51, 0.75; p < 0.0001; improvement in median IRF-assessed PFS of 6.1 months).

As seen in the WO20698/TOC4129g study and the WO20697 study, the toxicity of Ptz+T+D was manageable in patients with metastatic or non-metastatic disease, and so Roche considers that the likely benefits of Ptz+T+D outweigh the risks in patients with locally recurrent, unresectable disease, just as they do in patients with metastatic disease. Overall, therefore, Roche considers that the indication for pertuzumab should reflect the entry criteria for the pivotal study and that patients with locally recurrent unresectable disease should not be denied the benefits of pertuzumab. Although the approved US indication for pertuzumab does not include unresectable locally recurrent disease, the above rationale was acceptable to EU regulators and the EU indication is expected to include patients with unresectable, locally recurrent breast cancer.

References

- 10724: Cardoso F, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011; 22(6): 25-30

  Cardoso F, et al. 1st International consensus guidelines for advanced breast cancer (ABC 1). Breast 2012; 21 (3): 242-252

- 10725 Carlson RW, et al. NCCN Practice Guidelines in Oncology. Breast Cancer. Version 2. 2012 http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

11.1.3.2 Evaluator's comment

Following the first round assessment of the submitted data it was recommended that pertuzumab in combination with trastuzumab and docetaxel be approved for the treatment of patients with HER2-positive metastatic (Stage IV) or unresectable locally recurrent breast cancer who have not received previous treatment or whose disease has relapsed after adjuvant

therapy. This was the indication initially proposed by the sponsor and remains the sponsor's proposed indication

However, the FDA has approved Perjeta in combination with trastuzumab and docetaxel for the treatment of HER2-positive only in patients with metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. In contrast, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recently recommended the granting of marketing authorisation for Perjeta 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 (EMA Website, Summary of Opinion, 13 December 2012).

In view of the question from the TGA relating to the indication, the sponsor's response, the approved FDA indication and the recent CHMP recommendation relating to the indication, the relevant data in the original submission relating to the treatment population has been re-examined. Following this re-examination, it is considered that the indication for Perjeta in combination with trastuzumab and docetaxel should be restricted to patients with HER2-positive breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Review of the data suggests that there is a strong argument to restrict the indication to patients with HER2-positive metastatic breast cancer as very few patients in the total population in CLEOPATRA were categorised as having unresectable, locally recurrent disease. In the Pla+T+D arm, 8 out of 406 patients (2.0%) had unresectable, locally recurrent disease and the corresponding number in the Ptz+T+D arm was 11 out of 402 patients (2.7%). Of the 19 patients in the total study population with unresectable, locally recurrent disease, 7 actually had metastases noted on their baseline disease assessment (2 in the Pla+T+D arm and 5 in the Ptz+T+D arm). In the total study population in CLEOPATRA, almost all patients had metastases at study entry (98.0% in the Pla+T+D arm and 97.3% in the Ptz+T+D arm). CLEOPATRA (WO20698/TOC4129g) was the only study in the breast cancer clinical program that included patients with unresectable, locally recurrent breast cancer (see the summary table immediately below). NeoSphere (WO20697) included patients with locally advanced disease treated with one of the four regimens (including Ptz+T+D) but in the **neoadjuvant** setting.

Table 42: Breast cancer distribution in the clinical trial program.

	HER2-positive								HER2-negative	
	WO20698/TOC4129g (MBC)		WO20697 (EBC/LABC)				B017929 (MBC)		BO16934 (MBC)	
	Pla+T+D	Ptz+ T +D	T + D	Ptz+T+D	Ptz+T	Ptz+D	Cohorts 1 and 2 Ptz+T	Cohort 3 Ptz Ptz+T	Ptz (420 mg)	Ptz (1050mg)
Breast Cancer Type: N	*405*	*401*	*107*	*107*	*107*	*96*	*66*	*29*	*41*	*38*
Locally Recurrent [a]	8 (2.0)	11 (2.7)		0	0	0	0	0	0	0
Metastatic Disease [b]	397 (98.0)	390 (97.3)	0	0	0	0	66 (100.0)	29 (100)	41 (100.0)	38 (100)
Inflammatory	10 (2.5)	6 (1.5)	7 (6.5)	10 (9.3)	7 (6.5)	5 (5.2)	0	0	0	0
Locally Advanced	0	0	36 (33.6)	32 (29.9)	35 (32.7)	31 (32.3)	0	0	0	0
Operable (EBC)	0	0	64 (59.8)	65 (60.7)	65 (60.7)	60 (62.5)	0	0	0	0

Note: In this table, the total number of patients with locally recurrent or metastatic disease in the Pla+T+D and Ptz+T+D arms (405 and 401, respectively) is less than the number of randomized patients in the study (406 and 402, respectively). This suggests that baseline breast cancer status was unknown in a 1 patient in each treatment arm.
a = Includes de novo, locally advanced disease with no prior resection. Some patients also had metastases.
b = Includes inflammatory disease in the metastatic setting.

In CLEOPATRA, the statistical analysis was undertaken on the total study population. Subgroup analysis on patients with unresectable, locally recurrent breast cancer would not have been meaningful due to the small number of patients with this condition in the study (i.e., 19 out of 808 randomized patients; 2.4%). Therefore, it is likely that the statistically significant efficacy

results observed in CLEOPATRA were driven exclusively by the patients with metastatic disease. Furthermore, 7 of the 19 patients with unresectable, locally recurrent breast cancer appear to have had metastatic disease at baseline and would presumably have met metastatic disease treatment criteria. This leaves 12 patients (1.5%) in the study population with unresectable, locally recurrent disease without metastases. Consequently, it can be argued that a separate study should be undertaken in patients with unresectable, locally recurrent breast cancer without metastases in order to establish the efficacy of the proposed regimen in this patient group.

The sponsor argues that there is no biological reason to believe that patients with locally advanced recurrent, inoperable disease will respond differently to pertuzumab compared to patients with metastatic disease. The sponsor also notes that, in general, treatments that are effective for patients with metastatic breast cancer are also effective in patients with locally recurrent, unresectable disease, and treatment guidelines may group these patients together, along with patients with locally advanced breast cancer. The sponsor also notes that the results of NeoSphere clearly show that pertuzumab improves the efficacy (pathological complete response [pCR] rate) of trastuzumab and docetaxel in patients with locally advanced (i.e., non-metastatic) disease. However, NeoSphere was conducted in neoadjuvant setting in treatment-naive women with operable, locally advanced HER-2 breast cancer. Consequently, the results from NeoSphere are not necessarily relevant to women with unresectable, locally recurrent disease who may or may not have undergone prior adjuvant therapy. There were no data on pCR from CLEOPATRA as this end point was not evaluated in this study.

It is noted that both the FDA and CHMP indications are worded to include patients who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease, while the proposed Australian indication is worded to include patients who have not received previous treatment or have relapsed after adjuvant therapy. However, the FDA/CHMP and Australian wordings are basically describing the same patient population. The protocol excluded patients with a history of anti-cancer therapy for metastatic breast cancer (with the exception of one prior hormonal regimen for metastatic breast cancer, which had to be stopped prior to randomization). Anti-cancer therapy for metastatic breast cancer included any EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or more than one prior hormonal regimen for metastatic breast cancer. Therefore, in accordance with the protocol it is recommended that the wording of the indication should refer to patients who have not received previous anti-HER2 therapy or chemotherapy for metastatic disease.

Following consideration of the characteristics of the patient population included in CLEOPATRA the following indication is recommended:

> *Perjeta in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.*

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

The benefits of treatment in the total study patient population in CLEOPATRA are described below. However, it is considered that the benefits should be interpreted as referring to patients with metastatic HER2-positive breast cancer who have not been previously treated with trastuzumab or chemotherapy for metastatic breast cancer. The number of patients in CLEOPATRA with unresectable, locally recurrent breast cancer in the total treatment population (2.4% [n=19]) is considered to be too small to adequately assess the benefits in this patient population. In addition, of the 19 patients with unresectable, locally recurrent breast cancer, 7

had metastatic disease noted at baseline leaving 12 patients (1.5%) patients with unresectable, locally recurrent breast cancer without metastases.

The pivotal Phase III study (CLEOPATRA) satisfactorily established that treatment of the study population with pertuzumab in combination with trastuzumab and docetaxel resulted in a statistically significant and clinically meaningful improvement in the duration of IRF-assessed PFS of 6.1 months compared with placebo in combination with trastuzumab and docetaxel (median IRF-PFS 18.5 and 12.4 months, respectively). The risk of experiencing a PFS event (disease progression or death) was reduced by 38% in patients treated with Ptz+T+D compared with Pla+T+D (HR = 0.62 [95% CI: 0.51, 0.75], p<0.0001). The Kaplan-Meier analysis showed that the IRF-assessed PFS curves began to separate in favour of the Ptz+T+D arm at about 2 to 3 months after initiation of treatment, with separation being maintained throughout the remainder of the observation period. The IRF-assessed PFS was the primary efficacy endpoint in CLEOPATRA, and the treatment benefit of Ptz+T+D compared with Pla+T+D seen in this analysis was also observed in the secondary efficacy endpoint analysis of investigator assessed PFS.

In addition to investigator-assessed PFS, other key secondary efficacy endpoint analyses also supported the benefit of the Ptz+T+D combination compared with the Pla+T+D combination in the study population. There was an OS benefit in favour of the Ptz+T+D combination compared with the Pla+T+D combination (69 vs 96 deaths, respectively; HR = 0.64 [96% CI: 0.47, 0.88], p = 0.0053). However, the estimated HR did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets α-spending function for the interim OS analysis (HR ≤ 0.603, p ≤ 0.0012). Consequently, the observed OS benefit in favour of Ptz+T+D relative to Pla+T+D was deemed to be not statistically significant. The Kaplan-Meier analysis showed that the survival curves began to separate in favour of the Ptz+T+D arm at about 10 months. The median length of follow-up for survival was estimated to be 19.3 months in both treatment arms, but the median time to death had not been reached in either treatment arm at the time of data cut-off. Furthermore, at the time of the OS analysis only 43% (165/385) the prespecified number of deaths had occurred.

The ORR analysis showed a benefit for patients in the study population treated with the Ptz+T+D combination compared with the Pla+T+D combination (80.2% vs 69.3%, respectively; difference = 10.8% [95% CI: 4.2, 17.5]; p=0.0011). However, the statistically significant result must be considered to be exploratory rather than confirmatory, as the interim analysis of OS (preceding analysis in the pre-specified testing hierarchy of IRF-assessed PFS ⟶ OS ⟶ ORR) was deemed not statistically significant.

The duration of the IRF-assessed objective response was assessed in 233 patients in the Pla+T+D arm and 275 patients in the Ptz+T+D arm and showed that objective response was maintained for an estimated additional 33.5 weeks in patients receiving Ptz+T+D compared with Pla+T+D. The median duration of response in the Pla+T+D arm was 54.1 weeks (range: 5, 135 weeks) and 87.6 weeks (range: 7, 137) in the Ptz+T+D arm; HR = 0.66 (95% CI: 0.51, 0.85). The FACT-B analysis showed that time to symptom progression in both treatment arms was similar and represented about 6 treatment cycles (18.3, Pla+T+D vs 18.4 weeks, Ptz+T+D).

In pre-specified subgroup analyses, IRF-assessed PFS in the both the de nova (n=432) and prior adjuvant/neoadjuvant (n=376) treatment groups was greater in the Ptz+T+D arm relative to the Pla+T+D arm: HR (de novo group) = 0.63 (95% CI: 0.49, 0.82); HR (adjuvant or neoadjuvant group) = 0.61 (95% CI: 0.46, 0.81). In post-hoc exploratory subgroup analyses of IRF-assessed PFS undertaken post-database lock, in the subgroup of patients who had received trastuzumab (n=88) the HR was 0.62 (95% CI: 0.35, 1.07), and in the subgroup of patients in the prior neoadjuvant/adjuvant treatment group that did not include trastuzumab (n=288) the HR was 0.60 (95% CI: 0.43, 0.83). The pre-specified subgroup and exploratory subgroup analyses of IRF-assessed PFS support the primary efficacy analysis.

12.2. Second round assessment of risks

The risks of treatment in the total study population in CLEOPATRA are described below. However, for the reasons outlined above in Section 12.1 (first paragraph) it is considered that the risks of treatment with Perjeta in combination with trastuzumab and docetaxel observed in CLEOPATRA relate primarily to patients with HER2-positive metastatic breast cancer not previously treated with trastuzumab or chemotherapy for metastatic breast disease. The last three paragraphs in this second round assessment of risks expand on the information provided in the first round assessment of risks relating to patients with pertuzumab anti-therapeutic antibodies (ATAs).

In CLEOPATRA, nearly all patients treated with Ptz+T+D (99.8%) experienced at least one AE (all grades), as did patients treated with Pla+T+D (98.5%). The most commonly occurring AEs (all grades) reported with an incidence of ≥ 20% in the Ptz+T+D arm (vs Pla+T+D arm) were diarrhoea (66.8% vs 46.3%), alopecia (60.9% vs 60.5%), neutropenia (52.8% vs 49.6%), nausea (42.3% vs 41.6%), fatigue (37.6% vs 36.8%), rash (33.7% vs 24.2%), decreased appetite (29.2% vs 26.4%), mucosal inflammation (27.8% vs 19.9%), asthenia (26.0% vs 30.2%), vomiting (24.1% vs 23.9%), peripheral oedema (23.1% vs 30.0%), anaemia (23.1% vs 18.9%), myalgia (22.9% vs 23.9%), nail disorder (22.9% vs 22.9%), cough (21.4% vs 18.6%), and peripheral neuropathy (21.1% vs 20.2%).

While AEs occurred commonly in both treatment arms, they appeared to be manageable by dose interruptions/modifications rather than discontinuation of treatment with pertuzumab and trastuzumab. In addition, AEs also appeared to have been frequently managed by standard symptomatic and/or supportive treatments: e.g., diarrhoea ("AE to monitor") requiring treatment (46.2%, Ptz+T+D vs 23.2%, Pla+T+D); rash ("AE to monitor") requiring treatment (29.2%, Ptz+T+D vs 20.2%, Pla+T+D); leukopenia ("AE to monitor") requiring treatment (37.8%, Ptz+T+D vs 33.2%, Pla+T+D).

[According to the protocol], if pertuzumab/placebo or trastuzumab were discontinued due to toxicity then all three study drugs had to be discontinued and the patient was withdrawn from the study. AEs resulting in discontinuation of pertuzumab and trastuzumab treatment (excluding events that led to discontinuation of docetaxel only) occurred in a similar proportion of patients in the two treatment arms (5.3%, Pla+T+D vs 6.1%, Ptz+T+D). Dose interruption or modification was the term used to describe slowing down, temporary interruption or discontinuation of the current infusion, or reduction or delay of the subsequent dose (dose reductions were only allowed for docetaxel). AEs resulting in dose interruption or modification were reported more frequently in patients in the Ptz+T+D arm (60.0%) than in the Pla+T+D arm (53.1%).

AEs (all grades) occurring in at least 5% of patients in either treatment arm and at least 5% more frequently in the Ptz+T+D arm (vs the Pla+T+D arm) were diarrhoea (66.8% vs 46.3%), rash (33.7% vs 24.2%), mucosal inflammation (27.8% vs 19.9%), febrile neutropenia (13.8% vs 7.6%), and dry skin (10.6% vs 4.3%). However, treatment discontinuations of pertuzumab and trastuzumab due to these events (excluding discontinuations of docetaxel only for these events) occurred in less than 1% of patients in either treatment arm. Dose interruptions/modifications (Pla+T+D vs Ptz+T+D) for diarrhoea were 1.8% vs 5.4%, and for febrile neutropenia were 5.0% vs 7.6%. The proportion of patients in the Ptz+T+D arm was ≥ 2% to < 5% higher for a large number of AEs, with the majority of these events being Grade 1 or 2 in severity.

Grade ≥ 3 AEs (i.e., grades 3, 4, or 5) were reported in a similar proportion of patients in the Ptz+T+D arm (74.2%) and in the Pla+T+D arm (72.8%). The most frequently reported Grade ≥ 3 AEs were SOC "blood and lymphatic tissue disorders" (59.0%, Ptz+T+D vs 54.2%, Pla+T+D arm). The difference was predominantly due to the higher incidence in patients in the Ptz+T+D arm (vs Pla+T+D arm) of neutropenia (48.9% vs 45.8%) and febrile neutropenia (13.8% vs 7.6%),

while leukopenia occurred more frequently in the Pla+T+D arm than in the Ptz+T+D arm (14.6% vs 12.3%).

There was no increased risk of death during treatment due to AEs in the Ptz+T+D arm compared with the Pla+T+D arm. However, the risk of other SAEs was greater in the Ptz+T+D arm (34.4%) than in the Pla+T+D arm (26.2%). The most frequently reported SAEs were SOC "blood and lymphatic system" disorders (16.0%, Ptz+T+D vs 10.6%, Pla+T+D arm), mainly due to a higher incidence of febrile neutropenia in the Ptz+T+D arm (11.3%) than in the Pla+T+D arm (5.0%). Following SOC "blood and lymphatic system disorders", the next most frequently reported SAEs were SOC "infections and infestations" (10.8%, Ptz+T+D vs 7.3%, Pla+T+D). However, no particular SOC "infection and infestations" SAE accounted for the difference in incidence between the two arms, and individual SAEs accounted for no more than 2% of patients in either arm.

Patients in the Ptz+T+D arm did not have an increased risk of experiencing SOC "cardiac disorders" compared with patients in Ptz+T+D arm (14.5% vs 16.4%, respectively), and the incidence of LVD was similar in the two arms (1.0% vs 1.8%, respectively). However, the inclusion criteria for CLEOPATRA required patients to have a LVEF of ≥ 50% and the exclusion criteria excluded patients with prior history of congestive heart failure (any NYHA grading), symptomatic decreases in LVEF to < 50% during prior trastuzumab treatment, conditions that could impair left ventricular function, clinically significant cardiovascular disease, or cumulative prior anthracycline exposures to > 360 mg/m^2 of doxorubicin (or equivalent). There were no marked differences in ECG abnormalities (included QT prolongation) between the two treatment arms.

The risk of drug related hepatic disorders ("AE to monitor") was similar in patients in the two treatment arms (9.6%, Ptz+T+D vs 10.1%, Pla+T+D). The risk of LFT abnormalities (defined as AST > 5 x ULN or ALT > 5 x ULN or total bilirubin > 2 x ULN) was low in patients in both treatment arms (3.7%, Ptz+T+D vs 2.0%, Pla+T+D). There were no definite cases of drug induced hepatotoxicity meeting Hy's law criteria in either treatment arm. SOC "hepatobiliary disorders" occurred in a similar proportion of patients in both treatment arms (2.3%, Ptz+T+D vs 2.5%, Pla+T+D vs), and no AEs (PT) occurred with an incidence of more than 1% in patients in either of the two arms. However, CLEOPATRA excluded patients with impaired liver function (TBL > 1.5 x ULN; ALT or AST > 2.5 x ULN or > 5x ULN in patients with liver metastases), and there are no safety data in patients with hepatic impairment. SOC "renal and urinary disorders" occurred more commonly in patients in the Ptz+T+D arm (10.6%) than in the Pla+T+D arm (7.6%), due to the increased incidence of dysuria (5.4% vs 2.3%). However, increases in creatinine levels were reported infrequently in both treatment arms (about 1.5% of patients in each of the arms), but CLEOPATRA excluded patients with serum creatinine > 2 x ULN.

In the first treatment cycle (day 1), when placebo and pertuzumab were administered alone, 19.2% of patients given pertuzumab experienced an AE on the day of the infusion compared with 14.6% of patients given placebo, while reactions during the infusion occurred in 3.9% and 2.0% of patients, respectively. The majority of patients (84% in each arm) received pre-medication prior to an infusion, with corticosteroids (77% to 78%) and 5-HT3 antagonists (59% to 60%) being the most common classes of pre-medications received. Other pre-medications used by at least 10% of patients were antihistamines (47% to 49%), histamine H2-receptor antagonists (31% to 32%) and analgesics (19% to 22%). Colony stimulating factor was also used pre-infusion in 3.9% of patients in the Pla+T+D arm and 5.0% of patients in the Ptz+T+D arm.

The risk of hypersensitivity/anaphylaxis ("AE to monitor"), all grades, was similar in patients in the Ptz+T+D (10.8%) and Pla+T+D (9.1%) arms, as was the incidence of Grade ≥ 3 events (2.0%, Ptz+T+D vs 2.5%, Pla+T+D).

Overall, the risks of Ptz+T+D treatment are comparable in patients aged < 65 years and ≥ 65 years, while the risks Ptz+T+D are greater in Asian patients compared with "White" patients.

In CLEOPATRA, the proportion of patients positive for pertuzumab anti-therapeutic antibodies (ATA) post-baseline was lower in the Ptz+T+D arm (2.8%, 11/386) than in the Pla+T+D arm (6.2%, 23/372). A conservative approach was taken to calculating the incidence of ATA so that any patient confirmed to have an ATA positive sample after dosing was considered positive for ATA, regardless of baseline status. In the Pla+T+D arm, 2 patients positive for ATA experienced events described by the investigator as hypersensitivity reactions (during a pamidronate infusion in 1 patient, and during docetaxel infusions on 3 occasions in 1 patient). Most of the patients in the Pla+T+D arm identified as ATA positive continued to receive treatment after ATA were first detected.

In the Ptz+T+D arm, 1 patient positive for ATA experienced a serious Grade 4 anaphylactic reaction resulting in discontinuation of study medication. However, this event occurred on Study Day 2 (T and D administration), and no AEs were reported on Study Day 1 (P administration), suggesting that the reaction was not due to pertuzumab. In addition, the patient did not have detectable ATA at baseline suggesting that the reaction was not related to ATA. Two (2) other patients experienced AEs described by the investigator as "hypersensitivity" and "drug hypersensitivity" reactions. However, both patients continued on Ptz+T+D treatment following detection of ATA without further hypersensitivity reactions, suggesting that the observed events might have been infusion-related reactions rather than hypersensitivity reactions due to ATA.

Exploratory post-hoc analyses were performed of IRF-assessed PFS and ORR in patients with at least one post-baseline ATA assessment. The results of these analyses are summarised in the table at the end of this section. The IRF-PFS and the ORR were both lower in the ATA-positive treatment arms compared with the ATA-negative treatment arms. However, these results should be interpreted cautiously due to the small number of patients in both ATA-positive treatment arms compared with the ATA-negative treatment arms, and the presence of ATA-positive patients in the Pla+T+D arm. In addition, the 95% CIs for the point estimates in the ATA-positive arms for both treatments were very wide for both the IRF-PFS and the ORR indicating marked intersubject variability for these outcomes. Individual IRF-assessed PFS data for each patient showed that several of the ATA-positive patients in the Ptz+T+D arm achieved prolonged disease control, and there was no clear temporal association between a positive ATA and IRF-assessed progressive disease. Similarly, the sponsor reports that individual ATA-positive patients in the Pla+T+D arm achieved prolonged disease control despite the presence of detectable ATA, with no clear relationship between the development of ATA positivity and IRF-assessed PD. In addition, exploration of confounding risks for disease progression or death in the patients in the post-hoc analyses was not undertaken. Overall, the results for the efficacy outcomes based on ATA status are of interest, but it is difficult to draw meaningful conclusions about the clinical relevance of the observations based on the data.

Table 43: Summary of efficacy by ATA status

	Pla+T+D arm		Ptz+T+D arm	
	ATA -ve	**ATA +ve**	**ATA -ve**	**ATA +ve**
n	349	23	375	11
IRF-PFS (median in months)	12.5	6.3	18.7	12.5
95% CI	[10; 14]	[4; 17]	[16; 25]	[2; 14]
ORR	73.2%	45.0%	81.7%	45.5%
95% CI	[67.7; 78.1]	[23.1; 68.5]	[77.1; 85.7]	[16.7; 76.6]

ORR = Objective response rate; IRF-PFS = progression-free survival according to IRF

12.3. Second round assessment of benefit-risk balance

The benefit-risk balance is considered favourable for pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic breast cancer in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The data on patients with unresectable, locally recurrent breast cancer are too limited to allow for an adequate benefit-risk balance assessment for this patient group to be undertaken.

13. Second round recommendation regarding authorisation

It is recommended that pertuzumab in combination with trastuzumab and docetaxel be approved for the treatment of HER2-positive metastatic breast cancer in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

It is recommended that approval should not extend to patients with unresectable, locally recurrent breast cancer as the pivotal study (CLEOPATRA) was undertaken almost exclusively in patients with metastatic breast cancer (97.4%; n=787). Furthermore, of the 19 patients with unresectable, locally recurrent disease included in CLEOPATRA, 7 had metastases noted on baseline disease assessment. Therefore, it can be inferred that the statistically significant efficacy results in favour of the proposed treatment regimen observed in the pivotal study were driven by patients with metastatic breast cancer. The number of patients in CLEOPATRA with unresectable, locally recurrent disease is too small to undertake a statistically meaningful subgroup analysis comparing the proposed and control treatment regimens in this patient population. Furthermore, based on the small number of patients with unresectable, locally recurrent disease in CLEOPATRA no meaningful benefit-risk balance assessment can be made in this patient population.

It is recommended that the indication be changed to:

> *Perjeta in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.*

[Note: recommended revisions to product literature, including PI and CMI, are not included in this Extract from the CER]

14. References

Baselga J *et al.* Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *NEJM* 2012; 336: 109-110.

Ng CM *et al*. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. *Pharm Res* 2006; 23(6): 1275-1284.

Therasse P, Arbuck SG, Eisenhauer EA, *et al*. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. *J Natl Ca Inst* 2000;92(3):205–216.

15. Appendices

15.1. Appendix 1: ECOG performance status scale (with Karnofsky Equivalent).

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e., light housework, office work (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10-20)
5	Dead

15.2. Appendix 2: Tumor assessments (RECIST [Therasse et al. 2000])

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

- All measurements should be taken and recorded in metric notation, using a ruler or callipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, Ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

NB: Table continued on following page.

Appendix 2 (continued): Tumor Assessments (RECIST [Therasse et al. 2000])

Response Criteria

	Evaluation of target lesions
* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
	Evaluation of non-target lesions
* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Unequivocal progression of existing non-target lesions (1)

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until progressive disease/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
UA	Non-PD	No	UA
Non-PD	UA	No	UA

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of progressive disease at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of Overall Response

- The duration of overall response is measured from the time-measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of Stable Disease

- SD is measured from the start of the treatment until the criteria for progressive disease are met, taking as reference the smallest measurements recorded since the treatment started

15.3. Appendix 3: FACT-B (Version 4).

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

NB: Continued on the next page.

Appendix 3 (continued): FACT-B (Version 4).

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life	0	1	2	3	4

NB: Continued on next page.

Appendix 3 (continued): FACT-B (Version 4).

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

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