14 December 2017
EMA/44005/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Herzuma

International non-proprietary name: trastuzumab

Procedure No. EMEA/H/C/002575/0000

Note

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

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List of abbreviations

ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AUC	Area under the plasma concentration versus time curve
AUC_T	AUC during a dosage interval at steady state
BA	Bioavailability
BE	Bioequivalence
Cav	Average concentration
CBC	Complete blood count
CDR	Complementary determining regions
CE	Capillary electrophoresis
CE-SDS	Capillary electrophoresis - Sodium dodecyl sulphate
CL,	Clearance
CLSS	Clearance at steady-state
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CMO	Contract manufacturing organisation
Cpre	Pre-dosing concentration
CGE	Capillary gel electrophoresis
Ch	Chevallier classification
CI	Confidence interval
CR	Complete response
Ct	Last measured concentration
CT-P6	Trastuzumab (Celltrion)
CV	Coefficient of Variance
Da	Daltons
DCIS	ductal carcinoma in situ
DFS	Disease free survival
DSC	Differential Scanning Calorimetery
DSMB	Drug safety monitoring board
EBC	Early breast cancer
ECD	Extra cellular domain
ECG	Electrocardiograph
ELISA	Enzyme linked immunosorbent assay
ER	Oestrogen-receptor
ES-MS	Electrospray mass spectroscopy
F	Bioavailability
FEC	Combination of chemotherapy agents consisting of fluorouracil, epirubicin and cyclophosphamide
FISH	Fluorescence in-situ hybridisation
FITR	Fourier transform infrared spectroscopy
Fuc	Fucose
Gal	Galactose
GlcN	N-acetyglucosamine
HC	Heavy chain
HCP	Host cell protein
HERA	Herceptin adjuvant trial
Her-1	Human epidermal growth factor, Receptor 1
Her-2	Human epidermal growth factor, Receptor 2
Her-3	Human epidermal growth factor, Receptor 3
Her-4	Human epidermal growth factor Receptor 4
HPAEC-PAD	High-performance anion-exchange chromatography - pulsed amperometric detection
HPLC	High performance liquid chromatography
IEF	Isoelectric focusing
IE-HPLC	Isoelectric high performance liquid chromatography
i.v.	Intravenous
kDa	Kilodalton
λz	Terminal rate constant of elimination
LABC	Locally advanced breast cancer
LC	Light Chain
LC-MS	Liquid chromatography with mass spectrometric detection

LDC	Limiting dilution cloning
LVEF	Left ventricular ejection fraction
Man	Mannose
MBC	Metastatic breast cancer
MRTSS	Mean residence time at steady-state
MS	Mass spectroscopy
MTX	Methotrexate
ORR	Overall response rate
ORRc	ORR in control group
ORRt	ORR in active treatment group
OS	Overall survival
pCR	Pathologic complete response
pCRc	pCR in control group
pCRt	pCR in active treatment group
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Progesterone receptor
PR	Partial response
PTF	Peak to trough fluctuation
RT	Retention time
Sa	Sataloff's classification
SAE	Serious adverse event
SD	Standard deviation
SE-HPLC	Size-exclusion high performance liquid chromatography
SEC-MALS	Size exclusion chromatography - multi-angle light scattering
T1/2	Plasma concentration half-life
TK	Toxicokinetic
Tmax	Time of maximum plasma concentration
VSS	Volume of distribution at steady-state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celltrion Healthcare Hungary Kft. submitted on 10 October 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Herzuma, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Metastatic Breast Cancer (MBC)

Herzuma is indicated for the treatment of patients with HER2 positive metastatic breast cancer:

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.
- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab.

Early Breast Cancer (EBC)

Herzuma is indicated for the treatment of patients with HER2 positive early breast cancer.

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Herzuma therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Herzuma should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

Metastatic Gastric Cancer (MGC)

Herzuma in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herzuma should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see Sections 4.4 and 5.1).

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Not applicable.

Similarity

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 December 2008, 26 February 2009, 29 May 2009, 9 September 2009. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Reference product

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Herceptin, 150 mg, Powder for concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation:
- Marketing authorisation granted by: 28/08/2000
  - Community
- Community Marketing authorisation number: EU/1/00/145/001

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Herceptin, 150 mg, Powder for concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation:
- Marketing authorisation granted by: 28/08/2000
  - Community

- Community Marketing authorisation number: EU/1/00/145/001

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which comparability tests and studies has been conducted:

- Product name, strength, pharmaceutical form: Herceptin, 150 mg, Powder for concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation:
- Marketing authorisation granted by: 28/08/2000
  - Community
- Community Marketing authorisation number: EU/1/00/145/001

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Outi Mäki-Ikola

- The application was received by the EMA on 10 October 2016.
- The procedure started on 27 October 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 January 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 27 January 2017.
- During the meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 23 February 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 7 September 2017.
- The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - GCP inspections at PPD Bioanalytical Labs in United States, Institution of Healthcare in Belarus, and CELLTRION INC. Republic of Korea. The outcome of the inspection carried out was issued on 10 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 16 October 2017.
- During the PRAC meeting on 26 October 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 9 November 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 13 November 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of

Outstanding Issues to all CHMP members on 28 November 2017.

- During the meeting on 14 December 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Herzuma on 14 December 2017.

2. Scientific discussion

2.1. Problem statement

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). The HER2 (also known as ErbB2) is one of a number of transmembrane tyrosine kinases involved in regulating cell growth and survival, as well as cellular adhesion, migration, differentiation, and other cellular responses[1]. Overexpression of HER2 is observed in 20%-30% of primary breast cancers. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8% to 34.0% for IHC and 7.1% to 42.6% for FISH. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. HER2 overexpression was found in a number of disease states, including metastatic breast cancers, early breast cancer and metastatic gastric cancer (MGC). The extracellular domain of the receptor (ECD, p105) can be shed into the blood stream and measured in serum samples (Herceptin SmPC section 5.1).

Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody dependent cell mediated cytotoxicity (ADCC). In vitro, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2 (Herceptin SmPC section 5.1).

Trastuzumab (Herceptin) was first authorised in the EU on 28 August 2000 (see Herceptin EPAR) for the following indications:

Breast cancer

Metastatic breast cancer

Herceptin is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer:

(MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

[1] Hudis CA. Trastuzumab - mechanism of action and use in clinical practice. N Engl J Med. 2007 Jul 5;357(1):39-51.

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer

Herceptin is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC).

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1). following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Herceptin should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

Metastatic gastric cancer

- Herceptin in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.
- Herceptin should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1).

Herceptin is available as 150 mg powder for concentrate for solution for infusion for intravenous administration and 600 mg solution for injection for subcutaneous administration.

About the product

CT-P6 has been developed as a similar biological medicinal product to the reference product Herceptin for intravenous (IV) use with respect to pharmaceutical form, concentration and composition, and route of administration. The only difference is in the concentration of the excipient, trehalose. The formulated CT-P6 drug product is composed of 150 mg trastuzumab per vial. Herceptin was approved in the European Union (EU) in August 2000 (EMEA/H/C/000278).

CT-P6 selectively binds to the extracellular domain of the Human Epidermal Growth Factor Receptor 2 (HER2). Binding of CT-P6 to HER2 blocks its dimerisation with the other receptors of the erbB family, and so prevents the consequent receptor activation which leads to tumour cell growth. Moreover, binding of CT-P6 to HER2 prevents the proteolytic cleavage of its extracellular domain and subsequent activation of its intracellular kinase domain, again preventing HER2 from stimulating a signalling cascade that causes tumour cells to grow.

Type of Application and aspects on development

The marketing authorisation application of Herzuma is an abridged application for a biosimilar under Article 10 (4) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

2.2. Quality aspects

2.2.1. Introduction

Herzuma (also referred to as CT-P6) is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to the extracellular domain of human epidermal growth factor receptor 2 (HER2) and thereby prevents HER2 signalling. In addition, trastuzumab binds to Fc receptors on immune effector cells, facilitating immune destruction of HER2-expressing cancer cells.

Herzuma is presented as a powder for concentrate for solution for infusion. One vial contains 150 mg of trastuzumab produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by chromatographic and viral inactivation and filtration steps.

Trastuzumab is formulated with L-histidine hydrochloride, L-histidine, α,α-trehalose dihydrate and polysorbate 20.

The reconstituted Herzuma solution contains 21 mg/mL of trastuzumab.

2.2.2. Active Substance

General Information

CT-P6 has been developed as a similar biological medicinal product to the reference medicinal product Herceptin (trastuzumab). CT-P6 active substance is a humanised monoclonal antibody of the IgG1 subclass, produced in a CHO cell line. CT-P6 is a glycoprotein with one N-linked glycosylation site on the Asn300 in the CH2 domain of each heavy chain. The oligosaccharides are mostly G0F and G1F structures. The molecular formula for the heavy chain and light chain are $C_{2192}H_{3387}N_{583}O_{671}S_{16}$ and $C_{1032}H_{1603}N_{277}O_{335}S_6$, respectively. Each heavy chain consists of 449 amino acids (without the C-terminal lysine residue) with 11 cysteine residues and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteine residues in the heavy and light chains are involved in either intra- or inter-disulphide bonding. The molecular weight of CT-P6 is approximately 145 kDa.

Manufacture, characterisation and process controls

CT-P6 active substance is manufactured packaged, stability and quality-control tested at Celltrion Inc., Plant II, Incheon, Republic of Korea (CLT2) in accordance with current good manufacturing practice (cGMP).

The manufacturing process starts with thawing of one WCB vial followed by a series of cell culture expansion steps until the production bioreactor step is reached. The active substance is purified from the harvest using three chromatographic steps, followed by viral inactivation and removal steps, as well as an ultrafiltration/diafiltration step.

The manufacturing process and process controls applied are adequately described. Information is given on the purpose and the completion of each manufacturing step, including process parameters and in-process tests in place. The process parameter and in-process tests identified, as well as their criticality assignments are justified.

No reprocessing is foreseen for the manufacturing process of CT-P6.

Control of materials

The CT-P6 cell line was generated using the CHO strain. A two-tier cell bank system, consisting of a Master Cell Bank (MCB) and Working Cell Bank (WCB) was generated. MCB and WCB were characterised according to ICH requirements, e.g. Q5A (R1), Q5B and Q5D. Also, an End-of-Production Cell Bank (EPCB) was generated using the cells from commercial scale. Both MCB and WCB are stored frozen at two different geographical sites. Future replacement WCBs will be generated from the existing previously approved MCB. All newly prepared WCBs will be manufactured in accordance with cGMP guideline and qualified, complying with ICH Q5D and Q5A (R1)

Raw materials of biological origin, as well as other raw materials used in the manufacture of CT-P6 active substance are listed in CTD section S.2.3.3. All raw materials are purchased against an approved specification and from qualified suppliers. Prior to supplying raw materials, all suppliers are evaluated and qualified by Quality Assurance. An overview of the filters, disposable bags and bottles used during downstream process is presented.

Control of critical steps and intermediates

For CT-P6, putative Critical Quality Attributes (CQAs) relevant to CT-P6 active substance were established using a combination of risk assessment, data from early development, process characterisation studies and commercial scale production. The CQAs were finalised on the basis of commercial scale manufacturing experience and characterisation/similarity of CT-P6 to the reference medicinal product. The Applicant has established CQAs that require a control strategy during manufacture of active substance and/or at release.

For establishment of the acceptance ranges/limits of the critical process parameters (CPPs), the Applicant provided summaries with sufficient data on the process characterisation studies conducted to justify the upper and/or lower acceptance limit for each CPP.

Process validation

A formal process consistency validation study has been carried out at the intended production site for CT-P6. The commercial scale manufacturing process was run according to target operational set points and/or range. HCCF batches were produced and each one was purified and filled as a single active substance batch. All batches satisfied the pre-defined acceptance criteria and acceptable ranges for critical process parameters, non-critical process parameters, critical in-process tests and in-process tests, respectively, and met the specification criteria for active substance release testing.

An additional historical data assessment was undertaken after process validation, which incorporates an increased number of active substance batches that have been manufactured at commercial scale. Criteria for process related impurities were slightly adjusted following the historical data assessment. The capability of the purification process to reduce process-related impurities was sufficiently demonstrated by LRVs (Log10 reduction value) in small-scale studies. Historical data assessment through commercial scale demonstrates that HCP, DNA and rProtein A were removed predominantly by the affinity chromatography step and the product is polished with respect to these impurities, throughout the additional downstream process steps.

Initially, a target maximum resin lifetime for the chromatography steps has been tentatively based on results obtained from qualified small-scale models. In case that the commercial scale resin lifetime study does not support the small scale study, the resin life times will be revised on the basis of the results from commercial scale study. For the affinity and ion-exchange chromatography steps, the approach is considered acceptable. The stability of mixed mode chromatography load pool seems to be decreased during the course of resin lifetime study indicated by decrease in monomer content. Based on the data

and justification provided, a revised maximum resin re-use for mixed mode chromatography is acceptable.

Maximum hold times were established for the 6 in-process pools in the CT-P6 manufacturing process. As CT-P6 active substance is stored frozen, the frozen active substance needs to be thawed prior to finished product manufacture. The Applicant has completed a validation study on the freeze and thaw times to be applied during commercial manufacturing, as well as on the impact of freeze-thaw cycles on the quality of CT-P6.

Manufacturing process development

The development of the CT-P6 manufacturing process can be divided into two stages; the old process and the clinical process. During process development and scale up, active substance manufacturing process changes were introduced in order to optimise the process for commercial manufacture. There are major differences between the old and the clinical process, however, only the clinical process has been used for manufacture of material to support CT-P6 as a biosimilar to Herceptin. Hence a comparability exercise is not required.

Characterisation

For the characterisation of CT-P6 a comprehensive series of analytical methods have been used. These methods included state-of the art sensitive and orthogonal physicochemical and biological tests to determine the primary, secondary, and higher-order structure, post-translational modifications (PTMs) and associated heterogeneities, glycosylation, charge variants, purity/impurities, and quantity of CT-P6. In addition, biological activity has been characterised with regard to the trastuzumab primary mechanism of action (HER2 binding and inhibition of cell signalling for proliferation), as well as secondary mechanism of action (ADCC, as well as FcγR family, FcRn and C1q binding affinities). In combination with the characterisation study results provided in CTD section 3.2.R.5, these studies are considered adequate and sufficient to provide a detailed characterisation of CT-P6.

Clearance validation studies have been performed to demonstrate that the manufacturing process provides adequate clearance of impurities. The batch results indicate that levels of process-related impurities are consistently low among the active substance batches. There are only two impurities not present in the reference product Herceptin, which present an inherently low risk of immunogenicity. The levels of these impurities are monitored and controlled as an in-process testing item at the UF/DF step. The Applicant has developed and validated analytical methods for the detection of the two novel impurities. The proposed control strategy for the impurities is considered acceptable.

Further information related to characterisation of the active substance can be found in the biosimilarity section.

Specification

The active substance release specification for CT-P6 has been set taking ICH Q6B guideline into account; it contains tests for identity, glycosylation, purity/impurity profile, quantity and potency, as well as general and safety tests. The acceptance criteria are adequate. The release and the end-of-shelf-life specifications are identical, except that the tests for process-related impurities are only included in the release specification.

Release data derived from commercial scale active substance batches were statistically processed to set the acceptance criteria for commercial batch release tests. Where appropriate, putative acceptance limits for individual test parameters were generated from historical batch data. The acceptance criteria defined for the specifications are generally acceptable and represent state-of-the-art limits. The proposed upper limit for afucosylated glycans has been adequately justified and is considered acceptable. However, the initially proposed lower active substance specification limit for afucosylated glycans had to be adjusted in

order to be aligned to the levels seen in Herceptin pre-shift batches and ensure clinical performance of Herzuma (Kim *et al.*, 2017, *Drifts in ADCC-related quality attributes of Herceptin*). The Applicant has revised the acceptance criterion for afucosylated glycans for routine control at release and in the end-of-shelf-life specification. This is acceptable.

Analytical methods

CT-P6 active substance is tested using a combination of compendial and non-compendial methods. Non-compendial analytical methods used for CT-P6 routine testing have been validated in line with ICH Q2(R1). The performance of compendial methods has been verified in accordance with relevant Ph. Eur. Chapters.

Batch analysis

The proposed commercial specifications were developed based on statistical analysis of release data from the historical batches.

Results for the impurities not present in the reference product conducted as in-process tests are attached to the active substance certificate of analyses. For all batches the predefined acceptance criteria were met.

Reference standard

The CT-P6 primary reference standard was derived from active substance batch manufactured using the proposed commercial scale manufacturing process. The reference standard was qualified as the primary reference standard in accordance with ICH Q6B 'Specifications: Test procedures and acceptance criteria for biotechnological/biological products'. Testing according to the pre-defined specifications and additional characterisation testing was used to qualify the primary reference standard. The primary reference standard is stored at ≤ -60° C. Re-qualification will be performed periodically using an acceptable pre-defined assay panel and specification. Test Methods and Acceptance Criteria for Qualification and Requalification of a future CT-P6 Working Reference Standard is considered acceptable. A new reference standard will be assessed by the battery of methodologies and the pre-defined acceptance criteria for the current reference standard or, should the release acceptance criteria for active substance change, the acceptance criteria in place at that time.

Container closure

Leachable studies demonstrate that there is low level of leachable present in CT-P6 active substance, does not pose a safety risk when CT-P6 active substance. The bottles meet the relevant requirements of the Ph. Eur.

Stability

Long-term stability studies have been conducted on representative batches manufactured using the commercial manufacturing process and stored in reduced size containers representative for the commercial scale containers. Stability data at long-term conditions together with data from studies at accelerated and stress conditions support a shelf life when stored at proposed temperature, according to the principles outlined in ICH Q5C. Studies are planned to be continued according to stability protocol. The stability of CT-P6 active substance has been adequately addressed.

In addition to the long-term stability study, stability studies under intermediate condition, accelerated condition, stress condition as well as a photo-stability study have been performed.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The CT-P6 finished product is formulated for intravenous infusion as a sterile, white to pale yellow lyophilised powder containing 150 mg of CT-P6 active substance as the active ingredient, α,α-trehalose dihydrate, L-histidine HCl, L-histidine and polysorbate 20. There are no novel excipients or excipients of animal grade. The excipients used in CT-P6 finished product are the same as the excipients used in the formulation of the reference product, EU-approved Herceptin. However, the quantity of α,α-trehalose, dihydrate, has been increased for the formulation of CT-P6 finished product. According to the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), the formulation of the biosimilar should be selected taking into account state-of-the-art technology and does not need to be identical to that of the reference medicinal product. The formulation has been demonstrated to produce a product of acceptable quality and stability. All the excipients used in the formulation of CT-P6 finished product comply with Ph. Eur. requirements. To ensure the labelled dose of 150 mg can be withdrawn from each vial, a 4% volume overfill is applied during filling into vials.

CT-P6 finished product (150 mg) is stored in a glass vial with rubber stopper and a flip-off seal. Leachable studies confirmed that no leached elements or chemicals were detected. The safety of the glass vial and the elastomeric stopper are ensured through compliance with Ph. Eur. requirements. The lyophilized powder is reconstituted with 7.2 mL of sterile water for injections (SWFI) to yield a single dose formulation containing 21 mg/mL trastuzumab, at pH 6.0. Prior to administration, reconstituted CT-P6 finished product is diluted using 0.9% w/v sodium chloride in an infusion bag. The compatibility of the CT-P6 finished product with the infusion bags made from 3 different materials, polyethylene (PE), polypropylene (PP), and polyvinyl chloride (PVC) containing 9 mg/mL (0.9% w/v) sodium chloride solution for injection has been studied.

Manufacturing process development

During process development, several changes were implemented to optimise the production process for commercial manufacture. The pre-change finished product manufacturing process is referred to as Process A. The post-change finished product manufacturing process is referred to as Process B. Process B is the proposed commercial finished product manufacturing process. Considering the level of changes, no significant quality difference between Process A and Process B finished product lots were expected. However, an extensive comparability assessment was conducted by means of physicochemical and biological testing items including release and characterisation analysis methods. Stability data were also compared between Process A and Process B finished product lots. The results of comparability testing showed that CT-P6 finished product manufactured by the two processes is comparable.

Manufacture of the product and process controls

Commercial CT-P6 finished product is manufactured in accordance with cGMP. The CT-P6 finished product manufacturing process consists of formulation of active substance, 1st filtration, aseptic filling (2nd sterile filtration), lyophilisation, capping and visual inspection; a clear step-by-step description of the manufacturing process is provided.

The provided overall control strategy for the finished product manufacturing process is acceptable. Raw and starting materials are tested to ensure their suitability for use in manufacture of CT-P6 finished product. The control of the finished product manufacturing process for CT-P6 is achieved through applying acceptable ranges for process parameters (input variables). The successful control of the manufacturing process is evaluated through in-process tests (output variables). Process parameters and controls are indicated. CPPs and critical IPTs (CIPTs) are highlighted. The classification and the defined

ranges are considered acceptable. Each of the 34 evaluated process variables (input and output variables) have been classified as critical or non-critical on the basis of a risk assessment. All CPP and CIPT have designated acceptance criteria, that have been set based on development studies and/or historical manufacturing data and process validation. Protein content and microbiological purity have been identified as CQAs that can potentially be impacted by the finished product manufacturing process.

The Applicant submitted a post-approval change management protocol (PACMP) to introduce an alternative container closure system for the manufacturing of CT-P6 finished product to ensure the integrity of the supply chain in case of interruptions in the supply of the current primary packaging components. A new glass vial with a new suitable stopper will be used as an alternative primary container. The alternative container closure system will be used in parallel with the current one. The proposed implementation plan (Type IB variation) is acceptable. The PACMP is considered acceptable.

Process validation

The CT-P6 finished product manufacturing process was validated at the proposed commercial manufacturing site. The validation studies included validation of formulation of the final bulk, 1st filtration, sterilization, aseptic filling (2nd filtration), lyophilisation, capping, and visual inspection. Both controlled process parameters as well as output parameters with pre-determined acceptance criteria were evaluated.

Media fills have been performed on a routine basis in accordance with EU-GMP Annex I. Shipping validation of the active container for unlabelled finished product was performed through consecutive finished product shipments with maximum load configuration, which is considered acceptable.

Product specification

The test items proposed for release testing are largely in line with the requirements of the European Pharmacopoeia, as well as the CHMP guideline on monoclonal antibodies. The finished product release specification includes general and safety tests, identity, purity/impurity, content and potency. The end-of-shelf-life specification is identical to the release specification except that in the release specification identity is tested only. The acceptance criteria for commercial lot release has been established based on CT-P6 finished product manufactured throughout development; these lots were used in stability and similarity studies, as well as validation of the commercial finished product manufacturing site. The proposed acceptance limits are set sufficiently tight to reflect manufacturing experience, as well as the quality profile of batches used in clinical trials. Moreover, the proposed acceptance criteria for purity, content and potency give a final assurance that the commercial CT-P6 will have a quality profile that is similar to Herceptin in the comprehensive characterisation studies.

Analytical methods

CT-P6 finished product is tested using a combination of compendial and non-compendial methods. For compendial test methods, relevant pharmacopoeial references are given and for non-compendial test methods, descriptions of the assay procedures are provided. The assay verification/qualification results for both compendial and non-compendial assays are provided indicating that the assays are suitable for the intended use and precise, specific and robust.

Batch analysis

The proposed commercial specification is based on statistical evaluation of the batch analysis results. For all batches the predefined acceptance criteria were met.

Reference materials

The reference standards used for extended characterisation, comparability testing, stability testing and routine batch release testing of the finished product are the same as those employed for the active substance.

Stability of the product

The storage condition proposed for the CT-P6 finished product is 5±3°C. Thus, a long-term stability study at 5±3°C has been performed. In addition, and accelerated stability study at 25±2°C/60±5% RH (6 months) and a stress stability study at 40±2°C/75±5% RH (3 months) have been conducted. All evaluated stability parameters met acceptance criteria, and no significant trends could be observed. The applicant's shelf life claim of 36 months at 5±3°C is considered to be supported by the provided data and is agreed.

After reconstitution with sterile water for injection the reconstituted solution is physically and chemically stable for 48 hours at 2°C – 8°C. Any remaining reconstituted solution should be discarded.

After dilution, solutions of Herzuma for intravenous infusion are physically and chemically stable in polyvinylchloride (PVC), polyethylene (PE) or polypropylene (PP) bags containing sodium chloride 9 mg/mL (0.9%) solution for injection for 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and Herzuma infusion solution should be used immediately. The product is not intended to be stored after reconstitution and dilution unless this has taken place under controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

The results of the confirmatory photostability study indicate that the product is photostable when stored in its primary and secondary packaging.

Adventitious agents

The antibody is produced in a cell culture medium free of animal or human-derived components (except only one component used for active substance manufacturing). No raw materials of human origin are used during CT-P6 active substance and finished product manufacture. All animal derived raw materials used for the production of CT-P6 have been evaluated in relation to the risk of transmitting animal spongiform encephalopathy agents.

Mycoplasma and microbial bioburden are controlled during manufacture through use of a sanitary and/or aseptic process design. In-process materials, process buffers and media are filtered where applicable, with in-process tests to confirm their performance. In-process control testing for bioburden and endotoxin is also routinely carried out to ensure microbial safety throughout manufacture. Bioburden, sterility (finished product only) and endotoxin are included in the routine active substance and product release strategies which ensure only materials of suitable quality with respect to microbial safety are released for further processing or for commercial supply.

The potential presence of endogenous and adventitious viruses in the MCB, WCB and EPCB were tested with validated methods. The virus tests failed to demonstrate the presence of viral contaminants. Only retrovirus-like particles have been detected. CHO cells are well known to produce endogenous retrovirus like particles. The presence of retroviral particles is acceptable since there is excess reduction capacity for retroviral particles within manufacturing process. Routine testing on unprocessed bulk is performed using indicator cell lines.

Viral clearance studies have been conducted in accordance with the guidance given in ICH Q5A and other relevant guidelines. Four model viruses have been selected for the viral clearance studies (Xenotropic murine leukemia virus (XMuLV), Pseudorabies virus (PRV), reovirus type 3 (Reo-3) and minute virus of mice (MVM)). These viruses cover an adequate range of properties, including size, genome content, as

well as resistance low pH inactivation. The purification process includes four steps (2 chromatographic steps, low pH incubation and virus filtration) which have been validated for their virus reduction capacity. A sufficient overall virus inactivation/removal capacity has been demonstrated. Using scale-down models operating under worst-case conditions, four process steps have been assessed; affinity Chromatography, low pH treatment, Mixed Mode Chromatography and virus filtration. The overall minimum combined log10 reduction values for the four unit operations were considered satisfactory. A sufficient overall virus inactivation/removal capacity has been demonstrated. The maximum volumetric filter load and low pressure are considered a worst case for virus reduction.

Biosimilarity

Reference product

The reference product for CT-P6 in EU is the EU-authorised Herceptin (EU-Herceptin) presented as a single dose vial containing 150 mg trastuzumab. The presentation of the CT-P6 biosimilar intended for the EU market is the same as EU-Herceptin (i.e. 150 mg/vial). Also the excipients of CT-P6 are identical to EU-Herceptin, except for the quantity of α,α-trehalose, dihydrate, which has, based on formulation development studies been increased in CT-P6.

US-licensed Herceptin (US-Herceptin) is presented in a multidose formulation containing 440 mg trastuzumab to be reconstituted with 20 mL of bacteriostatic water for injection (BWFI) containing 1.1% benzyl alcohol. The final trastuzumab concentration in the reconstituted Herceptin is 21 mg/mL, which is the same as for EU-Herceptin. In the clinical studies, CT-P6 formulated as 440 mg/vial has been compared against US-Herceptin. The reference product, EU-Herceptin 150 mg/vial, has not been included in any clinical trial, therefore the bridge between the EU reference product (EU-Herceptin) and the comparator used in the clinical studies (US-Herceptin) needs to be established based on physicochemical and biological similarity studies. The Applicant has addressed this as part of the 3-way similarity assessment for biosimilarity.

CT-P6 batches in the biosimilarity studies

As the 440 mg/vial presentation of the biosimilar was used in the clinical trials, comparability between the 150 mg/vial and the 440 mg/vial presentation of the biosimilar also has to be established. Considering that the trastuzumab concentration of the reconstituted product is, in both cases the same (21 mg/mL trastuzumab), an analytical comparability exercise is deemed sufficient. In this regard, the Applicant has conducted a comprehensive analytical characterisation study to address the comparability between the CT-P6 150 mg/vial and 440 mg/vial presentations. No relevant differences can be seen between the two presentations, comparability can therefore be concluded. It is consequently also considered acceptable to apply both 150 mg and 440 mg batches in the analytical similarity exercise. Furthermore, the use of the 440 mg/vial presentation as the only CT-P6 included in the clinical studies is, from a quality point of view, justified.

For the biosimilarity exercise, CT-P6 finished product, EU-Herceptin and US-Herceptin were analysed. The analysed CT-P6 batches include the 150 mg/vial presentation corresponding to EU-Herceptin as well as the 440 mg/vial presentation which is the presentation intended for the US market. Overall, the number of batches is sufficient to both estimate the batch-to-batch variability present in the reference product, as well as to assess the similarity between CT-P6, EU-Herceptin and, US-Herceptin.

Similarity ranges

Ranges for the assessment of *biological* similarity have been established based on descriptive statistical ranges determined from the analysed EU-Herceptin batches. Similarity is concluded if at least 90% of the CT-P6 batches fall inside the similarity ranges. The similarity criteria applied is not considered to provide strong evidence for biosimilarity. However, as characterisation results from all batches analysed are given, similarity can be assessed independently of the established similarity ranges.

Study results of 3-way similarity assessment (Tables 1 and 2)

Analytical methods

All analytical methods used for the similarity assessment have either been validated (release and stability methods) or qualified for the intended use (additional physicochemical and biological test methods).

Primary- and higher order structures

The primary structures of CT-P6, EU- and US-Herceptin were compared by amino acid analysis, molar absorptivity (molar extinction coefficient), peptide mapping by HPLC, peptide mapping in combination with liquid chromatography mass spectrometry (LC/MS) (including assessment of deamidation, oxidation and isomerisation), intact mass analysis (LC-MS), N-terminal and C-terminal sequencing. Expect for a minor difference in C-terminal proline amidation which was found to be higher in CT-P6 compared EU- and US-Herceptin, no significant differences between the three products were detected. The difference in proline amidation is not expected to be clinically relevant. Similarity with regard to primary structures is thereby concluded.

The comparative results on disulphide bridging (peptide mapping and free thiol analysis), as well as the results from assays addressing higher order structures (Fournier transform infra-red (FTIR), circular dichroism (CD), differential scanning calorimetry (DSC) and antibody array), all suggest similarity between CT-P6, EU-Herceptin and US-Herceptin.

Purity and impurities

As measured by either SEC-HPLC or SEC multi-angle laser light scattering (SEC-MALS), the purity of all three finished products is higher than 99%. In SEC-HPLC, the range of high molecular weight (HMW) species for CT-P6 finished product was marginally lower than that of EU- and US-Herceptin. This minor difference is of no clinical significance. The results from AUC analyses confirm the similarity.

Using CE-SDS under reducing condition, a slightly higher level of non-glycosylated heavy chain variants were seen in CT-P6 compared to both EU- and US-Herceptin. In addition, under non-reducing conditions, the level of intact IgG was marginally lower in CT-P6 compared to EU- and US-Herceptin. These small differences are not expected to affect the function of the antibody.

Charge variants

While no differences between CT-P6, EU-Herceptin and US-Herceptin is seen by IEF, some minor differences appear to be present when analysed by IEC-HPLC. The acidic peaks (sum of peaks 1, 2, 3 and 4) of all three products show similar relative proportions. But for the main peak (peak 5), there could be a slight difference with a possibly lower relative proportion in CT-P6 and US-Herceptin compared to EU-Herceptin. In addition, for peak 6, slightly lower levels are seen in CT-P6. Also for peak 7 a small difference is detected with higher relative proportions in CT-P6 than in EU- or US-Herceptin.

In order to understand the impact of these minor differences, the Applicant conducted a comprehensive peak fractionation study, including identification of the molecular variants present in each peak. In addition, the biological activity was separately measured from the fractionated peaks. Except for peak 6

for which activity could not be calculated in the anti-proliferation assay, no significant differences in the anti-proliferation activity or in binding to HER2, C1q, FcγRIIIa, and FcRn of the 7 fractionated peaks can be seen. Since peak 6 represents a minor fraction of the total charge variants, based on characterisation results presented, it can be agreed that the differences in the charge variant profiles between CT-P6 and EU-Herceptin are of no clinical concern.

Glycosylation

In the 2-AB labelled oligosaccharide profiling using hydrophilic interaction liquid ultra-performance chromatography (HILIC-UPLC) analyses, generally good agreement on the types and proportions of glycans present in CT-P6 and EU- and US-Herceptin was seen. For the minor glycan variants, practically no differences are detected. However, based on mean contents from the analysed batches, the main glycoform G0F appears to be present at a lower level in CT-P6 compared to Herceptin. Similar results are also presented from N-linked glycan analysis based on peptide analyses by LC-MS.

With regard to sialic acid content, relatively higher N-acetylneuraminic acid (NANA) levels were obtained for all CT-P6 batches compared to EU-Herceptin and US-Herceptin. The N-glycolylneuraminic acid (NGNA) levels were similarly low in all three products.

In order to justify the minor differences in the glycan profiles, the Applicant has studied the influence of aglycosylation, agalactosylation, amannosylation and asialylation on the binding and anti-proliferation activities of Herceptin and CT-P6. As expected, aglycosylation impacted FcγRIIIa-V binding similarly in all samples. However, as no significant differences in aglycosylation levels are seen between CT-P6, EU- and US-Herceptin, this correlation is of no concern. Binding to FcRn and HER2, as well as the anti-proliferation activity of trastuzumab were not affected. Together these studies provide assurance that the minor differences in galactosylated species and sialylated glycans do not impact the function of the antibody.

Content

In the comparison for protein content, several CT-P6 batches were shown to have lower protein concentrations compared to the minimum concentration measured from the analysed EU-Herceptin batches. Despite this, the protein content of all measured CT-P6 batches are within margins of the EU Herceptin batches. Similarity between the three products with regard to protein content can thereby be concluded despite the observed minor difference in the mean protein concentration of the three products.

Biological similarity assessment

For the assessment of biological similarity the Applicant has compared HER2 binding (ELISA), cell-based binding affinity of CT-P6 and EU-/US-Herceptin to HER2 overexpressing cells, *in vitro* bioactivity in an anti-proliferation assay, C1q binding (ELISA), FcgRI, IIa, IIb, IIIa-V, IIIa-F, IIIb and FcRn binding (SPR), ADCC using peripheral blood mononuclear cells (PBMC) as effector cells, and ADCC using a reporter assay. The data suggest that CT-P6 and Herceptin can be considered similar as the pre-defined biosimilarity ranges are met. It is noted that regarding binding to FcγIIIa-V, IIIa-F, IIIb and ADCC activity there is a higher batch-to-batch consistency of CT-P6 compared to both EU- and US-Herceptin and considering the means of all batches there is a slightly higher binding affinity and ADCC activity of CT-P6 compared to EU- and US-Herceptin.

The binding results from the cell-based assay further confirm similarity with regard to binding to HER2. Altogether, similarity between CT-P6 and EU-Herceptin, as well as between EU- and US-Herceptin has been demonstrated for the *in vitro* bioactivity assay.

Additional mode of action studies

To further support the claim of biosimilarity between CT-P6 and EU-Herceptin, as well as between EU- and US-Herceptin, the Applicant has conducted an array of *in vitro* studies relevant or potentially relevant for

the mode of action of trastuzumab. These studies show comparable activities in the inhibition of proteolytic cleavage of HER2 extracellular domain (ECD), down-regulation of HER2 expression, inhibition of downstream signalling pathways, induction of cell cycle arrest, suppression of VEGF secretion activity, and in the induction of antibody-dependent cellular phagocytosis (ADCP). Higher variability is observed in the assay for inhibition of Akt1 and HER3 phosphorylation and in the FACS-based cell cycle arrest assay. These differences are, however, small and within the variability of the assays, and therefore they do not impact the similarity claim.

Forced degradation studies

In addition to the physicochemical and biological comparison, the Applicant has conducted comparative force degradation stability studies. The treatment conditions included; oxidizing (H_2O_2) conditions, UV exposed conditions, high temperature, as well as low and high pH conditions. As expected, all forced degradation conditions resulted in changes in the quality profiles of CT-P6 (both 150 mg and 440 mg presentation included), EU- and US-Herceptin. Importantly, however, similar degradation patterns were seen for all products thereby confirming the similarity between CT-P6 (150 mg and 440 mg), EU-Herceptin and US-Herceptin.

Table 1: Physico-chemical analytical similarity assessment between Herzuma and Herceptin

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Primary structure	Amino Acid Analysis	RP-HPLC	Similar ratio of each amino acid
	Molar Absorptivity		Similar molar absorptivity and extinction coefficient
	Extinction Coefficient		
	Tryptic peptide mapping	RP-HPLC	Similar visual peptide map
	Sequence Coverage and Modifications	Peptide mapping by LC-MS	100% amino acid sequence coverage. Slightly higher level of C-terminal proline amidation in Herzuma is not considered to have an impact on biological activities
	Molecular Weight	Intact mass by LC-MS	Similar masses for each species
	N-terminal and C-terminal Sequence	Peptide mapping by LC-MS	Identical N-terminal and C-terminal sequences of light chain and heavy chains
Higher order structure	Disulphide Bond	Peptide mapping by LC-MS	Same disulphide bond positions and arrangements
	Free Thiol Analysis	Ellman's assay	Similar levels of free thiol
	Secondary Structure	Fourier Transform Infrared Spectroscopy (FTIR)	Similar FTIR spectra
	Secondary and Tertiary Structure	Circular Dichroism (CD)	Similar secondary and tertiary structure
	Thermal stability	Differential Scanning Calorimetry (DSC)	Transition temperatures consistent with Herceptin
	Protein Conformation	HercBridge Protein Conformational Array (PCA) ELISA	Epitope exposure of Herzuma is consistent with Herceptin.

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Content	Protein Concentration	Spectrophotometrical absorbance at UV_{280}	Similar protein concentration
Purity	Aggregates and Fragments	SEC-HPLC	Similar level of monomer, HMW and LMW forms
		SEC-MALS	Similar molecular weights and levels of monomer and HMW
		AUC	Similar sedimentation coefficients and amounts of monomer and dimer
	intact H+L	Reduced CE-SDS	Comparable levels of heavy and light chain Slightly higher levels of non-glycosylated heavy chain for Herzuma
	Fragmentation	Non-reduced CE-SDS	Slightly lower levels of intact IgG for Herzuma
	Residual Impurities	Residual Host Cell Protein	No relevant difference
		Residual Host Cell DNA	No relevant difference
		Residual rProtein A	No relevant difference
Charge variants	Charge Isoforms and Distribution.	Isoelectric focusing	Similar pI values of the major bands
		IEC-HPLC	Similar qualitative charge profile and similar relative proportion of acidic peaks. Slightly lower relative proportion of the main peak and higher relative proportion of basic peaks in Herzuma.
Glycosylation	Types and proportions of Glycans	NP-UPLC	Similar qualitative glycosylation profile but quantitative differences. Lower level of G0F and higher level of G1F and G2F in Herzuma, ,
	Sialic Acid	RP-HPLC	Same sialic acids present NANA present at slightly higher level in Herzuma but at trace amount
	N-linked Glycan	Peptide mapping by LC-MS	Same glycan species Slightly lower level of G0F and higher level of G1F and G2F in Herzuma

Table 2: Biological analytical similarity assessment between Herzuma and Herceptin - In vitro bioactivity and Binding assays

Test		Methods / Cell line	Key findings
Binding Affinity	HER2 Binding	Enzyme-linked immunosorbent assay (ELISA)	Similar binding to Her2
		Cell-based ELISA	Similar binding to Her2
	C1q Binding Affinity	C1q Binding ELISA	Similar binding to C1q
	FcγRIIIa V Type Binding Affinity	Surface plasmon resonance assay	Slightly higher binding affinity to FcγRIIIa V Type when considering the means of all batches tested
	FcγRIIIa F Type Binding Affinity	Surface plasmon resonance assay	Slightly higher binding affinity FcγRIIIa F Type when considering the means of all batches tested
	FcγRIIIb Binding Affinity	Surface plasmon resonance assay	Slightly higher binding affinity to FcγRIIIb when considering the means of all batches tested
	FcγRIIa Binding Affinity	Surface plasmon resonance assay	Similar binding affinity to FcγRIIa
	FcγRIIb Binding Affinity	Surface plasmon resonance assay	Similar binding affinity to FcγRIIb
	FcγRI Binding Affinity	Surface plasmon resonance assay	Similar binding affinity to FcγRI
	FcRn Binding Affinity	Surface plasmon resonance assay	Similar binding affinity to FcRn
In vitro bioactivity	Anti-proliferation	Anti-proliferation activity against human breast cancer cell line	Similar potency
	ADCC assay	ADCC assay against human breast cancer cell line (PBMC effector cells)	Similar ADCC activity
		ADCC reporter assay	Slightly higher ADCC activity of Herzuma when considering the means of all batches tested

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Module 3 of the dossier for CT-P6 is of good quality and the information provided is sufficiently detailed. Overall, the quality of Herzuma is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

Similarity between CT-P6 and the reference product, EU-Herceptin, has been addressed in an extensive comparability exercise. The similarity between CT-P6 (150 mg/vial intended for the EU market) and EU-Herceptin can be confirmed. In addition, based on the comprehensive analytical and biological

characterisation studies conducted, the bridge between the reference product (EU-Herceptin) and the comparator (US-Herceptin) used in clinical trials has been successfully demonstrated.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall Quality of Herzuma is considered acceptable.

Biosimilarity with the reference medicinal product Herceptin has been sufficiently demonstrated. From a quality point of view, the observed differences and levels of these differences have been well documented and are acceptable.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A 3-way similarity exercise was undertaken, to demonstrate the similarity of CT-P6 to EU-approved Herceptin and also to demonstrate the similarity of US-licensed Herceptin (440 mg) to EU-approved Herceptin (150 mg).

The applicant submitted non-clinical studies with sensitive test methods to demonstrate similarity. The non-clinical studies included a 3-way similarity study comparing analysis of primary, secondary and tertiary structure, glycan profiles and of post-translational modifications. In addition, many biological and analytical assays were performed evaluating comparative affinity binding, ADCC function and FcγRII and FcγRIII binding as similarity to trastuzumab (Herceptin).

2.3.2. Pharmacology

Primary pharmacodynamic studies

Inhibition of HER2 Extracellular Domain Cleavage

Trastuzumab has been shown to block cleavage of the extracellular domain of HER2, thus, preventing formation of the constitutively active membrane-bound 95-kDa HER2 protein called p95 HER2[2]. HER2 shedding is also activated by 4-aminophenylmercuric acetate (APMA), a well-known matrix metalloprotease activator, in HER2-overexpressing breast cancer cells. Thus, the inhibition of APMA-induced cleavage of HER2 by trastuzumab and prevention of the production of an active truncated HER2 fragment represents one of the MoAs of trastuzumab.

BT-474 cells, a human breast cancer cell line, were incubated with EU-approved Herceptin, CT-P6 drug product and US-licensed Herceptin, at 3 concentrations with APMA and subsequently incubated for 2 hours with human ErBb2 detection antibody. Results of the extracellular cleavage domain are presented in Figure 1.

[2] Nahta R. Molecular Mechanisms of Trastuzumab-Based Treatment in HER2-Overexpressing Breast Cancer. ISRN Oncol. 2012;2012:428062

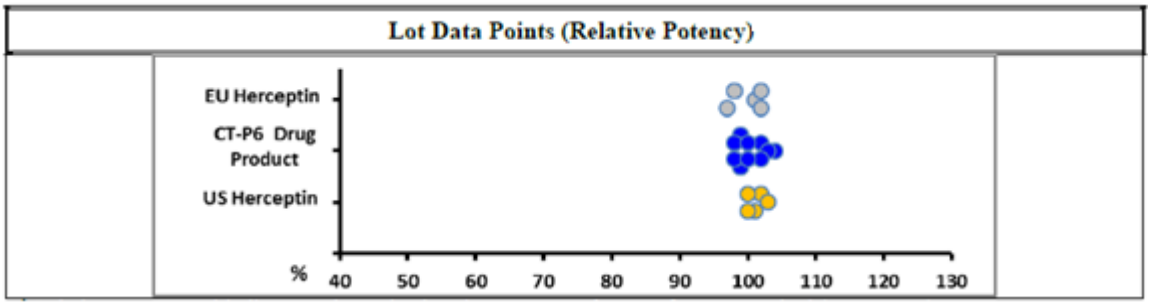


Figure 1: Scatter Plot for Inhibition of HER2 Extracellular Domain Cleavage Results

Binding to HER2

In vitro binding affinity to HER2 was analysed with ELISA and in a cell-based system. Binding to HER2 expressed on the cell surface is a key mechanism for trastuzumab to exert its therapeutic effect.

The total mean for relative binding affinities of CT-P6, EU-approved Herceptin and US-licensed Herceptin were within 97%-100% using an ELISA method.

The total mean for relative binding affinities on cell based system (on HER2 overexpressing human breast cancer cells SK-BR3) using cell-based ELISA (CELISA) of CT-P6, EU-approved Herceptin and US-licensed Herceptin were within 99% - 102%.

CT-P6 lots in these HER2 binding studies were within mean ± 3SD of EU-approved Herceptin and thus, the binding affinities of CT-P6 and reference products were considered highly similar.

Down-regulation of HER2 Expression

In vitro Herceptin treatment down-regulates the HER2 expression resulting in inhibition of downstream signaling pathways involved in cell survival, cell proliferation and metastasis. Hence, down-regulation of HER2 expression by the treatment of EU-approved Herceptin, CT-P6 drug product and US-licensed Herceptin to HER2-overexpressing SK-BR-3 cells on cell surface were determined using the cell-based HER2 binding affinity ELISA.

SK-BR-3 cells were incubated with EU-approved Herceptin, CT-P6 drug product and US-licensed Herceptin (5, 150 and 2,000 ng/mL)and cell surface HER2 expression was detected and measured. Results are presented in Figure 2.

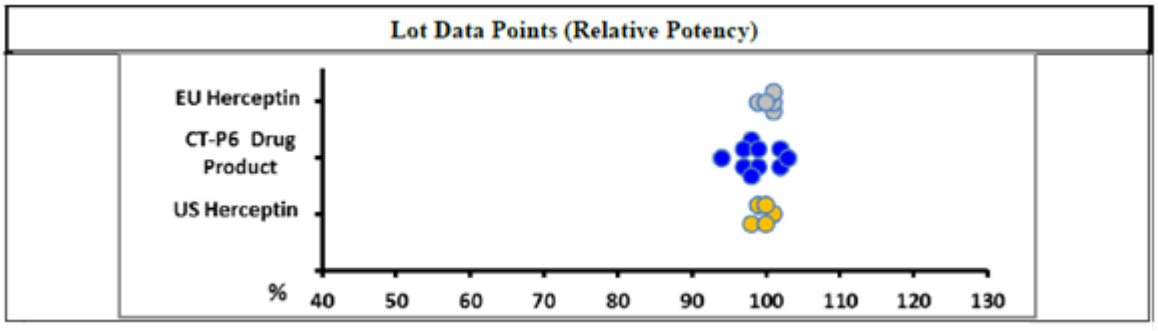


Figure 2: Scatter Plot for Down-Regulation of HER2 Expression Results

In vitro bioactivity (anti-proliferation activity)

The *in vitro* functional activity of CT-P6 and Herceptin were compared in HER2 overexpressing human breast cancer cells (BT-474). The total mean for relative *in vitro* bioactivity of CT-P6, EU-approved Herceptin and US-licensed Herceptin were within 101% - 105%. All lots of CT-P6 were within mean ± 3SD of EU-approved Herceptin for anti-proliferative activity. The potencies of CT-P6 and reference products were highly similar.

Induction of Cell Cycle Arrest

The cell cycle arrest effect of EU-approved Herceptin, CT-P6 drug product and US-licensed Herceptin at G1 phase was assessed using FACS analysis in breast cancer cell line, SK-BR-3 cells.

SK-BR-3 cells were incubated with EU-approved Herceptin, CT-P6 drug product and US-licensed Herceptin (final concentration: 133 ng/mL). The cell cycle arrest was assessed by flow cytometry to analyse the DNA content of target cells stained with propidium iodide (PI) using FACS analysis.

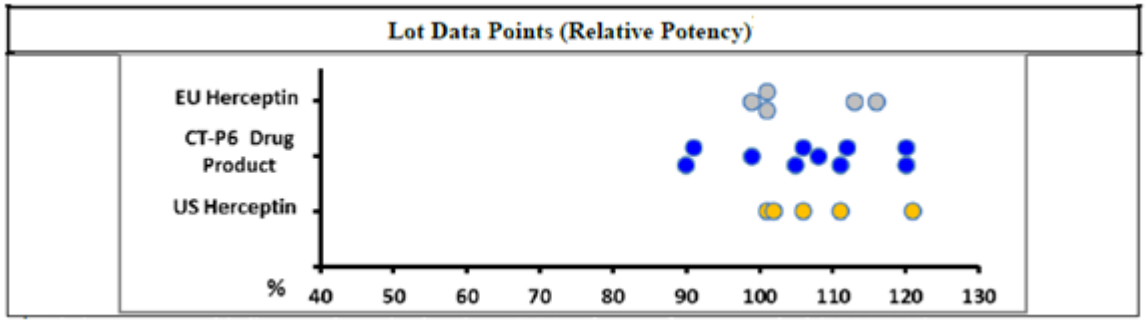


Figure 3: Scatter Plot for Induction of Cell Cycle Arrest Results

Suppression of VEGF Secretion

HER2-overexpressing human breast cancer cells secrete VEGF at high levels, which leads to angiogenesis in site of the tumour[3]. Herceptin is thought to act through suppression of VEGF secretion in breast tumour cell. In this study, the VEGF suppression activity of EU-approved Herceptin, CT-P6 drug product and US-licensed Herceptin was evaluated and compared in vitro.

BT-474 cells were incubated with EU-approved Herceptin, CT-P6 drug product and US-licensed Herceptin at three concentrations and VEGF production was measured with cell supernatant.

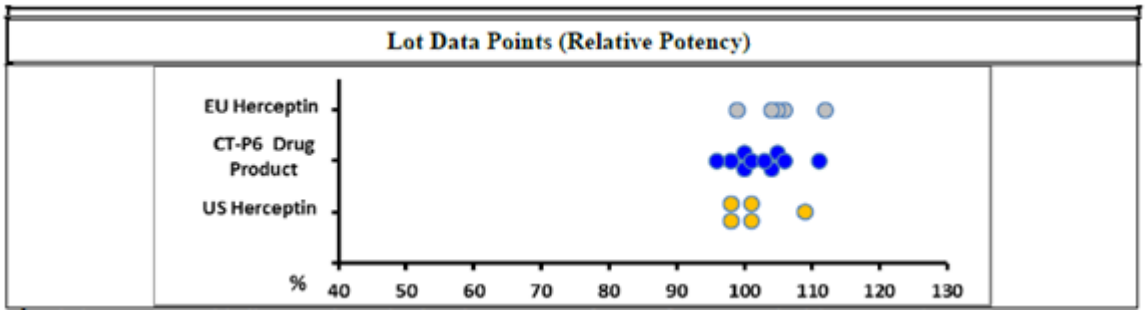


Figure 4: Scatter Plot for VEGF Suppression Results

[3] Le XF, Mao W, Lu C, Thornton A, Heymach JV, Sood AK, Bast RC Jr. Specific blockade of VEGF and HER2 pathways results in greater growth inhibition of breast cancer xenografts that overexpress HER2. Cell Cycle. 2008 Dec;7(23):3747-58

Antibody Dependent Cellular Phagocytosis

Monocytes were isolated from human PBMCs and treated with GM-CSF for 10 – 14 days to enable differentiation into macrophages. The SK-BR-3 cells were stained with PKH67 green fluorescent cell linker kit and incubated for 30 minutes with EU-approved Herceptin, CT-P6 drug product and US-licensed Herceptin. Macrophages were incubated for 3 hours at effector: target ratio of 1:1with antibody-treated SK-BR-3 cells and after incubation, were stained with CD11b-APC for FACS analysis.

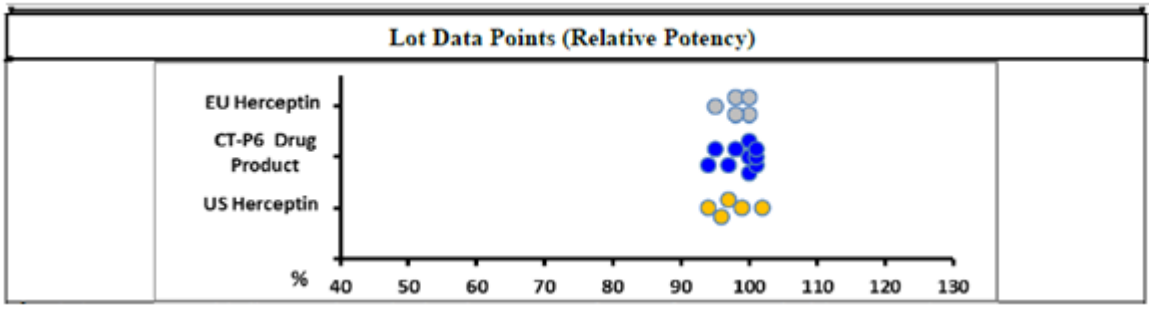


Figure 5: Scatter Plot for ADCP Results

Binding to FC receptors and C1q

The comparative *in vitro* to FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa V- and F-type receptors, FcγRIIIb, FcRn binding affinity studies with SPR were conducted. Relative KD values were calculated by comparison of KD values of test articles with those of reference standard. In addition, the binding affinity to C1q of CT-P6 was compared to Herceptin (EU, US) with the ELISA method. The total mean (range) for relative binding affinities of each parameters tested of CT-P6, EU-approved Herceptin and US-licensed Herceptin were considered highly similar.

Table 3: In vitro primary pharmacodynamics studies of CT-P6 and Herceptin and results (mean % ±SD)

Analytical Test Method	EU Herceptin	CT-P6	US Herceptin	CT-P6 vs EU Herceptin (EU Herceptin vs US)	Study Number
Fab -related analyses					
HER2 Binding Affinity (ELISA)	97.42±3.253	100.4±4.015	99.63±4.75	highly similar (highly similar)	GR2-RD-16-166
HER2 Binding Affinity (Cell-based ELISA)	99±7.3	100±8.8	102±9.3	highly similar (highly similar)	GR2-RD-16-157
In Vitro Bioactivity: Anti-proliferation ($HER2^+$ breast cancer cell line SK-BR-3)	105±4.3	101±2.8	105±5.7	highly similar (highly similar)	GR2-RD-16-159
	Fc -related analyses				
FcRn Binding Affinity (SPR)	99±3.1	100±2.0	99±4.0	highly similar (highly similar)	GR2-RD-16-158
FcγRI Binding Affinity (SPR)	99±2.3	98±2.4	97±1.9	highly similar (highly similar)	GR2-RD-16-167
FcγRIIa Binding Affinity (SPR)	99±2.1	100±1.4	97±2.2	highly similar (highly similar)	GR2-RD-16-155

FcγRIIb Binding Affinity (SPR)	96±3.9	99±2.0	95±3.9	highly similar (highly similar)	GR2-RD-16-161
FcγRIIIa F Type Binding Affinity (SPR)	91±11.6	99±2.2	90±7.3	highly similar (highly similar)	GR2-RD-16-165
FcγRIIIa V Type Binding Affinity (SPR)	90±9.2	96±3.4	87±11.1	highly similar (highly similar)	GR2-RD-16-164
FcγRIIIb Binding Affinity (SPR)	89±12.0	97±4.4	83±13.7	highly similar (highly similar)	GR2-RD-16-156
C1q Binding Affinity (ELISA)	100±6.2	104±7.1	102±6.8	highly similar (highly similar)	GR2-RD-16-162
ADCC ($HER2^+$ SK-BR-3 cells and healthy donors PBMC effector cells)	96±10.6	99±5.8	91±11.6	highly similar (highly similar)	GR2-RD-16-160
ADCC: Reporter Assay ($HER2^+$ SK-BR-3 cells and FcγRIIIa/V158 expressing Jurkat effector cells)	89±18.9	99±9.6	82±20.3	highly similar (highly similar)	GR2-RD-16-163

***In vitro* Fc-related bioactivity (ADCC activity)**

Two types of ADCC analyses were conducted in order to evaluate the comparability of CT-P6 and Herceptin (EU, US) in regards of their ADCC induction activities.

In first, cytotoxicity was studied with Calcein-AM assay using 3 concentrations (0.5 ng/mL, 1.3 ng/mL and 3.2 ng/mL) of antibody and with PBMCs as effector cells from healthy donors and HER2-expressing SK-BR3 breast cancer cells as target cells. PBMC to target cell ratio used was 16:1. The relative ADCC activities of CT-P6, EU-approved Herceptin and US-licensed Herceptin were calculated by comparison with % cell lysis of reference standard. The mean for ADCC activity of CT-P6, EU-approved Herceptin and US-licensed Herceptin were within 91% - 99%.

The second analysis, a reporter assay utilising luminescence for quantitation of the cytotoxicity was conducted on 2:1 ratio of engineered Jurkat cells as effector cells and HER2-expressing SK-BR3 breast cancer cells as target cells. The mean for ADCC activity of CT-P6, EU-approved Herceptin and US-licensed Herceptin were within 82% - 99%.

All lots of CT-P6 in both of the ADCC assays conducted were within mean ± 3SD of EU-approved Herceptin for ADCC activity. Therefore, the potencies of CT-P6 and reference products were highly similar.

Secondary pharmacodynamic studies

The applicant did not submit secondary pharmacodynamic studies (see non-clinical discussion).

Safety pharmacology programme

The applicant did not submit safety pharmacology studies (see non-clinical discussion).

Pharmacodynamic drug interactions

The applicant did not submit pharmacodynamic drug interaction studies (see non-clinical discussion).

2.3.3. Pharmacokinetics

GLP-compliant comparative toxicokinetic study was conducted as part of the repeated dose toxicity study in cynomolgus monkeys (Study ZIP0014). The monkeys (n=3 M, F / group) received CT-P6 and US Herceptin at doses of 14 and 42 mg/kg weekly by intravenous (IV) injections for 4 – weeks. Blood samples were collected pre-dose and on Day 1 and Day 22 and serum concentrations of CT-P6 or US Herceptin were analysed 0.5, 1, 2, 6, 12, 24, 72, 120 and 168 hours post dose.

Serum concentrations of CT-P6 and US Herceptin were measured with validated ELISA methods.

Mean C_{max} of CT-P6 and US Herceptin and mean AUC_{0-168h} with standard deviations (SD) on Day 1 and Day 22 are shown in Table 4 below. Serum concentration –time profiles for CT-P6 and US Herceptin are shown in Figure 6. The systemic exposure AUC_{0-168h} of monkeys to CT-P6, increased with increasing dose over the dose range 14 to 42 mg/kg on Day 1 and Day 22. The systemic exposure AUC_{0-168h} of monkeys to US Herceptin, increased approximately proportionately with increasing dose. The mean accumulation ratios, based on AUC_{0-168h} values, are indicated in Table 5.

Table 4: Mean (SD) Cmax and AUC0-168h Values for CT-P6 and US Herceptin in cynomolgus monkeys following IV doses for 4 weeks at 14 and 42 mg/kg

Dose level mg/kg	C_{max} µg/mL (SD)				AUC_{0-168h} µg.h/mL (SD)			
	Day 1		Day 22		Day 1		Day 22	
	Male	Female	Male	Female	Male	Female	Male	Female
CT-P6 14 mg/kg	344 (22)	342 (3)	557 (37)	619 (71)	27900 (1100)	29000 (3700)	60500 (2400)	62200 (4200)
CT-P6 42 mg/kg	1167 (144)	1093 (95)	1896 (82)	1922 (419)	96000 (5800)	93800 (13300)	213000 (31000)	200000 (29000)
US Herceptin 14 mg/kg	358 (19)	426 (67)	587 (68)	811 (153)	28500 (700)	37400 (2400)	59100 (10300)	80200 (5500)
US Herceptin 42 mg/kg	1140 (78)	1194 (11)	2218 (18)	1952 (84)	100000 (8000)	98500 (11300)	207000 (21000)	193000 (55000)

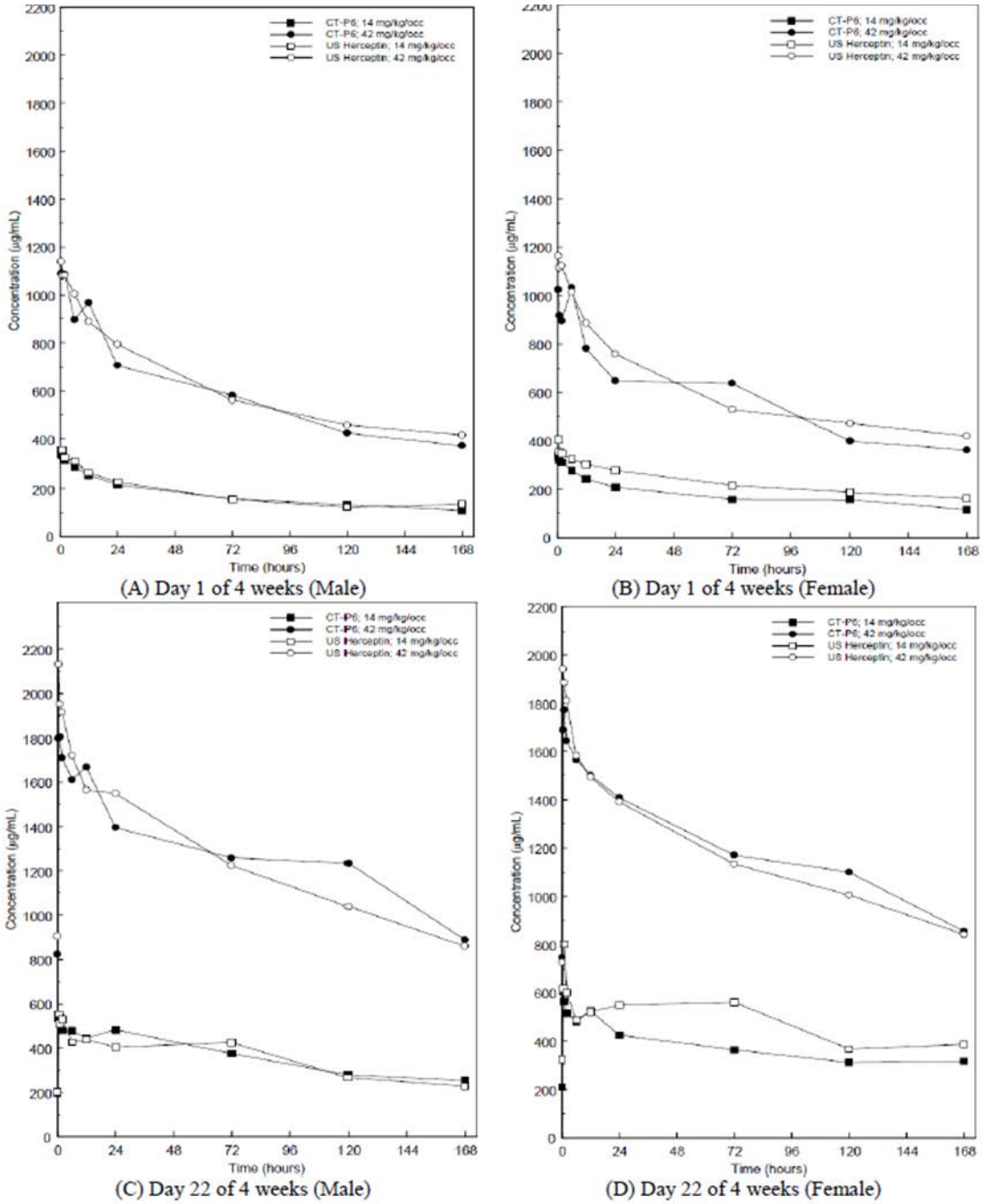


Figure 6: Mean serum concentrations (μg/mL) of CT-P6 and US Herceptin in cynomolgus monkeys

Table 5: The mean accumulation ratios of CT-P6 and US Herceptin, based on AUC0-168h

	Dose level mg/kg	Accumulation ratio	
		Males	Females
CT-P6	14	2.2	2.2
	42	2.2	2.1
US Herceptin	14	2.1	2.1
	42	2.1	1.9

There was no significant differences between the extent of systemic exposure AUC_{0-168h} to CT-P6 and US Herceptin at the 42 mg/kg dose level (p=0.963) and at dose level 14 mg/kg in male monkeys. However, the AUC_{0-168h} values of 14 mg/kg CT-P6 in females were ~22% lower and statistically significant (p=0.003) than those of US Herceptin.

2.3.4. Toxicology

Single dose toxicity

The applicant did not submit single dose toxicity studies (see non-clinical discussion).

Repeat dose toxicity

A 4-week repeat-dose toxicity study with weekly IV administration of CT-P6 and US-licensed Herceptin® was conducted in both male and female Cynomolgus monkeys at 2 doses of 14 and 42 mg/kg (Study No. ZIP0014), performed in compliance with OECD GLP according to EU requirements.

Clinical observations

There were no deaths during the treatment period and no clinical signs that were considered related to treatment.

Observations at the injection sites included bruising, thickening, swelling and eschar formation.

There were no consistent differences in the incidence of these findings for CT-P6 or US Herceptin® treated animals compared with the control. The findings were within the background of injection site findings observed with intravenous dosing and were therefore attributed to the method of dose administration.

Ophthalmoscopy

There were no treatment-related ophthalmic changes observed.

Electrocardiography and blood pressure

The electrocardiographic and blood pressure investigations performed in this study during Week 1 and 4 did not reveal any treatment-related effects of CT-P6 or US Herceptin administration.

Respiration rate

There were no treatment-related effects on respiration rate.

Body temperature

There were no treatment-related effects on body temperature.

Haematology, peripheral blood

There were no treatment-related effects on the haematological parameters investigated. All inter-group differences (including those attaining statistical significance) were either minor, lacked dose-relationship, were not consistent between sexes or reflected trends that were apparent before treatment commenced and were therefore attributed to normal biological variation.

Blood chemistry

There were no treatment-related effects on the blood chemistry parameters investigated. All inter-group differences (including those attaining statistical significance) were either minor, lacked dose-relationship,

were not consistent between sexes or reflected trends that were apparent before treatment commenced and were therefore attributed to normal biological variation.

Immunophenotyping of peripheral blood leucocytes

No clear or consistent differences were observed between dosing with CT-P6 and US Herceptin® in the cell types measured. Although some statistically significant differences in the group mean results were observed, there was either no relationship to dose level or no consistency between the sexes and they were therefore considered unrelated to treatment and due to normal background variation.

Urinalysis

The composition of the urine was considered unaffected by treatment. All inter-group differences (including those attaining statistical significance) were either minor, lacked dose-relationship, were not consistent between sexes or reflected trends that were apparent before treatment commenced and were therefore attributed to normal biological variation.

Organ weights

Intergroup differences seen in the organ weight analysis were small or were inconsistent between groups and sexes. Consequently, they were considered due to individual variation in results and were not treatment related.

Macropathology

The macroscopic examination performed after 4 weeks of treatment with CT-P6 or US Herceptin revealed no test article-related findings. Dark areas were occasionally observed in the subcutis of the right saphenous vein injection site (used for the last dose on Day 22) for treated and control animals, but were considered procedural in origin. The nature and incidence of all other findings were consistent with the commonly observed background of macroscopic changes

Histopathology

No treatment-related microscopic findings were observed. Occasional incidences of perivascular haemorrhage and perivascular fibrosis occurred in the saphenous vein injection sites. In the right injection site, the perivascular haemorrhage correlated with the dark areas observed macroscopically. These findings were observed for treated and control animals and were attributed to the intravenous administration procedure and were considered unrelated to treatment with CT-P6 or US Herceptin®.

The nature and incidence of all other findings were consistent with the commonly observed background of microscopic changes.

Genotoxicity

The applicant did not submit genotoxicity studies (see non-clinical discussion).

Carcinogenicity

The applicant did not submit carcinogenicity studies (see non-clinical discussion).

Reproduction Toxicity

The applicant did not submit reproduction toxicity studies (see non-clinical discussion).

Toxicokinetic data

See pharmacokinetic section.

Local Tolerance

Local tolerance in the injection site was assessed in the repeat-dose toxicity studies as part of the gross pathology and histopathology evaluations. Dark areas at the injection site were observed in the 4-week repeat-dose toxicity study (Study ZIP0014) in treated and control animals, suggesting their technical procedural relation. No differences were noted in the occasional incidences of these local tolerance findings (macroscopical: bruising, thickening, swelling and eschar formation; histopathology: perivascular haemorrhage, perivascular fibrosis in saphenous vein) between CT-P6 and US Herceptin treatments (Table 6).

Table 6: Incidence of injection site findings following IV administration of CT-P6 and US-licenced Herceptin in cynomolgus monkeys

Weekly Dose mg/kg	Group 1 0 (Control)	Group 2 14 (CT-P6)	Group 3 42 (CT-P6)	Group 4 14 (US Herceptin)	Group 5 42 (US Herceptin)
Macropathology (injection site)	Dark areas in right saphenous vein (M:1, F:1)	Dark areas in right saphenous vein (F: 1)	-	-	Dark areas in right saphenous vein (F: 1)
Histopathology Haemorrhage, perivascular	Saphenous, Rt (M: 1)	-	-	-	Saphenous, Rt (F: 1)
Fibrosis, perivascular	Saphenous, Rt and Lt (F: 1)	Saphenous, Rt (M: 2)	-	-	-

Other toxicity studies

During process development and scale up, drug substance manufacturing process changes were introduced in order to optimise the process for commercial manufacture.

Table 7: Summary of other toxicity study performed to evaluate process related impurities

Study Type	Species	Dose	Key Findings
Single dose IV administration toxicity study of 2-Deoxy-2-fluoro-L-fucose in Sprague-Dawley Rats GT13-00497 (GLP)	Sprague-Dawley Rats (5/sex per group)	0, 250, 500 and 1,000 mg/kg	It is considered that the lethal dose 50 (LD_{50}) of 2-Deoxy-2-fluoro-L-fucose is over than 1,000 mg/kg.
Bacterial reverse mutation test of 2-Deoxy-2-fluoro-L-fucose GT13-00498 (GLP)	*Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537) *Escherichia coli* (WP2*uvr*A)	0, 313, 625, 1250, 2500 and 5000 µg/plate	It is concluded that the test substance 2-Deoxy-2-fluoro-L-fucose does not induce reverse mutation in 5 strains which were used in this study.

GLP: Good laboratory practice, IV: Intravenous, LD_{50}: Lethal dose 50, US: United States

2.3.5. Ecotoxicity / environmental risk assessment

The applicant provided a justification for not providing an environmental risk assessment. Trastuzumab is already marketed and no significant increase in environmental exposure is anticipated with CT-P6. Furthermore, the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMENCHMP/SWP/4447/00 corr. 2*) makes specific reference for certain types of products such as proteins, that due to their nature they are unlikely to result in a significant risk to the environment. Therefore, considering that CT-P6 is a protein and there is no expected increased environmental exposure, the absence of formal environmental risk assessment studies for CT-P6 is considered justified.

2.3.6. Discussion on non-clinical aspects

CT-P6 has been developed as a similar biological medicinal product to the reference product Herceptin (trastuzumab). The marketing authorisation is an abridged application for a biosimilar under the scope of the Article 10(4) of Directive 2001/83/EC. According to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1, the applicant used a stepwise approach in order to demonstrate that CT-P6 is comparable to Herceptin with respect to PD/PK and toxicity. Studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity and on local tolerance are not required for non-clinical testing of biosimilars and therefore the lack of studies is acceptable.

A 3-way similarity exercise was undertaken, to demonstrate the similarity of CT-P6 to EU-approved Herceptin and also to demonstrate the similarity of US-licensed Herceptin (440 mg) to EU-approved Herceptin (150 mg). The 3-way similarity study included an extensive comparative analysis of primary, secondary and tertiary structure, glycan profiles and of post-translational modifications. In addition, many biological assays have been included to evaluate similarity in all biological activities associated with Fab- and Fc mediated functions involving primary mechanisms of actions (MoAs) of trastuzumab (Herceptin). No significant differences were observed in these assays. EU-approved Herceptin, CT-P6 drug product and US-licensed Herceptin were considered similar in binding affinity to HER2. These studies establish a robust scientific non-clinical bridge between the 3 products.

To evaluate PK and toxicity of CT-P6 and US-licensed Herceptin, a 4-week repeat-dose toxicity study in Cynomolgus monkeys was used in both male and female Cynomolgus monkeys at 2 doses of 14 and 42 mg/kg. The 14 and 42 mg/kg doses yielded measurable concentration up to 7 days on Week 1 and Week 4. Overall the results indicate that CT-P6 and US-licensed Herceptin had similar concentration-time profiles and PK parameters. The study showed no toxicological findings and no difference in response compared to treatment with US Herceptin.

All animals were confirmed to be negative for the presence of anti-CT-P6 or anti-US Herceptin antibodies.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical studies were considered comprehensive and support the comparability exercise to confirm the biosimilarity between CT-P6 and the reference product Herceptin.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme consisted in one PK similarity study conducted in healthy subjects (Study CT-P6 1.5) and one comparability clinical efficacy study conducted in patients with early breast cancer (EBC) (Study CT-P6 3.2). In addition, one pilot study to evaluate the safety and PK of Herzuma was conducted in healthy subjects (Study CT-P6 1.4) prior to the initiation of the two similarity studies.

GCP

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

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

Due to concerns raised with regard to the quality of the assays performed and to the overall quality of the data (see discussion on clinical pharmacology), an inspection was conducted to examine whether the study CT-P6 3.2 was conducted in accordance with ICH GCP, applicable regulations and internationally accepted ethical standards, and to verify the reliability of the data reported in the MAA. Despite some deviations from GCP, the final conclusion of the inspection was that the overall conduct of the trial was GCP-compliant. The data of the trial are consequently considered acceptable and the inspectors recommend using the data of the trial in context of the evaluation of the MAA of Herzuma.

- **Tabular overview of clinical studies**

Study	Study Design	Objectives and Endpoints	Treatment	Status
CT-P6 1.5 (Pivotal PK Similarity Study)	Phase 1, randomised, controlled, 2-arm, parallel-group, double-blind, single-dose prospective study in healthy male subjects **Study Periods:** • Screening Period: Day –21 to Day –2 • Admission: Day –1 • Study Period: Single dose at Day 1, follow-up to Day 70 • EOS Visit: Day 71 (Week 10)	**Primary:** To demonstrate similarity of PK in terms of $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max} of CT-P6 to Herceptin® over 71 days **Secondary:** To assess additional PK variables, safety and immunogenicity over 71 days	CT-P6 or Herceptin®: 6 mg/kg, IV infusion for 90 min (± 5 min) N=70 (35:35)	Final CSR is submitted
CT-P6 1.4 (Pilot PK Similarity Study)	Phase 1, randomised, controlled, 2-arm, parallel-group, double-blind, single-dose prospective study in healthy male subjects **Study Periods:** • Screening Period: Day –21 to Day –2 • Admission: Day –1 • Study Period: Single dose at Day 0, follow-up to Day 41 • EOS Visit: Day 42 (Week 6)	**Primary:** To demonstrate similarity of PK in terms of $AUC_{0\text{-last}}$ and C_{max} of CT-P6 to Herceptin® over 42 days **Secondary:** To assess additional PK variables, safety, tolerability and immunogenicity over 42 days	CT-P6 or Herceptin®: 6 mg/kg, IV infusion for 90 min N=70 (35:35)	Final CSR is submitted

Study	Study Design	Objectives and Endpoints	Treatment	Status
CT-P6 3.2 (Pivotal Therapeutic Similarity Study)	Phase 3, randomised, controlled, 2-arm, parallel-group, double-blind, multicentre, international, prospective study in patients with HER2-positive EBC **Study Periods:** • Screening Period: Day –21 to Day 0 • Neoadjuvant Period: 8 cycles (every 3 weeks); after a total of 8 treatment cycles of neoadjuvant therapy, surgery was performed within 3 to 6 weeks • Adjuvant Period: 3 to 6 weeks after surgery additional treatment initiated, every 3 weeks for up to 1 year (up to 10 cycles after surgery) • Post-treatment Follow-up Period: Until 3 years from the day of enrolment of the last patient	**Primary**: To demonstrate similarity of efficacy in terms of pCR for CT-P6 and Herceptin® during surgery after the Neoadjuvant Period (after Cycle 8) **Secondary**: To assess additional efficacy, PK, PD, safety, immunogenicity and biomarker (optional)	**Neoadjuvant Period** CT-P6 or Herceptin®: • Loading dose of 8 mg/kg on Day 1 of Cycle 1, and then 6 mg/kg repeated every 3 weeks on Day 1 of Cycles 2-8 • IV infusion for 90 min (± 5 min) Docetaxel: • 3-weekly for 12 weeks (Cycles 1-4) • 75 mg/m^2, IV infusion for 1h FEC: • 3-weekly for 12 weeks (Cycles 5-8) • Fluorouracil 500 mg/m^2, IV bolus for 3-5 min or IV infusion for over 30 min • Epirubicin 75 mg/m^2, IV bolus for 3-5 min or IV infusion for over 30 min • Cyclophosphamide 500 mg/m^2, IV bolus for over 3-5 min **Adjuvant Period** CT-P6 or Herceptin®: 6 mg/kg, 3-weekly for up to 1 year from the first day of study drug administration in the Neoadjuvant	Study is ongoing. First CSR is submitted for the analyses of PK, PD, efficacy, safety and immunogenicity up to Cycle 8 (24 weeks), covering Neoadjuvant Period and pCR assessment during surgery. Estimated final CSR completion: 4Q 2019

Study	Study Design	Objectives and Endpoints	Treatment	Status
			Period, excluding surgery (up to 10 cycles after surgery) N=549 (271:278)	

$AUC_{0\text{-}inf}$: Area under the serum concentration-time curve from time 0 extrapolated to infinity, $AUC_{0\text{-}last}$: Area under the serum concentration-time curve from time 0 to the last quantifiable concentration, C_{max}: Observed maximum serum concentration, CSR: Clinical study report, EBC: Early breast cancer, EOS: End of study, FEC: Fluorouracil, epirubicin, and cyclophosphamide, HER2: Human epidermal growth factor receptor 2, h: Hour, IV: Intravenous, min: Minutes, pCR: Pathological complete response, PD: Pharmacodynamics, PK: Pharmacokinetics, Q: Quarter

2.4.2. Pharmacokinetics

Pharmacokinetics data were generated from two clinical trials: the pivotal PK study healthy subjects (Study CT-P6 1.5) and the pilot study evaluating the initial safety and PK of Herzuma in healthy subjects (Study CT-P6 1.4). Supportive PK parameters were also determined as secondary endpoints during the pivotal efficacy trial, CT-P6 3.2. All three studies used the US-licensed Herceptin as the comparator. As the 440 mg/vial presentation of the biosimilar was used in the clinical trials, comparability between the 150 mg/vial and the 440 mg/vial presentation of the biosimilar has been established.

Analytical methods

CT-P6 and Herceptin levels in human serum from Study CT-P6 1.5, CT-P6 3.2 and CT-P6 1.4 were quantitatively measured using a ligand-binding immunoassay (Gyros method).

Re-analysis of study samples using a newly developed and validated ELISA assay was also conducted during the procedure (see discussion on clinical pharmacology).

Pivotal PK similarity study: Study CT-P6 1.5

Study CT-P6 1.5 was a randomised, double-blind, two-arm, parallel group, single-dose Phase 1 study to compare the pharmacokinetics, safety and immunogenicity of CT-P6 and Herceptin in healthy subjects and conducted at two sites in the US.

A total of 70 healthy male subjects (aged 18-55 years) were enrolled to the study; 35 subjects (including 12 Japanese subjects in each arm) in both treatment groups (i.e. in CT-P6 group and in US-licensed Herceptin group). In the CT-P6 group, all subjects completed the study, in the US-licensed Herceptin group, 1 subject discontinued (reason for discontinuation was other). The demographic baseline characteristics were comparable between studied treatment groups.

All subjects received a single-dose (6 mg/kg) of either CT-P6 or US-licensed Herceptin by intravenous (i.v.) infusion for 90 minutes (± 5 min) on day 1 followed by 10 weeks study period.

Blood samples for PK analysis of trastuzumab were drawn pre-dose, immediately after the end-of-infusion (1.5 hours from the start of infusion) at 3, 6, 12, and 24 hours from start of infusion, on days 3, 5, 8, 15, 22, 29, and 50, and at the end-of-study visit on day 71.

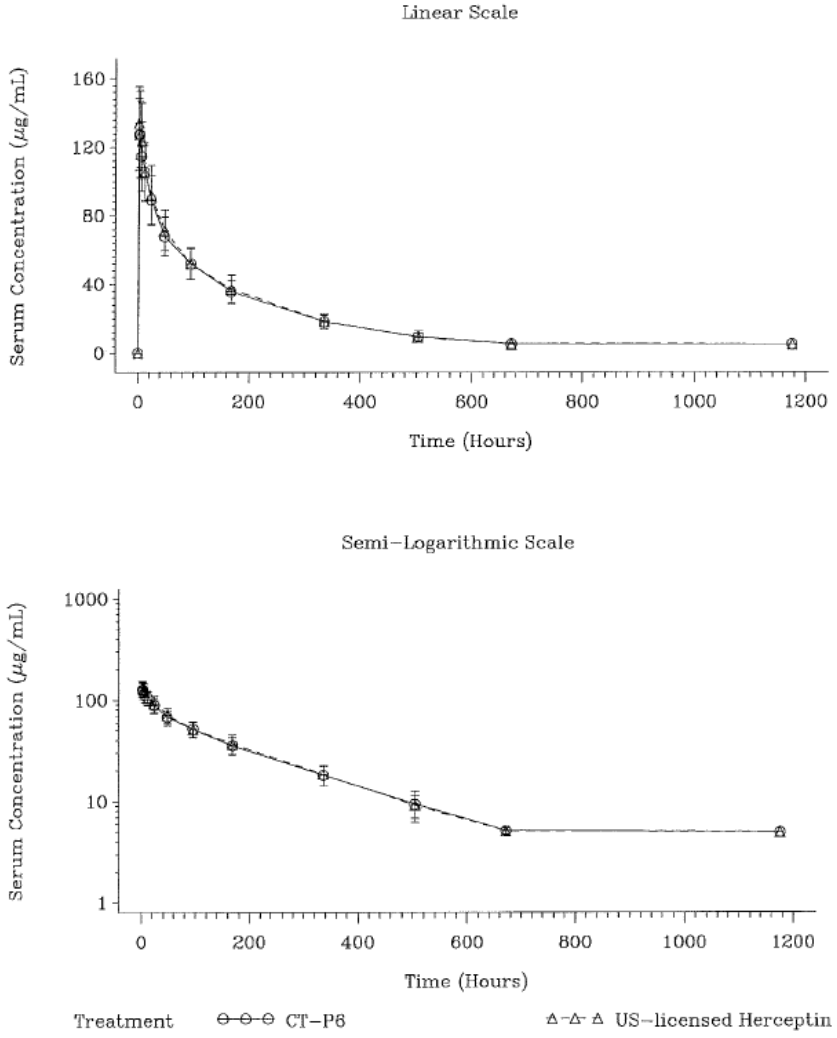
Immunogenicity of CT-P6 and US-licensed Herceptin was assessed before dosing on day 1 and on days 50 and 71. The potential immunogenicity of CT-P6 and US-licensed Herceptin was assessed by measuring ADA and Nab.

The primary objective of the study was to evaluate and compare the PK profiles of CT-P6 and US-licensed Herceptin in healthy subjects.

Primary PK endpoints were: Area under the concentration-time curve from the start of first infusion to infinity (AUC_{inf}), area under the serum concentration-time curve from the time zero to the last quantifiable concentration (AUC_{last}) and $C_{max.}$

Secondary PK endpoints were: $\%AUC_{ext}$, time to maximum serum concentration (T_{max}), volume of distribution during the terminal phase $V_{z,}$ terminal elimination rate constant λ_z, terminal elimination half-life $t_{1/2}$ and total body clearance CL.
The statistical analysis of the log-transformed primary endpoints (AUC_{inf}, AUC_{last}, and C_{max}) was based on an analysis of covariance (ANCOVA) model with treatment as a fixed effect and race (Japanese and Non-Japanese) as a covariate. The equivalence margin was pre-defined: 90% CIs around the ratio of geometric means for AUC_{inf}, AUC_{last} and C_{max} contained within 80-125%.

PK results



Abbreviation: SD, standard deviation.

Note: As serum concentration values of all samples are below the lower limit of quantification since Day 50, the figure does not present results of Day 71.

Figure 7: Mean (± SD) serum concentrations of CT-P6 and US-licensed Herceptin versus time (hours) (PK analysis set)

Table 8: Summary of serum PK parameters of trastuzumab by treatment group (PK analysis set)

Parameter	CT-P6 (N=35)	US-Licensed Herceptin (N=35)
Primary Pharmacokinetic Endpoints		
AUC_{inf} (h*µg/mL)		
Mean (SD)	20307.53 (3796.479)	20519.93 (3602.342)
CV	18.695	17.555
Geometric mean	20012.77	20203.75
Median	19073.71	20485.29
Minimum, maximum	15718.2, 32391.3	13373.3, 28730.8
AUC_{last} (h*µg/mL)		
Mean (SD)	18941.98 (3647.479)	19121.21 (3600.430)
CV	19.256	18.830
Geometric mean	18649.39	18781.49
Median	17766.08	19014.47
Minimum, maximum	14421.8, 30603.9	11904.3, 27727.2
C_{max} (µg/mL)		
Mean (SD)	133.01 (23.840)	137.29 (21.262)
CV	17.924	15.487
Geometric mean	131.03	135.66
Median	128.00	134.00
Minimum, maximum	92.2, 185.0	87.3, 194.0

Abbreviations: AUC_{inf}, area under the serum concentration-time curve from time 0 to infinity; AUC_{last}, area under the serum concentration-time curve from time 0 to the last quantifiable concentration; C_{max}, observed maximum measured serum concentration; CV, coefficient of variation; SD, standard deviation.

Table 9: Analysis of AUC0-inf; AUC0-last and C max of CT-P6 and Herceptin in study CT-P6 1.5 (Ancova) PK analysis set

Parameter	Treatment	N	Geometric LS Mean[1]	Ratio (%) of Geometric LS Means[1]	90% CI of Ratio (%)[1]
$AUC_{0\text{-}inf}$ (h·µg/mL)	CT-P6	35	19523.05	99.05	93.00 - 105.51
	Herceptin®	35	19709.36		
$AUC_{0\text{-}last}$ (h·µg/mL)	CT-P6	35	18183.73	99.30	92.85 - 106.20
	Herceptin®	35	18312.53		
C_{max} (µg/mL)	CT-P6	35	127.95	96.58	90.93 - 102.59
	Herceptin®	35	132.48		

[1]The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (CT-P6/ Herceptin®) and 90% CIs for the ratios.
Note: An ANCOVA was performed with the natural log-transformed pharmacokinetic parameters as the dependent variable, treatment as a fixed effect, and race as a covariate.
ANCOVA: Analysis of covariance, $AUC_{0\text{-}inf}$: Area under the serum concentration-time curve from time 0 to infinity, $AUC_{0\text{-}last}$: Area under the serum concentration-time curve from time 0 to the last measurable concentration, CI: Confidence interval, C_{max}: Observed maximum serum concentration, LS: Least squares, N: Number of subjects in the PK analysis set, PK: Pharmacokinetics

Table 10: Summary of serum secondary PK parameters of trastuzumab by studied treatments (PK analysis set)

Parameter	CT-P6 (N=35)	US-Licensed Herceptin (N=35)
Secondary Pharmacokinetic Endpoints		
$\%AUC_{ext}$		
Mean (SD)	6.81 (1.170)	7.00 (2.523)
CV	17.191	36.018
Geometric mean	6.71	6.68
Median	6.79	6.40
Minimum, maximum	4.5, 9.3	3.5, 18.1
T_{max} (h)		
Median	1.550	1.517
Minimum, maximum	1.52, 6.00	1.52, 6.02
$t_{1/2}$ (h)		
Mean (SD)	189.31 (36.034)	183.68 (37.534)
CV	19.035	20.435
Geometric mean	186.13	180.45
Median	180.64	176.46
Minimum, maximum	102.6, 291.4	132.7, 302.0
λ_z (1/h)		
Mean (SD)	0.003788 (0.0007351)	0.003902 (0.0006678)
CV	19.4063520	17.1137261
Geometric mean	0.003724	0.003841
Median	0.003837	0.003928
Minimum, maximum	0.00238, 0.00675	0.00230, 0.00522
V_z (L)		
Mean (SD)	6.377 (1.4237)	6.085 (1.7092)
CV	22.3244	28.0889
Geometric mean	6.223	5.865
Median	6.284	5.649
Minimum, maximum	3.74, 9.95	3.29, 11.23
CL (L/h)		
Mean (SD)	0.02360 (0.004344)	0.02299 (0.004810)
CV	18.409412	20.919330
Geometric mean	0.02317	0.02253
Median	0.02362	0.02232
Minimum, maximum	0.0118, 0.0321	0.0148, 0.0372

Abbreviations: λ_z, terminal elimination rate constant; $\%AUC_{ext}$, percentage of the area extrapolated for calculation of AUC_{inf}; CL, total body clearance; CV, coefficient of variation; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max}, time to observed maximum measured serum concentration; V_z, volume of distribution during the terminal phase.

Additional analysis of the PK samples from Study CT-P6 1.5 using a new ELISA method resulted in increased AUC levels compared to the results presented above (i.e. from the original data using the Gyros method) with AUC levels comparable to the values from other published studies (about 30000 h*µg/mL versus 20000 h*µg/mL with the Gyros assay). The statistical analysis of AUC_{inf}, AUC_{last} and C_{max} is presented below.

Table 11: Statistical analysis of AUCinf, AUClast and Cmax for trastuzumab in study CT-P6 1.5 using the new ELISA method (ANCOVA) (PK analysis set)

Parameter	Treatment	N	Geometric LS Mean[1]	Ratio (%) of Geometric LS Means[2]	90% CI of Ratio (%)[2]
AUC_{inf} (h*µg/mL)	CT-P6	35	30885.56	94.73	88.86 - 100.99
	Herceptin®	35	32603.72		
AUC_{last} (h*µg/mL)	CT-P6	35	30661.61	95.00	89.04 - 101.35
	Herceptin®	35	32276.28		
C_{max} (µg/mL)	CT-P6	35	130.05	96.75	91.12 - 102.73
	Herceptin®	35	134.42		

Note: Serum concentration values BLQ (< 200 ng/mL) prior to the administration were set to 0 and all other BLQ values were set to missing.
[1] Geometric LS Mean was estimated using ANCOVA. ANCOVA was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect, and race as a covariate.
[2] The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (CT-P6/ Herceptin®) and 90% CIs for the ratios.
ANCOVA: Analysis of covariance, AUC_{inf}: Area under the serum concentration-time curve from time 0 to infinity, AUC_{last}: Area under the serum concentration-time curve from time 0 to the last measurable concentration, BLQ: Below the lower limit of quantification, CI: Confidence interval, C_{max}: Observed maximum serum concentration, ELISA: Enzyme-linked immunosorbent assay, LS: Least squares, N: Number of subjects in the PK analysis set

Pilot PK Similarity Study: Study CT-P6 1.4

Study CT-P6 1.4 was a randomised, double blind, two-arm, parallel-group, single-dose initial Phase 1 study designed to evaluate the PK profile, safety, tolerability and immunogenicity of CT-P6 and Herceptin in healthy subjects and conducted in one site in the Philippines.

A total of 70 healthy males (aged 18 to 55 years) were enrolled to the study (35 subjects in both studied treatment groups); 34 subjects and 33 subjects completed the study in the CT-P6 group and in the US-licensed Herceptin group, respectively. One subject in the US-licensed Herceptin had major protocol deviation and was excluded from the PK analyses (i.e. n = 32 in the US-licensed Herceptin group). The demographic characteristics were similar in the two treatment groups.

The test product was CT-P6 440 mg/vial powder for concentrate for solution for injection manufactured by Celltrion Inc. and the reference product was US-licensed Herceptin (440 mg/vial powder for concentrate for solution for injection) manufactured by Genentech Inc.

All subjects received a single dose of 6 mg/kg trastuzumab of CT-P6 or US-licensed Herceptin as a 90 minutes i.v. infusion with an infusion pump. The study period was up to 6 weeks.

Blood samples for PK assessments were collected into serum sample tubes at pre-dose (within 60 minutes prior to the beginning of the IMP infusion), 1.5 hours (immediately after the end of infusion), and then at 3, 6, 12 hours after the start of infusion and at days 1, 2, 4, 7, 14, 21, 28 and 42 (after the start of the infusion). The blood samples for assessment of antibodies to trastuzumab were collected on day 0 pre-dose, at days 14, 28 and 42.

The primary objective of the study was to evaluate and compare the PK profiles of CT-P6 and US-licensed Herceptin in healthy male subjects.

Primary PK endpoints were: AUC_{last} and C_{max}
Secondary PK endpoints were: AUC_{inf}, T_{max}, V_z, λ_z, $t_{1/2}$ and CL
Immunogenicity endpoint was: Immunogenicity of CT-P6 and US-licensed Herceptin

Bioequivalence of PK parameters was determined by constructing 90% confidence intervals around the estimated difference between the test and reference treatments using ANOVA based on natural log transformed data (treatment as fixed effect and group as covariate).

PK results

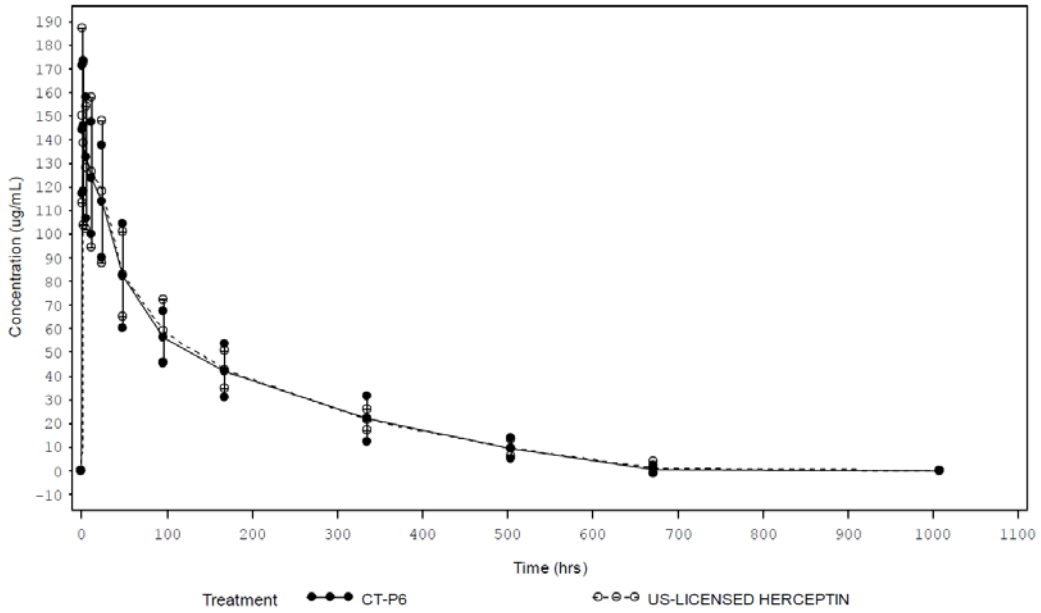


Figure 8: Mean (± SD) serum concentration (µg/ml) of trastuzumab versus time (hours) by the treatment (PK analysis set)

Note: Values that were below the lower limit of quantification have been set zero to the lower limit of quantification (5 µg/ml).

Table 12: Analysis of AUClast and Cmax of CT-P6 and US-licensed Herceptin (ANOVA; PK analysis set)

Parameter	Treatment	N	Geometric Mean[1]	Ratio (%) of Geometric Means[1]	90% CI of Ratio (%)[1]
$AUC_{0\text{-last}}$ (h·µg/mL)	CT-P6	34	19742.36	96.51	88.82 - 104.87
	Herceptin®	32	20455.82		
C_{max} (µg/mL)	CT-P6	34	151.20	97.19	89.11 - 106.00
	Herceptin®	32	155.58		

[1]The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (CT-P6/ Herceptin®) and 90% CIs for the ratios.
$AUC_{0\text{-last}}$: Area under the serum concentration-time curve from time 0 to the last measurable concentration, CI: Coefficient of variation, C_{max}: Observed maximum serum concentration, N: Number of subjects in the PK analysis set, PK: Pharmacokinetics

The secondary PK endpoints i.e. AUC_{inf}, T_{max}, V_z, CL, λ_Z and $t_{1/2}$ were similar in the CT-P6 and US-licensed Herceptin groups.

Pivotal Therapeutic Equivalence Study: Study CT-P6 3.2 in Patients with HER2-Positive Early Breast Cancer

Study CT-P6 3.2 was a pivotal Phase 3, double-blind, randomised, parallel-group, active-controlled study in patients with human epidermal growth factor receptor 2 (HER2) positive EBC conducted globally which also provided supportive PK data with C_{trough} and C_{max} as secondary endpoints.

This study compared the efficacy and safety of CT-P6 and Herceptin during the neoadjuvant period (24 weeks (8 cycles) including surgery) as primary endpoint and PK as secondary endpoints (see section on clinical efficacy).

The PK was studied during the neoadjuvant period (8 cycles i.e. 24 weeks). In the neoadjuvant period, CT-P6 or Herceptin was administered as a 90-minute i.v. infusion (± 5 min, with an adequate infusion pump) at a loading dose of 8 mg/kg on day 1 of cycle 1, and then 6 mg/kg repeated every 3 weeks (from cycle 2 to cycle 8). Patients also received docetaxel during Cycles 1 through 4 and FEC during Cycles 5 through 8. Docetaxel and FEC were administered on the day of CT-P6 or Herceptin administration (Day 1, 3-week cycles).

Pharmacokinetic samples were collected before study drug (CT-P6 or US-licensed Herceptin) administration (within 15 minutes prior to the beginning of the study drug infusion) and within 15 minutes after the end of the study drug infusion for each cycle during the neoadjuvant period. After the completion of treatment, an additional PK sample was collected at the first end-of-treatment visit.

The following PK parameters were included as secondary endpoints:

- Observed C_{max} after administration, at each dose
- Observed trough serum concentration (C_{trough}), prior to next dose for cycles 1 through 7 and at the first end-of-treatment visit for cycle 8.

PK results

Mean (%CV) values for C_{max} and C_{trough} at Each Cycle for CT-P6 and Herceptin from study CT-P6 3.2 are presented below.

Table 13: Mean (CV%) Cmax and Ctrough at each cycle for CT-P6 and Herceptin in Study CT-P6 3.2, Safety Analysis Set

Parameter Neoadjuvant Period	CT-P6 (N=271)		Herceptin® (N=278)	
C_{max} (µg/mL)				
Cycle 1	n=268	186.43 (37.06)	n=276	178.57 (31.01)
Cycle 2	n=267	145.08 (32.94)	n=272	138.99 (32.89)
Cycle 3	n=265	145.18 (30.68)	n=265	141.13 (31.05)
Cycle 4	n=260	148.54 (36.54)	n=264	137.47 (33.24)
Cycle 5	n=261	136.21 (32.75)	n=261	135.31 (34.88)
Cycle 6	n=259	143.57 (29.57)	n=262	143.61 (35.71)
Cycle 7	n=262	146.73 (32.73)	n=258	141.47 (30.52)
Cycle 8	n=263	145.08 (28.63)	n=258	144.24 (39.77)
C_{trough} (µg/mL)				
Cycle 1	n=269	18.92 (121.58)	n=275	18.91 (112.65)
Cycle 2	n=267	17.35 (103.64)	n=268	16.77 (100.24)
Cycle 3	n=262	16.80 (102.65)	n=265	17.82 (131.03)
Cycle 4	n=261	17.85 (112.92)	n=264	15.90 (99.82)
Cycle 5	n=257	18.40 (108.16)	n=263	17.96 (99.89)
Cycle 6	n=261	18.90 (106.97)	n=258	18.26 (96.94)
Cycle 7	n=264	18.54 (77.30)	n=258	18.72 (99.35)
Cycle 8	n=257	17.90 (40.34)	n=260	17.13 (58.67)

Note: [redacted] and [redacted] who were randomised as the CT-P6 treatment group received Herceptin® once at Neoadjuvant Period Cycle 6 and Cycle 4, respectively. For [redacted] in the CT-P6 treatment group, serum concentration for predose sample at Neoadjuvant Period Cycle 1 was treated as missing sample in the [redacted] since the investigator confirmed that this was sampled after study drug administration.
C_{max}: Observed maximum serum concentration, C_{trough}: Observed trough serum concentration, CV: Coefficient of variation, N: Number of patients in the safety analysis set, n: Number of evaluable patients in the safety analysis set

C_{trough} levels for Study CT-P6 3.2 using a new ELISA method replicated the PK results from the HannaH study[4] showing increased absolute values (mean C_{trough} Cycle 8: 61.2 and 59.7 µg/mL vs. 18.4 and 17.8 µg/mL with the Gyros assay) as well as accumulation trend over the Neoadjuvant Period Cycles 1 to 8 (from about 40 to 60 µg/mL), and lower CV% (35.9%-57.7 %). The results showed similar C_{trough} between the treatment groups.

Table 14: Comparison of the Ctrough values of the neoadjuvant period in study CT-P6 3.2 using the Gyros and the ELISA method (safety analysis set)

	Gyros Method		ELISA Method	
Parameter Neoadjuvant Period	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)
C_{trough} (µg/mL)				
Cycle 1	n=259	n=265	n=268	n=274
Mean (SD)	19.453 (23.2710)	19.429 (21.5204)	36.643 (20.5711)	36.327 (19.6053)
CV (%)	119.63	110.76	56.14	53.97
Geometric mean	15.648	15.800	33.176	32.758
Median (min, max)	15.200 (5.22, 191)	15.100 (5.19, 188)	33.500 (0.82, 185.00)	33.600 (0.72, 167.00)

[4] Ismael G, Hegg R, Muehlbauer S, Heinzmann D, Lum B, Kim SB, Pienkowski T, Lichinitser M, Semiglazov V, Melichar B, Jackisch C. Subcutaenous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I - III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol. 2012 Sep;13(9): 869-78

	Gyros Method		ELISA Method	
Parameter Neoadjuvant Period	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)
Cycle 2	n=259	n=258	n=266	n=269
Mean (SD)	17.727 (18.1197)	17.229 (16.9732)	44.177 (24.5397)	42.318 (15.8477)
CV (%)	102.22	98.52	55.55	37.45
Geometric mean	14.873	14.778	40.351	39.334
Median (min, max)	14.800 (5.14, 163)	14.850 (5.08, 167)	41.550 (11.10, 260.00)	40.600 (2.81, 158.00)
Cycle 3	n=258	n=255	n=261	n=264
Mean (SD)	16.979 (17.3111)	18.319 (23.6573)	45.240 (20.2908)	46.756 (26.9887)
CV (%)	101.96	129.14	44.85	57.72
Geometric mean	14.614	14.987	42.112	42.093
Median (min, max)	14.650 (5.29, 200)	14.700 (5.02, 217)	42.900 (12.20, 236.00)	44.300 (2.93, 278.00)
Cycle 4	n=254	n=255	n=260	n=263
Mean (SD)	18.205 (20.3190)	16.289 (16.0186)	49.058 (24.6801)	46.444 (19.6073)
CV (%)	111.61	98.34	50.31	42.22
Geometric mean	14.864	13.838	44.035	42.484
Median (min, max)	14.400 (5.46, 172)	13.800 (5, 177)	45.850 (3.14, 188.00)	44.500 (2.42, 179.00)
Cycle 5	n=253	n=258	n=258	n=263
Mean (SD)	18.615 (19.9892)	18.213 (18.0244)	53.131 (22.5587)	54.619 (26.2525)
CV (%)	107.38	98.96	42.46	48.06
Geometric mean	15.508	15.471	49.167	50.088
Median (min, max)	15.400 (5.28, 178)	15.400 (5.34, 190)	50.450 (9.18, 187.00)	50.700 (2.28, 268.00)
Cycle 6	n=254	n=253	n=260	n=258
Mean (SD)	19.285 (20.3631)	18.518 (17.7713)	56.290 (25.6965)	55.631 (22.4527)
CV (%)	105.59	95.97	45.65	40.36
Geometric mean	15.965	15.819	50.980	51.921
Median (min, max)	16.050 (5.27, 201)	15.400 (5.38, 157)	52.450 (0.25, 215.00)	53.250 (12.50, 188.00)
Cycle 7	n=261	n=251	n=264	n=257
Mean (SD)	18.696 (14.3394)	19.101 (18.7120)	59.685 (24.1841)	60.406 (26.1797)
CV (%)	76.70	97.96	40.52	43.34
Geometric mean	16.222	16.174	54.813	55.908
Median (min, max)	16.700 (5.27, 147)	16.200 (5.37, 154)	56.750 (4.72, 189.00)	55.900 (9.21, 225.00)
Cycle 8	n=247	n=246	n=257	n=260
Mean (SD)	18.423 (6.8712)	17.820 (9.8929)	61.234 (23.1756)	59.741 (21.4395)
CV (%)	37.30	55.52	37.85	35.89
Geometric mean	17.190	16.364	55.835	54.518
Median (min, max)	17.600 (5.95, 44.5)	16.600 (5.34, 140)	59.700 (4.11, 140.00)	59.500 (0.46, 171.00)

Note: Concentration values BLQ (< 5 µg/mL in the Gyros method and 200 ng/mL in the ELISA method) prior to the administration were set to 0 and all other values BLQ were set to missing.
BLQ: Below the lower limit of quantification, C_{trough}: Observed trough serum concentration, CV: Coefficient of variation, ELISA: Enzyme-linked immunosorbent assay, Max: Maximum, Min: Minimum, N: Number of patients in the safety analysis set, n: Number of evaluable patients in the safety analysis set, SD: Standard deviation

2.4.3. Pharmacodynamics

Mechanism of action

See discussion on clinical pharmacology.

Primary and Secondary pharmacology

No clinical pharmacology studies were submitted. See discussion on clinical pharmacology.

In study CT-P6 3.2 serum HER2 receptor (shed antigen) levels were measured and are presented below.

Table 15: HER2 shed antigen in Study CT-P6 3.2 (safety analysis set)

Visit Statistics (Mean ± SD)	CT-P6 (N=271)				Herceptin (N=278)			
	Actual Value		Change from Baseline		Actual Value		Change from Baseline	
Baseline	n=265	12426.8 (±9176.83)	-	-	n=274	11925.3 (±8578.63)	-	-
After Neoadjuvant Cycle 4	n=249	5983.3 (±2544.86)	n=243	-6284.6 (±8658.38)	n=245	5959.3 (±1501.63)	n=241	-6043.2 (±8593.95)
EOT 1	n=259	6658.7 (±1953.97)	n=253	-5569.8 (±8751.77)	n=270	6733.9 (±1681.72)	n=266	-5290.2 (±8708.25)

EOT: End of treatment , HER2: Human epidermal growth factor receptor 2, NP: Neoadjuvant period, SD: Standard deviation

2.4.4. Discussion on clinical pharmacology

The design of the pivotal PK study in male healthy volunteers is in-line with the guidance in the CHMP biosimilar monoclonal antibody guideline (EMA/CHMP/BMWP/403543/2010) and is acceptable. As the 440 mg/vial presentation of the biosimilar was used in the clinical trials, comparability between the 150 mg/vial and the 440 mg/vial presentation of the biosimilar has been established.

Single doses of 6 mg/kg CT-P6 and Herceptin were selected in the two PK studies as this represents the recommended dose of Herceptin used to treat patients with trastuzumab in both breast cancer and gastric cancer (Herceptin SmPC 2016) which is agreed.

The comparative repeat dose PK was further investigated in Study CT-P6 3.2 in early breast cancer (EBC) patients as secondary objective with a three-weekly regime as recommended in breast and gastric cancer patients. This is considered acceptable as EBC patients are less likely to be exposed to prior chemotherapy treatments and represent a more sensitive and homogenous patient population for evaluating similarity in clinical pharmacology and immunogenicity as well as efficacy compared to MBC and AGC patients.

The comparison of the presented single dose PK results ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max}) and also of secondary PK endpoints (T_{max}, V_z, λ_z, $t_{1/2}$, CL) of CT-P6 versus US Herceptin in study CT-P6 1.4 and CT-P6 1.5 in healthy volunteers indicates biosimilarity.

Likewise, the presented PK data in EBC patients (study CT-P6 3.2) supports similarity between the CT-P6 and Herceptin treatment groups. However, a marked difference in exposure (geometric mean C_{trough}

pre-dose cycle 8: 15.7 µg/mL; CV 99%) was observed for both drugs compared to the value expected in that population (51.8 µg/mL). In addition, the observation that C_{trough} after cycle 1 was not different from end of cycle 8 and all C_{trough} were constant over all 7 cycles for both CT-P6 and Herceptin is uncommon. Usually, accumulation would take place with the given posology, as is observed in population predicted cycle 1 and steady state PK for all indications, i.e. MBC, EBC and MGC (SmPC Herceptin 2016, Table 14 and 15).

The applicant undertook a multidisciplinary investigation in order to find explanations for the unexpected PK findings of both CT-P6 and Herceptin in study CT-P6 3.2.

Firstly, the applicant re-evaluated the PK assay method validation. The sensitivity of the assay was questioned as LOQ was close to the lowest C_{trough} levels (mean: 18 µg/mL, CV% > 100). The low sensitivity was attributed to a high minimum required dilution (MRD) of 1:1000. However, accuracy and precision in the low concentration range (LQC) was within acceptable limits. Additional validation tests by the applicant confirmed a strong similarity of calibration curves of all three products, as well as dilutional linearity for a 1:100 dilution (pre-dilution to fall within the quantitative range of the assay). Additional validation tests showed that neither sHER2 and ADAs present in samples have any impact on the accuracy of the PK determination. In addition, a review of the QC performance during clinical sample analysis did not reveal any bias. Overall, validation of the PK assays used for sample analysis from clinical studies is considered adequate.

Secondly, a GCP inspection of the laboratory did not identify critical findings. Further to this inspection, no GCP-related reasons for the high CV% or for underestimation of samples could be identified.

Thirdly, the applicant conducted a thorough comparison of Study CT-P6 3.2 and the HannaH study[4] including inclusion/exclusion criteria in order to determine any differences between the studies. No significant differences were observed which could have impacted PK.

Fourthly, re-calculated results of primary PK parameters from Studies CT-P6 1.5, CT-P6 1.4 and CT-P6 3.2 after setting all values BLQ (< 5 µg/mL) to 0 or missing did not change the results significantly (data not shown). Furthermore, dose-response evaluation has not confirmed a threshold of 20 µg/mL for a therapeutic response of trastuzumab as previously suggested in the HannaH study.

Finally, a comparison of the PK method used in Study CT-P6 3.2 with the ELISA platform used for measurement of clinical samples in the HannaH study was done and highlighted differences. As a consequence, the applicant has developed and validated a new assay mimicking the assay format used in the Hannah study. Using the newly developed ELISA method, C_{trough} samples from the Neoadjuvant Period of Study CT-P6 3.2 in EBC patients were re-analysed and the results replicated the results from the HannaH study and supported similarity. The additional analysis of the PK samples from Study CT-P6 1.5 using the new ELISA method resulted in increased AUC levels compared to the result from the original data using the Gyros method. The 90% CIs of ratios of geometric means for AUC_{inf}, AUC_{last} and C_{max} were entirely contained within the equivalence margin of 80% to 125% further supporting the PK similarity between CT-P6 and Herceptin.

Potential source of the differences in PK results between the Gyros and the ELISA methods was thoroughly discussed by the applicant, e.g. possible factors such as pre-existing immunocomplexes of trastuzumab and sHER2, and known in vivo modifications of trastuzumab (e.g. deamidation, glycation). High baseline levels of HER2 shed antigen were observed in the CT-P6 and Herceptin treatment groups which might have influenced free trastuzumab levels.

Overall, it was concluded that the assay platform was the cause for the difference between observed and expected results in the original submission, i.e. systematically lower trastuzumab levels in both healthy subjects and patients (irrespective of the study sites) and a lack of accumulation.

Plausible and consistent PK data of trastuzumab in healthy volunteers and EBC patients have now been obtained by the applicant after re-analysis of study samples using a newly developed and validated ELISA assay. PK similarity between CT-P6 and Herceptin was replicated across both Studies CT-P6 1.5 and CT-P6 3.2.

Only the US-Herceptin has been used in the PK comparability studies. Comparability between the two CT-P6 presentations (150 mg/vial intended for EU and 440 mg/vial used in the similarity exercise) has been demonstrated and the bridge between the reference product (EU-Herceptin) and the comparator used in clinical studies (US-Herceptin) has been confirmed.

No clinical comparability PD studies have been performed which is considered acceptable considering no validated PD biomarkers exist for trastuzumab efficacy. Studies on the mechanism of action were not provided which is acceptable for a biosimilar.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic data support the comparability exercise between Herzuma and the reference product Herceptin. It is considered that similarity, from a PK perspective, has been established.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

2.5.2. Main study(ies)

Study CT-P6 3.2: A Phase 3, Double-Blind, Randomized, Parallel-Group, Active-Controlled Study to Compare the Efficacy and Safety of CT-P6 and Herceptin as Neoadjuvant and Adjuvant Treatment in Patients with HER2-Positive Early Breast Cancer

Methods

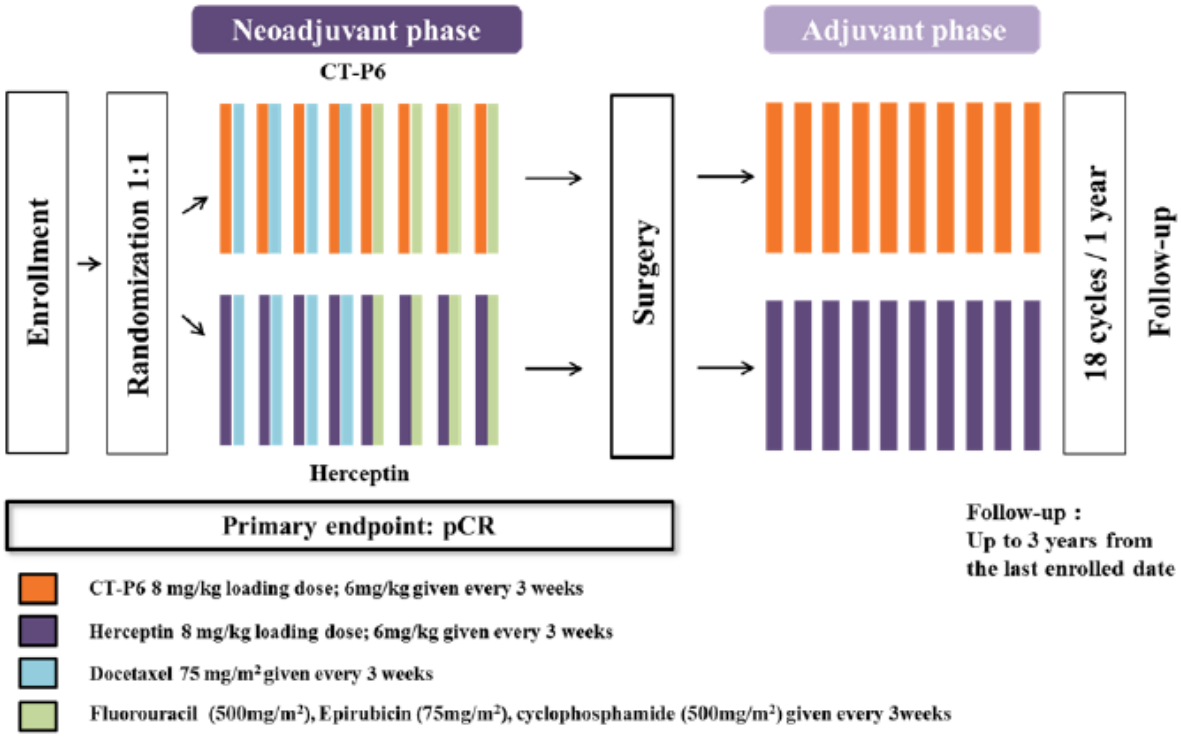


Figure 9: Study design of study CT-P6 3.2

Study Participants

Inclusion Criteria

Each patient had to meet all of the following criteria to be enrolled in this study:

1. Patient was a female 18 years of age or older.

2. Patient had Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1

3. Patient had histologically confirmed and newly diagnosed breast cancer.

4. Patient had clinical Stage I, II, or IIIa operable breast adenocarcinoma according to the American Joint Committee on Cancer (AJCC) Breast Cancer Staging 7th edition

5. At least 1 measurable lesion by RECIST Version 1.1

a. Tumor lesions: ≥10 mm in long axis by computerized tomography (CT) scan

b. Malignant lymph nodes: ≥15 mm in short axis when assessed by CT scan

6. Patient had HER2-positive status confirmed locally, defined as 3+ score by immunohistochemistry (IHC). When the IHC result was equivocal (defined as 2+ score), patient had a positive fluorescence in situ hybridization (FISH) or a chromogenic in situ hybridization (CISH) result.

7. Patient had a normal left ventricular ejection fraction (LVEF) (≥55%) at baseline, as determined by either 2-dimensional echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan. If the patient was randomized, the same method of LVEF assessment, ECHO or MUGA, was required to be used throughout the study.

8. Patient had known estrogen receptor and progesterone receptor status.

9. Patient had adequate bone marrow function, defined as:

a. Absolute neutrophil count ≥1500/µL

b. Hemoglobin ≥10.0 g/dL

c. Platelets ≥100 000/µL

10. Patient had adequate hepatic and renal function, defined as:

a. Aspartate aminotransferase (AST) and alanine aminotransferase

(ALT) ≤2.5 × upper limit of normal (ULN)

b. Total bilirubin ≤1.5 × ULN

c. Alkaline phosphatase ≤2.5 × ULN

d. Serum creatinine ≤1.5 mg/dL

11. Patient had the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.

12. Patient was required to voluntarily sign an IRB/IEC-approved ICF before any study specific procedures.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

1. Patient had bilateral breast cancer.

2. Patient was pregnant or lactating.

3. Patient had received prior treatment for breast cancer, including chemotherapy, biologic therapy, hormone therapy, immunotherapy, radiation, or surgery, with the exception of diagnostic biopsy for primary breast cancer.

4. Patient had received any prior therapy with anthracyclines.

5. Patient had other concomitant active malignancy or history of malignancy in the past 5 years except treated basal cell carcinoma of the skin or carcinoma in situ of the cervix.

6. Serious cardiac illness or medical conditions that could preclude the use of trastuzumab, specifically: New York Heart Association (NYHA) class ≥2, history of documented congestive heart failure (CHF), myocardial infarction (MI), high-risk uncontrolled arrhythmias, angina pectoris requiring medication, clinically significant valvular disease, evidence of transmural infarction on electrocardiogram (ECG), poorly controlled hypertension.

7. Patient had a current history of infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus, or had a positive result to the screening test for those infections.

8. Patient had any recent infection requiring a course of systemic anti-infectives that were completed ≤14 days before randomization (with the exception of uncomplicated urinary tract infection).

9. Patient was a woman of childbearing potential who did not consent to use highly effective methods of birth control (e.g., intra-uterine device, barrier methods including condom and diaphragm, also in conjunction with spermicidal jelly, or total abstinence; oral, injectable, or implant hormonal contraceptives were not acceptable) during treatment and for an additional 7 months after the last administration of the protocol-specified treatment.

10. Patient was currently receiving treatment with another investigational device or medical product, or less than 30 days or 5 half-lives, whichever was longer, spanned since ending treatment with another investigational device or medical product.

11. Patient had known sensitivity to any of the products to be administered during the study, including mammalian cell derived drug products, trastuzumab, and murine proteins, or to any of the excipients.

12. Patient had previously participated in this study.

13. Patient was likely not to be available to complete all protocol-required study visits or procedures.

14. Patient had history or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion.

15. Patient had pre-existing, clinically significant (>Grade 1 by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.03) peripheral neuropathy.

Treatments

CT-P6 or Herceptin

During the Neoadjuvant Period, study drug was administered at a loading dose of 8 mg/kg body weight on Day 1 of Cycle 1, and then 6 mg/kg body weight repeated every 3 weeks (from Cycles 2 through 8).

During the adjuvant treatment, patients will receive 6 mg/kg body weight of CT-P6 or Herceptin as randomized, repeated every 3 weeks for up to 1 year from the first day of study drug administration in the Neoadjuvant Period, excluding surgery (up to 10 cycles after surgery).

Study drug was administered as a 90-minute IV infusion (±5 minutes) with an adequate infusion pump.

Patients also received docetaxel (75 mg/m2) during Cycles 1 through 4 and FEC (5-fluorouracil 500 mg/m2, epirubicin 75 mg/m2, and cyclophosphamide 500 mg/m2) during Cycles 5 through 8. Docetaxel and FEC were administered on the day of CT-P6 or Herceptin administration (Day 1, 3-week cycles).

Premedication consisting of an oral corticosteroid was administered prior to docetaxel unless contraindicated. Premedication with corticosteroids, antihistamines, and antipyretics could have been used before study drug infusion (CT-P6 or Herceptin) in patients who had experienced infusion-related

symptoms, at the investigator's discretion. Patients who experienced a life-threatening (NCI CTCAE grade 4) infusion reaction (e.g., acute respiratory distress syndrome, tachypnea, bronchospasm, hypotension, or hypoxia) were required to discontinue treatment.

Following surgery (lumpectomy or mastectomy, including axillary lymph node assessment [sentinel lymph node biopsy or axillary lymph node dissection], was completed within 3 to 6 weeks after the last dose of CT-P6 or Herceptin during the Neoadjuvant Period) followed by monotherapy trastzumab every 3 weeks for up to one year from the first day of study drug administration in the Neoadjuvant period.

During the Adjuvant Period, patients may undergo radiotherapy and/or hormone therapy (e.g. tamoxifen or aromatase inhibitors), at the investigator's discretion.

Objectives

Primary Objective

The primary objective of this study was to demonstrate equivalence of CT-P6 and Herceptin, both given in combination with docetaxel (Cycles 1 through 4) followed by 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) (Cycles 5 through 8), in terms of efficacy as determined by pathological complete response (pCR), in patients with HER2-positive operable early breast cancer.

Secondary Objectives

The secondary objectives of this study were to evaluate the following additional efficacy parameters:

- Overall response rate (ORR), defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) as assessed by Response Evaluation Criteria In Solid Tumours (RECIST) Version 1.1
- Disease-free survival (DFS), measured from the time of occurrence of attained CR to disease recurrence or death as a result of any cause
- Progression-free survival (PFS), measured from the randomization to disease recurrence, progression or death from any cause
- Overall survival (OS), defined as time from randomization to death from any cause
- Breast conservation rate, measured as the proportion of patients who undergo breast conservation surgery

Other pCRs

- pCR of the breast only (pCRB) – different from definition used in the HannaH trial, where bpCR was defined as "absence of invasive neoplastic cells in the breast".
- pCR of breast and axillary nodes with absence of ductal carcinoma in situ (DCIS)

and to obtain additional PK, pharmacodynamic, safety, and biomarker data in patients with HER2-positive early breast cancer.

Outcomes / endpoints

- **Outcomes / endpoints**

The primary efficacy endpoint of Study CT-P6 3.2 is the proportion of patients achieving pCR, defined as the absence of invasive tumour cells in the breast and in axillary lymph nodes regardless of DCIS. The

pCR was determined following surgery, using haematoxylin and eosin evaluation of the resected breast specimen.

Pathological CR was be evaluated at the local level for treatment practice. The pathological review report, which is issued locally, will be evaluated centrally by an independent reviewer for reporting purposes. Review of pathological tumour assessment results will be performed by a blinded medical reviewer.

- Evaluation of pCRs:
  - pCR of breast and axillary nodes with absence of DCIS
  - pCR of breast only
- Breast pCR in accordance with criteria in the HannaH study (here: post-hoc analysis).
- ORR, defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) as assessed by RECIST guideline Version 1.1
- Breast conservation rate, measured as the proportion of patients who underwent breast conservation surgery
- Time-To-Event Analysis: Due to the extremely low number of expected events in the Neoadjuvant Period of the study, the Time-To-Event Analyses will be carried out upon completion of the Adjuvant Period.
  - DFS measured from the date of occurrence of attained CR to disease recurrence or death from any cause whichever occurs first
  - PFS defined as the interval between randomisation and determined disease recurrence, progression, or death from any cause
  - OS defined as the interval between randomisation and death from any cause

An Independent Tumour Review Committee (ITRC) was used to review the pathology reports and safety assessments, and determine tumour response for the purposes of data analysis and reporting.

Secondary purposes of this study are also to obtain additional PK, PD, safety, immunogenicity and biomarker (optional) data in patients with HER2-positive EBC.

Sample size

From a meta-analysis of 6 studies conducted with FEC with taxane, pCR rate was estimated about 15.88%. Pooling results from the 4 key experimental studies performed with trastuzumab, patients who received taxane (paclitaxel or docetaxel) with trastuzumab followed by FEC plus trastuzumab regimen showed a 53.74% pCR rate. The difference in the pCR between patient groups who received the regimen without trastuzumab and with trastuzumab was 37.86%. This difference was used to define the equivalence margin (+/- 15%) as it represents half of the combined difference mentioned above. Furthermore it was expected that replacement of the FEC regimen with EC and 3-weekly administration of trastuzumab would not change the size of the effect of trastuzumab treatment.

Based on the results seen in the individual studies mentioned above it has been assumed that 50% of patients in each treatment group will have pCR. Assuming 15% equivalence margin, with alpha = 0.025 (two one-sided), analysis of 239 patients in each treatment group during Neoadjuvant Period (total n = 478) will provide at least 80% power to establish equivalence (i.e. that the 95% CI of the difference in the proportions of responders will be entirely bounded by the interval (–0.15, 0.15)).

Considering a dropout rate of 10%, it was calculated that 532 patients have to be enrolled in order to achieve 478 evaluable patients.

Randomisation

Patients were randomized applying a 1:1 ratio to receive CT-P6 or Herceptin. Randomization was balanced by using permuted blocks and was stratified for disease stage (Stage I or II versus Stage IIIa), oestrogen and progesterone receptor status (positive versus negative), and country. An IVRS/IWRS was used to administer the randomization schedule.

Blinding (masking)

This was a double blind study.

Statistical methods

Data were summarized using descriptive statistics (continuous data: n, mean, standard deviation, median, minimum, and maximum; categorical data: absolute and relative frequencies) unless otherwise indicated.

There were 3 analysis sets: intent-to-treat (ITT) set consisting of all patients who were allocated a randomization number by IVRS/IWRS (analyzed as randomized), per-protocol set (PPS) excluding patients with major protocol violations, and safety analysis set (SAF). A total of 13 GCP non-compliant patients who enrolled in a Latvian site were excluded from all analysis sets. Due to vial label manipulation and incorrect investigational product assignment, the identity of treatment could not be verified in 13 out of 18 patients enrolled at the site. Post-hoc analysis for including those patients was performed.

The primary set for the efficacy analysis was the PPS. The ITT set was used for supportive and sensitivity analyses.

The primary efficacy endpoint was the proportion of patients achieving pCR, defined as the absence of invasive tumour cells in the breast and in axillary lymph nodes, regardless of DCIS. The proportion of patients achieving pCR was analyzed by the exact binomial approach, calculating a point estimate and 95% confidence interval (CI) on the PPS and ITT set for the difference in proportion between the 2 treatment groups (CT-P6 and Herceptin). The exact CI was produced by the unconditional approach. Equivalence with regard to pCR was concluded if the confidence limits of the 95% CI of the difference in the proportions of responders were entirely bounded by the interval (-0.15 – 0.15).

A sensitivity analysis was performed on the primary endpoint, utilizing a logistic regression model, with treatment group (CT-P6 or Herceptin) as a fixed effect and disease stage (Stage I or II versus Stage IIIa), estrogen and progesterone receptor status (positive versus negative), and country as covariates. For disease stage, estrogen and progesterone receptor status, the variables recorded in the eCRF were used. Country was pooled into region (EMEA versus America versus Asia) for statistical models, as appropriate. Region was only to be used in the statistical model when there were not enough patients within each country to allow the analysis to converge. Use of region instead of country in the statistical model was confirmed at the blinded DRM. The resulting odds ratio and 95% CI was converted into difference of proportions using the Delta method for the purpose of comparison.

According to the protocol there were 4 secondary efficacy parameters: ORR, breast conservation rate (BCR), other pCRs (pCRB, pCR of breast and axillary nodes with absence of DCIS) and time to event endpoints (DFS, PFS, OS). The categorical endpoints ORR, BCR and other pCRs were described using

summary table and calculating exact 95% CI's for the corresponding point estimates. In addition for other pCRs a point estimate and 95% CI on the PPS and ITT set for the difference in proportion between the 2 treatment groups (CT-P6 and Herceptin) was calculated.

The analyses of secondary time-to-event endpoints (DFS, PFS, and OS) were not included for the current analyses.

Results

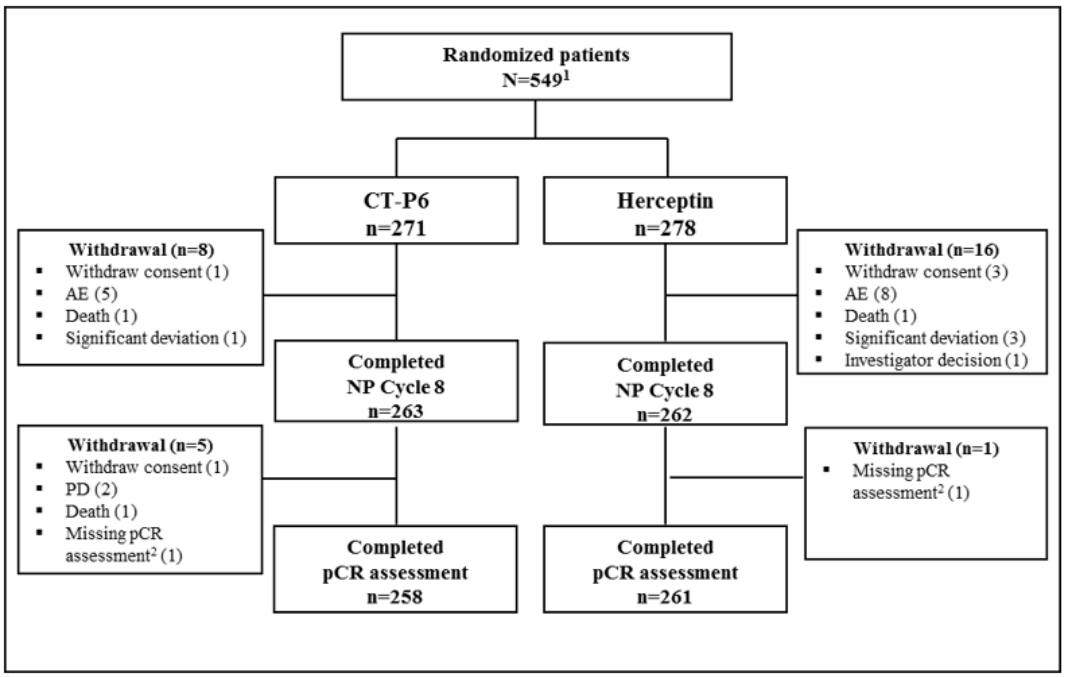
Participant flow

A total of 549 patients were randomly assigned to study drugs and initiated the Neoadjuvant Period (271 patients and 278 patients in the CT-P6 and Herceptin treatment groups, respectively).

The majority of patients in each treatment group completed the Neoadjuvant Period including pCR assessment (258/271 [95.2%] patients and 261/278 [93.9%] patients in the CT-P6 and Herceptin treatment groups, respectively).

Table 16: Patient Disposition in Study for Neoadjuvant Period (up to Cycle 8) in CT-P6 3.2

	CT-P6 (n=271)	Herceptin® (n=278)	Total (n=549)
	Number (%) of Patients		
Total number of Patients			
Randomised	271 (100.0)	278 (100.0)	549 (100.0)
Initiated Neoadjuvant Period	271 (100.0)	278 (100.0)	549 (100.0)
Completed Neoadjuvant Period (including pCR assessment)[1]	258 (95.2)	261 (93.9)	519 (94.5)
Discontinued Neoadjuvant Period	12 (4.4)	16 (5.8)	28 (5.1)
Missing pCR assessment[2]	1 (0.4)	1 (0.4)	2 (0.4)
Primary Reason for Early Treatment Discontinuation (Neoadjuvant Period)			
Adverse event that, in the opinion of the investigator, precludes further participation in the study	5 (1.8)	8 (2.9)	13 (2.4)
Patient withdrew consent to continue study treatment	2 (0.7)	3 (1.1)	5 (0.9)
Significant deviation from the treatment plan specified in the protocol	1 (0.4)	3 (1.1)	4 (0.7)
Patient died	2 (0.7)	1 (0.4)	3 (0.5)
Progressive disease	2 (0.7)	0	2 (0.4)
Investigator decision	0	1 (0.4)	1 (0.2)



[1] Thirteen patients of one site from Latvia were excluded from all populations due to GCP non-compliance. For details of GCP non-compliance, refer to GCP compliance of this document.
[2] [redacted] and [redacted] underwent surgery. However, pCR assessments were not available due to lost pathological samples.
ITT: Intent-to-treat

Figure 10: Patient Disposition for Neoadjuvant Period (up to Cycle 8) in Study CT-P6 3.2 (ITT set)

Recruitment

First patient was entered in the study on 7/8/2014 and the last patient had her last visit for surgery on 6/5/16.

Conduct of the study

Two global amendments and 7 country specific protocol amendments were made to the original protocol (dated 11 November 2013).

The original protocol (Version 1.0), dated 11 November 2013, was amended 9 times during the course of the study:

Global Protocol Amendment, Dated 20 January 2014 (Version 2.0)

Summary of significant changes included the following:

• Trastuzumab monotherapy was allowed by investigator discretion if a site had a practice that had been notified to the sponsor or its appropriate designee prior to the initiation of study treatment.

• Tumour assessments by sonogram and physical examinations on tumour sites in the Adjuvant Period were changed to be optional on Day 1 of Cycle 1, after Cycle 3, and after Cycle 6.

• The drug-switching design in the Adjuvant Period was deleted.

Country-Specific Protocol Amendment (Spain), Dated 23 January 2014 (Version 2.1)

Summary of significant changes included the following:

• MRI was allowed as an imaging method to perform tumour assessment.

• All changes from Global Protocol Amendment, dated 20 January 2014 (Version 2.0).

Global Protocol Amendment, Dated 24 December 2014 (Version 3.0)

Summary of significant changes included the following:

• Inclusion criterion (#4) was updated to specify breast cancer type.

• Biopsy period was updated from within 4 weeks to 6 weeks before study drug administration and inclusion criterion (#8) and sections referring to the biopsy period were updated accordingly.

• Myocardial infarction was added as an example of serious cardiac illness or medical conditions in exclusion criterion (#6).

• Exclusion criterion (#9) was updated to change the duration of birth control according to the SmPC.

• Exclusion criterion (#15) was added to exclude patients with pre-existing peripheral neuropathy.

• A sentence describing lymph node assessment was added to specify the surgery process in the study design section.

• The eligibility for Post-treatment Follow-up Period was changed to include a patient who did not complete neoadjuvant therapy or did not undergo adjuvant treatment.

• Assessment time points were added to confirm the response before regimen change.

• Clinical response rate and radiological response rate were combined as tumour response rate additional since CT assessment was added after Neoadjuvant Period Cycle 4. The relevant text was updated accordingly.

Baseline data

Table 17: Analysis Set in Study CT-P6 3.2

Statistic/Characteristic	CT-P6 (n=271)	Herceptin® (n=278)	Total (n=549)
	Number (%) of Patients		
Age (Year)			
Mean (SD)	51.8 (10.97)	52.1 (10.45)	52.0 (10.70)
Median (Min, Max)	53.0 (24, 78)	53.0 (22, 74)	53.0 (22, 78)
Race			
Not Available as per Local Regulation	0	2 (0.7)	2 (0.4)
American Indian or Alaska Native	1 (0.4)	1 (0.4)	2 (0.4)
Asian	51 (18.8)	48 (17.3)	99 (18.0)
Black or African American	2 (0.7)	5 (1.8)	7 (1.3)
Hispanic or Latino	9 (3.3)	8 (2.9)	17 (3.1)
White	207 (76.4)	214 (77.0)	421 (76.7)
Other[1]	1 (0.4)	0	1 (0.2)
Height (cm)			
Mean (SD)	161.0 (7.25)	161.1 (6.70)	161.0 (6.97)
Median (Min, Max)	161.0 (137, 183)	161.0 (136, 181)	161.0 (136, 183)
Weight (kg)			
Mean (SD)	69.86 (14.676)	70.80 (14.577)	70.34 (14.620)
Median (Min, Max)	68.00 (44.0, 124.0)	69.00 (43.4, 120.0)	68.40 (43.4, 124.0)
Region			
EMEA	209 (77.1)	222 (79.9)	431 (78.5)
America	12 (4.4)	10 (3.6)	22 (4.0)
Asia	50 (18.5)	46 (16.5)	96 (17.5)
Fertility Status			
Pre-menarche	0	0	0
Surgically sterilised	11 (4.1)	13 (4.7)	24 (4.4)
Post-menopausal (last menstrual period more than 1 year)	146 (53.9)	158 (56.8)	304 (55.4)
Potentially able to bear children	113 (41.7)	107 (38.5)	220 (40.1)
Other[2]	1 (0.4)	0	1 (0.2)
ECOG Performance Status (Screening)			
0	239 (88.2)	250 (89.9)	489 (89.1)
1	32 (11.8)	28 (10.1)	60 (10.9)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
Disease Duration (Day)			
Mean (SD)	29.1 (22.81)	28.1 (18.22)	28.6 (20.60)
Median (Min, Max)	25.0 (1, 278)	25.0 (1, 140)	25.0 (1, 278)

[1] One patient [redacted] [redacted]
[2] One patient [redacted] was congenitally uterus absent according to the eCRF.
ECOG: Eastern Cooperative Oncology Group, eCRF: electronic case report form, EMEA: Europe and the Middle East and Africa, ITT: Intent-to-treat, Min: Minimum, Max: Maximum, SD: Standard deviation

Table 18: Baseline Hormonal Status in Study CT-P6 3.2, ITT Set

	CT-P6 (n=271)	Herceptin[2] (n=278)	Total (n=549)
	Number (%) of Patients		
Estrogen receptor status			
Positive	154 (56.8)	154 (55.4)	308 (56.1)
Negative	117 (43.2)	124 (44.6)	241 (43.9)
Progesterone receptor status			
Positive	112 (41.3)	108 (38.8)	220 (40.1)
Negative	159 (58.7)	170 (61.2)	329 (59.9)
Hormone receptor status			
Positive[1]	160 (59.0)	162 (58.3)	322 (58.7)
Negative	111 (41.0)	116 (41.7)	227 (41.3)

[1]If a patient had positive result in estrogen receptor or progesterone receptor, hormone receptor status was positive.
ITT: Intent-to-treat

Table 19: Pathological Status in Study CT-P6 3.2, ITT Set

	CT-P6 (n=271)	Herceptin® (n=278)	Total (n=549)
	Number (%) of Patients		
Location of primary tumour			
Left breast	129 (47.6)	139 (50.0)	268 (48.8)
Right breast	142 (52.4)	139 (50.0)	281 (51.2)
Pathology of primary tumour type			
Ductal	202 (74.5)	210 (75.5)	412 (75.0)
Lobular	6 (2.2)	7 (2.5)	13 (2.4)
Tubular	3 (1.1)	4 (1.4)	7 (1.3)
Medullary	2 (0.7)	0	2 (0.4)
Mucinous	5 (1.8)	1 (0.4)	6 (1.1)
Papillary	0	1 (0.4)	1 (0.2)
Other	53 (19.6)	55 (19.8)	108 (19.7)
Histological grade			
Well differentiated	17 (6.3)	23 (8.3)	40 (7.3)
Moderately differentiated	109 (40.2)	110 (39.6)	219 (39.9)
Poorly differentiated	86 (31.7)	88 (31.7)	174 (31.7)
Unknown	57 (21.0)	57 (20.5)	114 (20.8)
Disease Stage			
Stage I	23 (8.5)	31 (11.2)	54 (9.8)
Stage IIa	75 (27.7)	86 (30.9)	161 (29.3)
Stage IIb	105 (38.7)	98 (35.3)	203 (37.0)
Stage IIIa	64 (23.6)	61 (21.9)	125 (22.8)
Stage IIIb[1]	1 (0.4)	0	1 (0.2)
Stage IIIc[1]	3 (1.1)	1 (0.4)	4 (0.7)
Stage IV[1]	0	1 (0.4)	1 (0.2)
T stage			
T0	3 (1.1)	0	3 (0.5)
Tis	0	1 (0.4)	1 (0.2)
T1	33 (12.2)	31 (11.2)	64 (11.7)
T1a	1 (0.4)	0	1 (0.2)
T1b	0	1 (0.4)	1 (0.2)
T1c	20 (7.4)	20 (7.2)	40 (7.3)
T2	179 (66.1)	188 (67.6)	367 (66.8)
T3	34 (12.5)	37 (13.3)	71 (12.9)
T4[2]	1 (0.4)	0	1 (0.2)
N stage			
N0	73 (26.9)	102 (36.7)	175 (31.9)
N1	156 (57.6)	138 (49.6)	294 (53.6)
N2	36 (13.3)	35 (12.6)	71 (12.9)
N2a	2 (0.7)	2 (0.7)	4 (0.7)
N2b	1 (0.4)	0	1 (0.2)
N3[3]	3 (1.1)	1 (0.4)	4 (0.7)
M stage			
M0	271 (100.0)	277 (99.6)	548 (99.8)
M1[4]	0	1 (0.4)	1 (0.2)

Concomitant Medication

Overall, 549/549 (100%) patients had taken at least one concomitant medication. The most frequently reported concomitant medications by class were glucocorticoids taken by 515/549 (93.8%) patients (253/271 [93.4%] patients and 262/278 [94.2%] patients in the CT-P6 and Herceptin treatment groups, respectively) and serotonin (5ht3) antagonists taken by 482 (87.8%) patients (242/271 [89.3%]

patients and 240/278 [86.3%] patients in the CT-P6 and Herceptin treatment groups, respectively). Both glucocorticoids and serotonin (5ht3) antagonists were used as premedication for chemotherapy.

Study drug and Chemo backbone

The mean (standard deviation) relative dose intensity (%) of study drug in the Neoadjuvant Period was similar between the 2 treatment groups (97.5 [2.91] in the CT-P6 treatment group and 97.3 [2.90] in the Herceptin treatment group) – see clinical safety section.

Numbers analysed

Table 20: Analysis Set in Study CT-P6 3.2

	CT-P6 (n=271)	Herceptin[2] (n=278)	Total (n=549)
	Number (%) of Patients		
Intent-to-Treat	271 (100)	278 (100)	549 (100)
Safety	271(100)	278 (100)	549 (100)
Per-protocol	248 (91.5)	256 (92.1)	504 (91.8)
Patients with at least one major protocol deviation	23 (8.5)	22 (7.9)	45 (8.2)
Patients who have not received all doses of study treatment during Neoadjuvant Period or discontinued early[1]	12 (4.4)	18 (6.5)	30 (5.5)
Patients who do not fully comply with inclusion or exclusion criteria[1]	4 (1.5)	4 (1.4)	8 (1.5)
Patients who have a missing primary efficacy assessment during surgery	5 (1.8)	3 (1.1)	8 (1.5)
Misrandomisations	1 (0.4)	0	1 (0.2)
Patients who have received a prohibited therapy	2 (0.7)	0	2 (0.4)

Note: Patients receiving at least one dose of CT-P6 were analysed under the CT-P6 treatment group in the safety population. Treatment randomised was used for the other analysis populations.
[1] One patient [redacted] in the CT-P6 treatment group and 3 patients [redacted] in the Herceptin® treatment group were discontinued early as inclusion or exclusion criteria were not fully complied with.

Outcomes and estimation

Primary endpoint

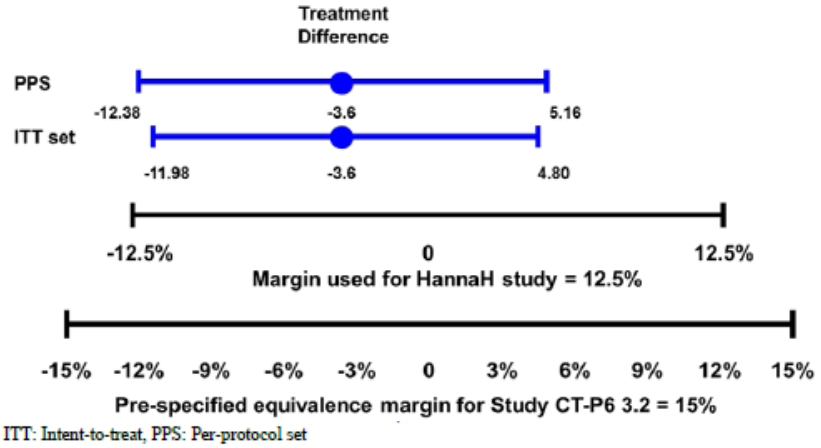
The primary endpoint in study CT-P6 3.2 is proportion of patients achieving pCR, defined as the absence of invasive tumour cells in the breast and in axillary lymph nodes regardless of DCIS (tpCR).

Table 21: Proportion of patients achieving pCR after neoadjuvant therapy in Study CT-P6 3.2, ITT Set and PPS

	PPS		ITT	
	CT-P6 (n=248)	Herceptin® (n=256)	CT-P6 (n=271)	Herceptin® (n=278)
Number of Responders[1] n (%)	116 (46.8)	129 (50.4)	118 (43.5)	131 (47.1)
Number of Non-Responders n (%)	132 (53.2)	127 (49.6)	153 (56.5)	147 (52.9)
Response Rate (%) (95% CI)[2]	46.8 (40.4 – 53.2)	50.4 (44.1 – 56.7)	43.5 (37.6 – 49.7)	47.1 (41.1 – 53.2)
Treatment Difference (CT-P6 – Herceptin®) (95% CI)[3]	-0.0362 (-0.1238 – 0.0516)		-0.0358 (-0.1198 – 0.0480)	

[1] The number of responders included the patients with pCR of breast and axillary nodes regardless of DCIS.
[2] 95% CI was based on exact binomial approach.
[3] The exact 95% CI for difference was based on unconditional approach.
CI: Confidence interval, ITT: Intent-to-treat, pCR: Pathological complete response, PPS: Per-protocol Set

The primary endpoint of the study was met. The number of responders in the CT-P6 and Herceptin treatment groups were 46.8% patients and 50.4% patients, respectively, leading to a minor difference of – 3.6% for CT-P6 treated patients. The 95% CI for the estimate of treatment difference was - 12.38%, 5.16% which is entirely contained within the equivalence range of -15% to 15% thus supporting biosimilarity. In the HannaH study[4], Gianni et al.[5] and Buzdar et al.[6] studies, a direct comparison of the reference product with placebo, was used to justify a ± 12.5% non-inferiority margin and the results from Study CT-P6 3.2 have met this criterion when applied retrospectively as well (see Figure 11).



ITT: Intent-to-treat, PPS: Per-protocol set

Figure 11: 95% CI for Differences in pCR Rate (Binomial Method) in Study CT-P6 3.2

[5] Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, Zambetti M, Vazquez F, Byakhow M, Lichinitser M, Climent MA, Ciruelos E, Ojeda B, Mansutti M, Bozhok A, Baronio R, Feyereislova A, Barton C, Valagussa P, Baselga J. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2 negative cohort. Lancet. 2010 Jan 30;375(9712):377-84.
[6] Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Pusztai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D, Hortobagyi GN. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and eirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2– positive operable breast cancer. J Clin Oncol. 2005 Jun 1;23(16):3676-85.

Comparing the efficacy results of studyCT-P6 3.2 with "reference" trials in EBC, the observed pCR results fell into the range of reported pCR data as observed in the literature (65.2% [15/23] in Buzdar et al., 61.4% [51/83] in Pernas et al.[7], 58.3% [137/235] in Bayraktar et al.[8].

Secondary endpoints

Breast Surgery and Pathological Response

After completion of neoadjuvant treatment, patients underwent primary surgery for breast cancer. Methods of surgical procedures performed were similar between the 2 treatment groups within the PPS as shown below.

Table 22: Breast Surgery and Pathological Response Study CT-P6 3.2 (PPS)

	CT-P6 (n=248)	Herceptin® (n=256)	Total (n=504)
	Number (%) of Patients		
Type of Surgery			
Mastectomy	168 (67.7)	173 (67.6)	341 (67.7)
Quadrantectomy	23 (9.3)	31 (12.1)	54 (10.7)
Lumpectomy	56 (22.6)	52 (20.3)	108 (21.4)
Sectoral resection[1]	1 (0.4)	0	1 (0.2)
Axillary dissection only	0	0	0
Axillary dissection			
Sentinel node biopsy only	19 (7.7)	26 (10.2)	45 (8.9)
First level only	13 (5.2)	12 (4.7)	25 (5.0)
First and second level	45 (18.1)	52 (20.3)	97 (19.2)
All three levels	170 (68.5)	166 (64.8)	336 (66.7)
Axillary dissection, not specified[2]	1 (0.4)	0	1 (0.2)

[1] [redacted] in the CT-P6 treatment group had sectoral resection which was specified in the eCRF.
[2] [redacted] in the CT-P6 treatment group underwent axillary dissection, but the level was not specified.

pCR of Breast and Axillary Nodes with Absence of DCIS

The secondary endpoint pCR of breast and axillary nodes with absence of DCIS is comparable between the two arms with 39.9% CT-P6 patients and 41.4% Herceptin patients, respectively. The 95% CI for the estimate of treatment difference is (-10.22%, 7.31%) The results are confirmed in the ITT analysis.

[7] Pernas S, Gil-Gil M, de Olza MO, Gumà A, Climent F, Petit A, Pla MJ, García-Tejedor A, López-Ojeda A,Falo C, Fernandez-Otega A, Mesia C, Pérez-Martin FJ, Urruticoechea A, Germà JR. Efficacy and safety of concurrent trastuzumab plus weekly paclitaxel-FEC as primary therapy for HER-2 positive breast cancer in everyday clinical practice. Breast Cancer Res Treat. 2012 Aug;134(3):1161-8.
[8] Bayraktar S, Gonzalez-Angulo AM, Lei X, Buzdar AU, Valero V, Melhem-Bertrandt A, Kuerer HM, Hortobagyi GN, Sahin AA, Meric Bernstam F. Efficacy of neoadjuvant therapy with trastuzumab concurrent with anthracycline- and non-anthracycline-based regimens for HER2- positive breast cancer. Cancer. 2012 May 1;118(9):2385–93.

Table 23: Pathological Complete Response Rate of the Breast and Axilla nodes with absence of DCIS in Study CT-P6 3.2 (PPS and ITT set)

	PPS		ITT	
	CT-P6 (n=248)	Herceptin® (n=256)	CT-P6 (n=271)	Herceptin® (n=278)
Number of Responders[1] n (%)	99 (39.9)	106 (41.4)	101 (37.3)	108 (38.8)
Number of Non-Responders n (%)	149 (60.1)	150 (58.6)	170 (62.7)	170 (61.2)
Response Rate (%) (95% CI)[2]	39.9 (33.8 – 46.3)	41.4 (35.3 – 47.7)	37.3 (31.5 – 43.3)	38.8 (33.1 – 44.9)
Treatment Difference (CT-P6 – Herceptin®) (95% CI)[3]	-0.0149 (-0.1022 – 0.0731)		-0.0158 (-0.0996 – 0.0685)	

[1] The number of responders included the patients with pCR of breast and axillary nodes with absence of DCIS.
[2] 95% CI is based on exact binomial approach.
[3] The exact 95% CI for difference was based on unconditional approach.
CI: Confidence interval, ITT: Intent-to-treat, PPS: Per-protocol set

pCR of the Breast Only

The secondary endpoint data for breast only pCR (pCRB) seem comparable between the two treatment arms at 4.8% versus 4.7%, respectively.

The study results demonstrate highly similar efficacy of both treatment arms regardless of definition of pCR thus supporting biosimilarity (see Table 24).

Table 24: Response Rate (95% CI) of pCR Results in Study CT-P6 3.2

Terminology in Study CT-P6 3.2	Terminology in historical studies	PPS		ITT	
		CT-P6 (n=248)	Herceptin® (n=256)	CT-P6 (n=271)	Herceptin® (n=278)
Breast pCR [Post-hoc analysis] = Total pCR + pCR of Breast Only					
Breast pCR	BpCR[1,2] (ypT0/is)	51.6 (45.2 – 58.0)	55.1 (48.8 – 61.3)	49.1 (43.0 – 55.2)	52.2 (46.1 – 58.2)
pCR of breast and axillary nodes regardless of DCIS	tpCR[1,2] (ypT0/is ypN0)	46.8 (40.4 – 53.2)	50.4 (44.1 – 56.7)	43.5 (37.6 - 49.7)	47.1 (41.1 - 53.2)
pCR of breast and axillary nodes with absence of DCIS	GBG pCR[2] (ypT0 ypN0)	39.9 (33.8 - 46.3)	41.4 (35.3 - 47.7)	37.3 (31.5 – 43.3)	38.8 (33.1 – 44.9)
pCR of breast only	N/A	4.8 (2.5 - 8.3)	4.7 (2.5 - 8.0)	5.5 (3.1 - 9.0)	5.0 (2.8 - 8.3)

Note: 95% CI is based on exact binomial approach.
Breast pCR: Absence of invasive tumour cells in the breast regardless of DCIS.

Overall Response Rate (ORR)

The proportion of patients who achieved an overall response was the same in the two arms with CT-P6 (84.3%) and Herceptin (84.0%) patients thus supporting similarity. Albeit differences in assessment method between CT-P6 3.2. and HannaH, the observed ORR, also differentiating CR, PR are highly similar and in the range of those observed for iv trastuzumab by Ismael et al., 2012, i.e. CR: 21.2%, PR: 67.7% versus 21.4 % and 62.9%. Further, time to response (ORR) in the CT-P6 treatment group was similar to that in the Herceptin treatment group in the neoadjuvant part of the study.

Table 25: Overall Response Rate during Neoadjuvant Period in Study CT-P6 3.2 (PPS and ITT set)

	PPS		ITT	
	CT-P6 (n=248)	Herceptin® (n=256)	CT-P6 (n=271)	Herceptin® (n=278)
Number of Responders (%)	209 (84.3)	215 (84.0)	224 (82.7)	228 (82.0)
Number of Non-Responders (%)	39 (15.7)	41 (16.0)	47 (17.3)	50 (18.0)
Overall Response Rate (%) (95% CI)	84.3 (79.1 – 88.6)	84.0 (78.9 – 88.3)	82.7 (77.6 – 87.0)	82.0 (77.0 – 86.4)

Note: Overall response rate is calculated as the number of patients with a response of CR or PR divided by the number of patients in the PPS/ITT set.
95% CI was based on exact binomial approach .
CI: Confidence interval, ITT: Intent-to-treat, ORR: Overall response rate, PPS: Per-protocol set

The results for breast conservation from the PPS and ITT set were consistent supporting the similarity between the CT-P6 and Herceptin treatment groups.

Breast Conservation Rate

In the PPS, the proportions of patients who underwent 'lumpectomy (breast conservation surgery)' were similar between the CT-P6 and Herceptin treatment groups (56/248 [22.6%] patients and 52/256 [20.3%] patients, respectively). The 95% CI were similar between the CT-P6 and Herceptin treatment groups ([17.5%, 28.3%] and [15.6%, 25.8%], respectively).

The proportions of patients who underwent 'lumpectomy' in the ITT set were consistent with those in the PPS.

Ancillary analyses

Pathological Complete Response Rate: Logistic Regression Method

A logistic regression analysis of the primary endpoint, pCR, with the treatment group (CT-P6 or Herceptin) as a fixed effect and disease stage (Stage I or II vs. Stage IIIa), estrogen receptor status (positive vs. negative), progesterone receptor status (positive vs. negative), region as covariates was performed in order to further investigate the consistency of the results when compared to the unadjusted result.

The logistic regression results for the primary efficacy endpoint are summarised for the PPS and ITT set as shown below.

Table 26: Proportion of patients achieving pCR after Neoadjuvant Period (Logistic Regression Method) in study CT-P6 3.2 (PPS and ITT)

	PPS		ITT	
	CT-P6 (n=248)	Herceptin® (n=256)	CT-P6 (n=271)	Herceptin® (n=278)
Odds Ratio[1]	0.90		0.89	
Treatment Difference (CT-P6 – Herceptin®) (95% CI)[2]	-0.0274 (-0.1180 – 0.0632)		-0.0288 (-0.1146 – 0.0570)	
P-value[1]	0.460		0.189	

Note: Logistic regression model included treatment group (CT-P6 or Herceptin®) as fixed effect and disease stage (Stage I or II vs. Stage III or IV), estrogen receptor status (positive vs negative), progesterone receptor status (positive vs negative) and region (EMEA vs America vs Asia) as covariates.
[1] Odds ratio was calculated from regression model and p-value is calculated using the Hosmer-Lemeshow test for the goodness-of-fit of the logistic regression model. The test was significant at the 5% level.
[2] Estimate and 95% CI for the difference was based on the Delta method.
CI: Confidence Interval, EMEA: Europe, the Middle East, and Africa, ITT: Intent-to-treat, pCR: pathological Complete Response, PPS: Per-protocol set

Sensitivity Analysis in ITT – Pathological Complete Response Rate Including GCP Noncompliant patients in one Latvian site: Binomial Method

In a post-hoc manner, a sensitivity analysis including GCP non-compliant 13 patients in the ITT set was carried out to assess the impact on the inclusion of these patients on the primary efficacy endpoint, pCR.

The proportions of patients achieving pCR including GCP non-compliant patients were analysed in the ITT set only and the result was similar between the CT-P6 and Herceptin treatment groups (43.2% [95% CI: 37.3%, 49.2%] patients and 47.2% [95% CI: 41.3%, 53.2%] patients respectively). The 95% CI for the estimate of treatment difference (-12.33%, 4.26%) was entirely contained within the range -15% to 15% further supporting therapeutic equivalence between the treatment groups

Sensitivity Analysis in PPS – Pathological Complete Response Rate Excluding 3 Additional Patients with Major Deviations: Binomial Method

The proportions of patients achieving pCR excluding the 3 patients with major deviations in the PPS were similar between the CT-P6 and Herceptin treatment groups (46.7% [95% CI: 40.4%, 53.2%] patients and 50.2% [95% CI: 43.9%, 56.5%] patients, respectively). The 95% CI for the estimate of treatment difference (-12.23%, 5.35%) was entirely contained within the range -15% to 15% supporting therapeutic equivalence between the treatment groups

Summary of main study(ies)

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

Table 27: Summary of Efficacy for trial CT-P6 3.2

Title:
A Phase 3, Double-Blind, Randomized, Parallel-Group, Active-Controlled Study to Compare the Efficacy and Safety of CT-P6 and Herceptin as Neoadjuvant and Adjuvant Treatment in Patients with HER2-Positive Early Breast Cancer

Study identifier	CT-P6 3.2			
Design	Parallel-group, active-controlled			
	Duration of main phase:		8 cycles (~ 6 month)	
	Duration of Run-in phase:		not applicable	
	Duration of Extension phase:		not applicable	
Hypothesis	Equivalence			
Treatments groups	CT-P6		IV 8 mg/kg bwt (cycle 1), 6 mg/kg bwt (cycles 2 through 8) N = 271	
	Herceptin		IV 8 mg/kg bwt (cycle 1), 6 mg/kg bwt (cycles 2 through 8) N = 278	
Endpoints and definitions	Primary endpoint	pCR	absence of invasive tumour cells in the breast and in axillary lymph nodes, regardless of the ductal carcinoma in situ (DCIS). Determined at the time of surgery, using hematoxylin and eosin evaluation of the resected breast specimen.	
	Secondary	ORR	BOR of CR or PR as assessed by RECIST 1.1 (local assessment)	
	Secondary	BCR	Breast conservation rate	
Database lock	26 August 2016 (Neoadjuvant Period)			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Per protocol population, time of surgery			
Descriptive statistics and estimate variability	Treatment group	Ct-P6	Herceptin	
	Number of subject	248	256	
	pCR	116 (46.8%)	129 (50.4%)	
	95%-CI	(40.4%, 53.2%)	(44.1%, 56.7%)	
	ORR	209 (84.3%)	215 (84.0%)	
	95%-CI	(79.1%, 88.6%)	(78.9%, 88.3%)	
	BCR	56 (22.6%)	52 (20.3%)	
	95%-CI	(17.5%, 28.3%)	(15.6%, 25.8%)	

Effect estimate per comparison	Primary endpoint	Comparison groups	CT-P6 vs. Herceptin
		Difference in incidences	-3.62%
		95%-CI	(-12.38%, 5.16%)
		Equivalence margin	(-15%, 15%)
Notes	Equivalence has been shown. The primary analysis results are supported by the outcome of the ITT analysis as the 95%-CI for the difference in incidences for the ITT (-11.98%, 4.8%) is within the pre-specified equivalence range. Sensitivity analyses by means of a logistic regression accounting for the strata used for randomisation also support the conclusion of equivalence within the pre-defined equivalence range.		

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

The Applicant has also conducted a number of additional meta-analyses in order to ascertain the application of constancy assumption in determining the equivalence margin used for Study CT-P6 3.2 in all 3 new meta-analyses that were performed which included 1) newly published studies 2) allowing different periods of trastuzumab exposure and 3) less rigid requirements for similar chemotherapy regimen (fluorouracil not mandated). Of note is that despite the difference meta-analyses performed applying different selection criteria, the overall pCR rate barely changed; the original meta-analysis gave an overall pCR rate of 54% (95% CI: 38% - 70%), and the meta-analysis which expanded to include the 3 newly identified studies gave an overall pCR rate of 50% (95% CI: 39% - 61%). In addition, the meta-analyses which were expanded to 11 studies with wider inclusion criteria or 15 studies encompassing regimens both with and without the inclusion of fluorouracil gave an overall rate of 49% (95% CI: 43% - 56%) and 47% (95% CI: 40% - 53%), respectively.

Efficacy data from Study CT-P6 3.2 were indirectly compared to historical data from the pivotal Herceptin studies.

Table 28: Comparison of Efficacy between Study CT-P6 3.2 and key Herceptin Studies with Similar Design

Efficacy Parameter	Historical data				Study CT-P6 3.2[5]	
	Buzdar *et al.*, 2005[1]	Pernas *et al.*, 2012[2]	Bayraktar *et al.*, 2012[3]	Ismael *et al.*, 2012[4] (HannaH study)	CT-P6	Herceptin®
pCR	65.2%[6] (15/23)	61.4%[7] (51/83)	58.3%[8] (137/235)	34.2%[9] (90/263)	46.8%[10] (116/248 PPS) 43.5%[10] (118/271 ITT set)	50.4%[10] (129/256 PPS) 47.1%[10] (131/278 ITT set)
					51.6%[11] (128/248 PPS) 49.1%[11] (133/248 ITT set)	55.1%[11] (141/256 PPS) 52.2%[11] (145/256 ITT set)
ORR[12]	95.7% (22/23)	n/a	97.0% (226/235)	88.8% (231/260)	84.3% (209/248 PPS) 82.7% (224/271 ITT set)	84.0% (215/256 PPS) 82.0% (228/278 ITT set)
Breast Conservation Rate	n/a	54.2% (45/83)	30.0% (69/235)	17.9% (47/263 EPP) 16.8% (50/298 SP)	22.6% (56/248 PPS) 22.1% (57/258 ITT set)	20.3% (52/256 PPS) (20.3% (53/261 ITT set)

[1] Paclitaxel (225 mg/m^2, 3 weeks) + trastuzumab (4 mg/kg →2 mg/kg, weekly) × 4 cycles (12 weeks) followed by FEC (Fluorouracil 500 mg/m^2, Epirubicin 75 mg/m^2, Cyclophosphamide 500 mg/m^2, 3 weeks) + trastuzumab (4 mg/kg →2 mg/kg, weekly) × 4 cycles (12 weeks)
[2] Paclitaxel (80 mg/m^2, weekly) + trastuzumab (4 mg/kg →2 mg/kg, weekly) × 12 cycles (12 weeks) followed by FEC (Fluorouracil 500 mg/m^2, Epirubicin 75 mg/m^2, Cyclophosphamide 500 mg/m^2, 3 weeks) + trastuzumab (4 mg/kg →2 mg/kg, weekly) × 4 cycles (12 weeks)
[3] Paclitaxel (80 mg/m^2, weekly or 225 mg/m^2, 3 weeks) + trastuzumab (4 mg/kg →2 mg/kg, weekly) × 4 cycles (12 weeks) followed by FEC (Fluorouracil 500 mg/m^2, Epirubicin 75 mg/m^2, Cyclophosphamide 500 mg/m^2, 3 weeks) + trastuzumab (4 mg/kg →2 mg/kg, weekly) × 4 cycles =12 weeks)
[4] Docetaxel (75 mg/m^2, 3 weeks) + trastuzumab (8 mg/kg →6 mg/kg, 3 weeks) × 4 cycles (12 weeks) followed by FEC (Fluorouracil 500 mg/m^2, Epirubicin 75 mg/m^2, Cyclophosphamide 500 mg/m^2, 3 weeks) + trastuzumab (6 mg/kg, 3 weeks) × 4 cycles (12 weeks)
[5] Docetaxel (75 mg/m^2, 3 weeks) + trastuzumab (8 mg/kg →6 mg/kg, 3 w
followed by FEC (Fluorouracil 500 mg/m^2, Epirubicin 75 mg/m^2, Cyclophosphamide 500 mg/m^2, 3 weeks) + trastuzumab (6 mg/kg, 3 weeks) × 4 cycles (12 weeks)
[6] pCR was defined as no evidence of residual invasive cancer, both in breast and axilla.
[7] pCR was defined as no invasive residual carcinoma in both the breast and lymph nodes, regardless of the presence of ductal carcinoma in situ (ypT0/is ypN0).
[8] pCR was defined as the absence of invasive disease in the breast, and the absence of micro- or macro-metastases in the ipsilateral axillary lymph nodes.
[9] pCR was defined as the absence of invasive neoplastic cells in the breast; remaining ductal carcinoma in situ was accepted.
[10] pCR was defined as the absence of invasive tumour cells in the breast and in axillary lymph nodes, regardless of ductal carcinoma in situ (DCIS).
[11] pCR was defined as sum of the two pCR definition used in Study CT-P6 3.2 (pCR of the breast only and pCR of breast and axillary nodes regardless of DCIS), in accordance with HannaH study
[12] Image method (not specified) has been used in Bayraktar *et al.,* 2012; sonogram and physical exam method has been used in Ismael *el al.,* 2012; computerised tomography (RECIST v.1.1) method has been used in Study CT-P6 3.2.
EPP: Efficacy per protocol population, ITT: Intent-to-treat, ORR: Overall response rate, pCR: Pathological complete response, PPS: Per-protocol set, SP: Safety analysis population.

Clinical studies in special populations

Not applicable.

Supportive study(ies)

The applicant did not submit supportive studies.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme to show biosimilarity between CT-P6 and Herceptin is based on a single Phase III study comparing the efficacy and safety of CT-P6 and US Herceptin in women with newly diagnosed HER2 positive early or locally advanced breast cancer in the neoadjuvant setting. This study is on-going but data on the primary efficacy endpoint and several key secondary endpoints obtained during the neoadjuvant period is complete. As per cut-off date of 28 February 2017, median follow up of patients was 19.3 months in the CT-P6 arm and 19.6 months in the Herceptin arm and, respectively and 234/ 271 patients in the CT-P6 arm and 254/278 patients in the Herceptin arm entered the Post-treatment Follow-up Period phase. The adjuvant period is of special interest as the study drug was administered in the absence of concomitant chemotherapy and thus allows for sensitive comparison between the biosimilar candidate and the reference drug.

The choice of the indication, the clinical setting, the primary and secondary endpoints and the chosen equivalence range are endorsed. The clinical model is considered sufficiently sensitive to enable the detection of differences between the two products. As primary endpoint the applicant has justified the use of tpCR (= total pCR, breast and axilla regardless of, i.e. including DCIS) as opposed to bpCR (=breast pCR) for demonstrating comparability on the basis of other approvals which is acceptable. Primary assessment was conducted by the local investigators and independently reviewed data was used for the purposes of data analysis and reporting.

Efficacy data and additional analyses

Baseline characteristics, region (EMEA vs. America vs. Asia), fertility status, ECOG status at screening and disease duration (days) are well balanced. The majority of patients were enrolled in the EMEA region (431/549 [78.5%] patients). Especially regarding hormone receptor status, which is known to correlate with pCR response, no difference between the patient populations could be observed. The use of concomitant medication in Study CT-P6 3.2 was in line with the profile of concomitant medications and specifically usage of chemotherapy backbone regimen and may have positively impacted safety results in both arms. Study drug exposure (CT-P6 and Herceptin) and also Docetaxel and FEC exposure were similar. In summary demographic data, baseline characteristics reveal only minor differences not leading to any unidirectional bias. Mastectomy, lumpectomy and all 3 levels of the most frequently reported types of axillary dissection were largely similar between the 2 treatment groups. Overall, demographic data, baseline characteristics and type of surgery reveal some minor differences between the two arms not leading to an unidirectional bias, that could potentially impact the clinical outcome, e.g. slightly more advanced stages for the CT-P6 arm ; but higher rate of sentinel node biopsy with lower positive detection rate in Herceptin arm.

The primary endpoint of this study was total pCR (tpCR) and an equivalence margin was chosen such that it preserves half of the difference between chemotherapy only and combined therapy with trastuzumab seen in comparable studies. Specifically, as a result from a meta-analysis of 6 studies conducted with FEC with taxane, pCR rate was estimated about 16%. Pooling results from the 4 key experimental studies performed with trastuzumab, patients who received taxane (paclitaxel or docetaxel) with trastuzumab followed by FEC plus trastuzumab regimen showed a 54% pCR rate. The difference in the pCR between patient groups who received the regimen without trastuzumab and with trastuzumab was 38%. This difference from a statistical viewpoint justifies a 15% equivalence margin for planning purposes. However, the equivalence margin for a biosimilar product to its reference product also needs to be clinically justified on a difference that can be considered clinically irrelevant.

The primary endpoint of the study was met. The number of responders in the CT-P6 and Herceptin treatment groups were 46.8% patients and 50.4% patients, respectively, leading to a minor difference of – 3.6% for CT-P6 treated patients. The 95% CI for the estimate of treatment difference was - 12.38%, 5.16%. Also, based on a direct comparison of the reference product with placebo as investigated in the HannaH[4] and other studies, Gianni et al. and Buzdar et al. a ± 12.5% non-inferiority margin could be defined and the results from Study CT-P6 3.2 have met this criterion when applied retrospectively as well.

There were differences in the pCR rates in the Herceptin arm in the Study CT-P6 3.2 and the original HannaH-study even though the two trial designs were highly similar, questioning the validity of the statistical assumptions and sensitivity of the trial to detect a difference between the Herzuma and Herceptin study arms. Consequently, the applicant provided upon CHMP's request, a detailed comparison of the study design and baseline characteristics of the patient populations and a comprehensive review of factors that might affect the pCR rates including other relevant studies identified through a comprehensive literature search. The most likely contributing factor to the observed differences in the pCR rates was a difference in the disease stage at baseline, which was substantially higher in the HannaH

study. A subgroup analysis of CT-P6 patients indicated that the patients with the highest disease stage within the respective study, Stage IIIA or above, showed a lesser response in terms of tpCR compared to patients with lower disease stage, which is also supported by the literature.

Further, the applicant conducted meta-analyses in order to demonstrate that the pCR rates seen in Study CT-P6 3.2 align well with the results of the historical studies with different trastuzumab exposures and chemotherapy regimens.

In conclusion, the lower pCR rate noted in the HannaH study is likely due to a greater proportion of patients being at Stage III and T4.

Herceptin is authorised in the treatment of HER2-positive MBC, early breast cancer, and metastatic gastric cancer. The mechanism of action of trastuzumab is the same in all three indications and the target receptor involved is also the same in early breast cancer, metastatic gastric cancer and MBC (i.e., HER2). Results of the physico-chemical, structural, and biological characterisation studies together with the evidence from non-clinical studies and PK studies support extrapolation to the other oncology indications.

2.5.4. Conclusions on the clinical efficacy

The primary efficacy endpoint of pCR for study CT-P6 3.2 was met and efficacy data appears to be comparable between the treatment arms and supported by secondary efficacy endpoints. The clinical efficacy data therefore support biosimilarity.

Extrapolation to the other approved indications of Herceptin is supported by the efficacy results from the clinical trials, in addition to the quality comparability data, including results from functional assays and the PK results.

2.6. Clinical safety

Key safety information is derived from 2 completed Phase 1 clinical studies in healthy subjects (Studies CT-P6 1.4 and CT-P6 1.5) and 1 ongoing Phase 3 study in patients with HER-2 positive early breast cancer (EBC) (Study CT-P6 3.2).

Patient exposure

Study CT-P6 1.4

In the supportive healthy volunteer study CT-P6 1.4, among the 70 randomized subjects (35 subjects in each treatment group), three subjects withdrew from the study before drug administration due to an adverse event (1 subject and 2 subjects in the CT-P6 and US-licensed Herceptin groups, respectively). Therefore, the Safety Analysis Set includes 34 subjects treated with CT-P6 and 33 subjects treated with US-licensed Herceptin.

Study CT-P6 1.5

In the pivotal healthy volunteer study CT-P6 1.5, all 70 randomized subjects (35 in each treatment group) received the study treatment (35 subjects received a mean dose of 466.54 mg CT-P6 and 35 subjects received a mean dose of 459.90 mg US-licensed Herceptin). No dosing interruptions or discontinuations were reported for any subject. To avoid infusion-related reactions, premedication with oral acetaminophen (650 mg) was administered 30 to 60 minutes prior to the infusion of CT-P6 or US-licensed Herceptin in this study.

Study CT-P6 3.2

The patient exposure for the pivotal therapeutic similarity study in patients with HER-2 positive EBC is as follows as of cut-off date 28 February 2017:

Table 29: Exposure of patients in Study CT-P6 3.2

	CT-P6 (N=271)	Herceptin® (N=278)	Total (N=549)
	Number (%) of patients		
Randomised	271 (100.0)	278 (100.0)	549 (100.0)
Initiated Neoadjuvant Period	271 (100.0)	278 (100.0)	549 (100.0)
Completed Neoadjuvant Period (including pCR assessment)	258 (95.2)	261 (93.9)	519 (94.5)
Discontinued Neoadjuvant Period[1]	12 (4.4)	16 (5.8)	28 (5.1)
Missing pCR assessment[2]	1 (0.4)	1 (0.4)	2 (0.4)
Did not initiate Adjuvant Period after surgery	5 (1.8)	0	5 (0.9)
Initiated Adjuvant Period[2]	254 (93.7)	262 (94.2)	516 (94.0)
Completed Adjuvant Period	243 (89.7)	249 (89.6)	492 (89.6)
Discontinued Adjuvant Period	11 (4.1)	13 (4.7)	24 (4.4)
Initiated Post-treatment Follow-up Period	234 (86.3)	254 (91.4)	488 (88.9)

Adverse events

Safety summary Study CT-P6 1.4

In the CT-P6 group, 28 (82.35%) subjects experienced a total of 47 AEs, compared to 28 (84.85%) subjects experiencing 55 AEs in the US-licensed Herceptin groups. Most were mild to moderate.

The proportion of subjects who experienced at least 1 TEAE was similar between both treatment groups. The TEAEs most frequently reported were infusion related reactions. It should be noted that patients were not premedicated. The number of infusion reactions was 15 [44.12%] subjects in the CT-P6 group and 14 [42.42%] subjects in the US-licensed Herceptin group.

No subjects in the CT-P6 treatment group experienced any event of cardiotoxicity while 1 (3.0%) subject in the Herceptin treatment group experienced a moderate event of ejection fraction decreased. This patient recovered without any treatment for cardiotoxicity.

Safety summary Study CT-P6 1.5

Infusion reactions occurred more frequently in the US-Herceptin arm (5.7% versus 2.9%) and no treatment-emergent adverse events due to cardiotoxicity were reported.

Overall, a total of 7 TEAEs (nausea, vomiting, chills, feeling of body temperature change, myalgia, dizziness, and headache) of IRRs or hypersensitivity or anaphylactic reactions were reported. Three subjects (4.3%) reported at least 1 TEAE of IRRs or hypersensitivity or anaphylactic reactions.

Safety summary Study CT-P6 3.2

Table 30: Summary of TEAEs (reported for ≥ 3% of patients in either treatment group) by SOC and PT in Study CT-P6 3.2 (Safety Analysis Set)

Period	Neoadjuvant Period		Adjuvant Period		Overall Period	
System Organ Class Preferred Term	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)
	Number (%) of Patients					
Total Number of TEAEs	**2431**	**2661**	**457**	**472**	**2898**	**3135**
Number of patients with ≥ 1 TEAE	**255 (94.1)**	**264 (95.0)**	**141 (52.0)**	**148 (53.2)**	**263 (97.0)**	**265 (95.3)**
Blood and lymphatic system disorders	**128 (47.2)**	**149 (53.6)**	**21 (7.7)**	**31 (11.2)**	**133 (49.1)**	**155 (55.8)**
Anaemia	54 (19.9)	61 (21.9)	11 (4.1)	19 (6.8)	60 (22.1)	67 (24.1)
Febrile neutropenia	17 (6.3)	19 (6.8)	0	0	17 (6.3)	19 (6.8)
Leukopenia	24 (8.9)	38 (13.7)	6 (2.2)	9 (3.2)	29 (10.7)	40 (14.4)
Neutropenia	94 (34.7)	111 (39.9)	8 (3.0)	12 (4.3)	97 (35.8)	116 (41.7)
Thrombocytopenia	1 (0.4)	4 (1.4)	0	5 (1.8)	1 (0.4)	9 (3.2)
Cardiac disorders	**23 (8.5)**	**29 (10.4)**	**10 (3.7)**	**14 (5.0)**	**31 (11.4)**	**38 (13.7)**
Palpitations	6 (2.2)	6 (2.2)	5 (1.8)	4 (1.4)	10 (3.7)	8 (2.9)
Eye disorders	**22 (8.1)**	**27 (9.7)**	**7 (2.6)**	**4 (1.4)**	**25 (9.2)**	**29 (10.4)**
Lacrimation increased	16 (5.9)	15 (5.4)	1 (0.4)	1 (0.4)	16 (5.9)	15 (5.4)
Gastrointestinal disorders	**134 (49.4)**	**147 (52.9)**	**15 (5.5)**	**18 (6.5)**	**135 (49.8)**	**149 (53.6)**
Abdominal pain	3 (1.1)	9 (3.2)	0	2 (0.7)	3 (1.1)	11 (4.0)
Abdominal pain upper	8 (3.0)	9 (3.2)	2 (0.7)	1 (0.4)	10 (3.7)	10 (3.6)
Constipation	24 (8.9)	18 (6.5)	3 (1.1)	0	24 (8.9)	18 (6.5)
Diarrhoea	52 (19.2)	48 (17.3)	1 (0.4)	5 (1.8)	52 (19.2)	50 (18.0)
Gastritis	3 (1.1)	9 (3.2)	0	1 (0.4)	3 (1.1)	9 (3.2)
Nausea	99 (36.5)	91 (32.7)	2 (0.7)	7 (2.5)	99 (36.5)	94 (33.8)
Stomatitis	46 (17.0)	33 (11.9)	1 (0.4)	0	46 (17.0)	33 (11.9)
Vomiting	27 (10.0)	26 (9.4)	0	2 (0.7)	27 (10.0)	26 (9.4)
General disorders and administration site conditions	**116 (42.8)**	**119 (42.8)**	**32 (11.8)**	**29 (10.4)**	**125 (46.1)**	**126 (45.3)**
Asthenia	43 (15.9)	36 (12.9)	12 (4.4)	7 (2.5)	47 (17.3)	38 (13.7)
Fatigue	48 (17.7)	60 (21.6)	14 (5.2)	10 (3.6)	53 (19.6)	62 (22.3)
Malaise	9 (3.3)	7 (2.5)	1 (0.4)	0	10 (3.7)	7 (2.5)
Oedema peripheral	8 (3.0)	13 (4.7)	0	5 (1.8)	8 (3.0)	18 (6.5)
Pyrexia	29 (10.7)	28 (10.1)	2 (0.7)	4 (1.4)	31 (11.4)	30 (10.8)
Infections and infestations	**55 (20.3)**	**50 (18.0)**	**35 (12.9)**	**27 (9.7)**	**78 (28.8)**	**65 (23.4)**
Nasopharyngitis	6 (2.2)	3 (1.1)	6 (2.2)	3 (1.1)	12 (4.4)	4 (1.4)
Pharyngitis	6 (2.2)	5 (1.8)	3 (1.1)	1 (0.4)	8 (3.0)	6 (2.2)

Period	Neoadjuvant Period		Adjuvant Period		Overall Period	
System Organ Class Preferred Term	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)
	Number (%) of Patients					
Upper respiratory tract infection	7 (2.6)	5 (1.8)	13 (4.8)	4 (1.4)	17 (6.3)	8 (2.9)
Injury, poisoning and procedural complications	**38 (14.0)**	**37 (13.3)**	**46 (17.0)**	**46 (16.5)**	**75 (27.7)**	**76 (27.3)**
Infusion related reaction	23 (8.5)	25 (9.0)	11 (4.1)	5 (1.8)	31 (11.4)	29 (10.4)
Procedural pain	10 (3.7)	11 (4.0)	0	1 (0.4)	10 (3.7)	12 (4.3)
Radiation skin injury	1 (0.4)	0	31 (11.4)	33 (11.9)	32 (11.8)	33 (11.9)
Investigations	**51 (18.8)**	**55 (19.8)**	**29 (10.7)**	**30 (10.8)**	**68 (25.1)**	**68 (24.5)**
Alanine aminotransferase increased	15 (5.5)	23 (8.3)	7 (2.6)	10 (3.6)	18 (6.6)	30 (10.8)
Aspartate aminotransferase increased	11 (4.1)	20 (7.2)	4 (1.5)	11 (4.0)	14 (5.2)	25 (9.0)
Blood alkaline phosphatase increased	4 (1.5)	6 (2.2)	3 (1.1)	7 (2.5)	7 (2.6)	11 (4.0)
Blood lactate dehydrogenase increased	6 (2.2)	9 (3.2)	2 (0.7)	5 (1.8)	6 (2.2)	9 (3.2)
Ejection fraction decreased	9 (3.3)	6 (2.2)	12 (4.4)	3 (1.1)	20 (7.4)	9 (3.2)
Neutrophil count decreased	14 (5.2)	13 (4.7)	1 (0.4)	1 (0.4)	14 (5.2)	13 (4.7)
White blood cell count decreased	9 (3.3)	13 (4.7)	3 (1.1)	0	11 (4.1)	13 (4.7)
Metabolism and nutrition disorders	**27 (10.0)**	**32 (11.5)**	**5 (1.8)**	**9 (3.2)**	**29 (10.7)**	**40 (14.4)**
Decreased appetite	21 (7.7)	18 (6.5)	0	2 (0.7)	21 (7.7)	20 (7.2)
Musculoskeletal and connective tissue disorders	**66 (24.4)**	**73 (26.3)**	**21 (7.7)**	**28 (10.1)**	**76 (28.0)**	**86 (30.9)**
Arthralgia	28 (10.3)	33 (11.9)	7 (2.6)	12 (4.3)	34 (12.5)	40 (14.4)
Back pain	6 (2.2)	4 (1.4)	0	3 (1.1)	11 (4.1)	5 (1.8)
Bone pain	11 (4.1)	17 (6.1)	5 (1.8)	1 (0.4)	11 (4.1)	20 (7.2)
Myalgia	27 (10.0)	28 (10.1)	1 (0.4)	0	27 (10.0)	28 (10.1)
Nervous system disorders	**50 (18.5)**	**50 (18.0)**	**21 (7.7)**	**15 (5.4)**	**60 (22.1)**	**59 (21.2)**
Dizziness	7 (2.6)	5 (1.8)	7 (2.6)	4 (1.4)	14 (5.2)	8 (2.9)
Dysgeusia	10 (3.7)	7 (2.5)	0	0	10 (3.7)	7 (2.5)
Headache	20 (7.4)	18 (6.5)	9 (3.3)	5 (1.8)	25 (9.2)	21 (7.6)
Paraesthesia	9 (3.3)	8 (2.9)	0	1 (0.4)	9 (3.3)	9 (3.2)
Peripheral sensory neuropathy	13 (4.8)	18 (6.5)	1 (0.4)	2 (0.7)	14 (5.2)	20 (7.2)
Psychiatric disorders	**16 (5.9)**	**12 (4.3)**	**11 (4.1)**	**5 (1.8)**	**27 (10.0)**	**16 (5.8)**
Insomnia	10 (3.7)	5 (1.8)	6 (2.2)	2 (0.7)	16 (5.9)	7 (2.5)

Period	Neoadjuvant Period		Adjuvant Period		Overall Period	
System Organ Class Preferred Term	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)
	Number (%) of Patients					
Respiratory, thoracic and mediastinal disorders	**33 (12.2)**	**36 (12.9)**	**19 (7.0)**	**11 (4.0)**	**50 (18.5)**	**43 (15.5)**
Cough	10 (3.7)	11 (4.0)	4 (1.5)	3 (1.1)	14 (5.2)	14 (5.0)
Dyspnoea	5 (1.8)	6 (2.2)	7 (2.6)	4 (1.4)	12 (4.4)	9 (3.2)
Epistaxis	12 (4.4)	11 (4.0)	1 (0.4)	2 (0.7)	13 (4.8)	13 (4.7)
Skin and subcutaneous tissue disorders	**210 (77.5)**	**224 (80.6)**	**26 (9.6)**	**24 (8.6)**	**210 (77.5)**	**224 (80.6)**
Alopecia	196 (72.3)	213 (76.6)	8 (3.0)	6 (2.2)	196 (72.3)	213 (76.6)
Dry skin	9 (3.3)	12 (4.3)	1 (0.4)	1 (0.4)	9 (3.3)	12 (4.3)
Erythema	7 (2.6)	5 (1.8)	1 (0.4)	3 (1.1)	8 (3.0)	8 (2.9)
Nail discolouration	9 (3.3)	6 (2.2)	0	1 (0.4)	9 (3.3)	7 (2.5)
Palmar-plantar erythrodysaesthesia syndrome	9 (3.3)	7 (2.5)	0	0	9 (3.3)	7 (2.5)
Rash	16 (5.9)	10 (3.6)	2 (0.7)	0	18 (6.6)	10 (3.6)
Scar pain	8 (3.0)	6 (2.2)	0	1 (0.4)	8 (3.0)	6 (2.2)
Vascular disorders	**36 (13.3)**	**20 (7.2)**	**14 (5.2)**	**17 (6.1)**	**47 (17.3)**	**35 (12.6)**
Hypertension	16 (5.9)	4 (1.4)	3 (1.1)	7 (2.5)	19 (7.0)	11 (4.0)

During the Post-treatment follow-up Period in which patients were not treated with the study drug, TEAEs were collected after EOT date (or the last dose date +30 days unless patients have EOT visit). According to Study CT-P6 3.2 protocol, TEAEs were assessed until up to 30 days from the last dose of study drug and afterward, only related AEs and cardiac AEs were reported until the end of the study. Eight patients in the CT-P6 treatment group and 2 patients in the Herceptin treatment group experienced at least 1 TEAE during the Post-treatment Follow-up Period.

Both ejection fraction decreased and neutropenia were reported for 2 patients each in the CT-P6 treatment group and other TEAEs (Adams-Stokes syndrome, abdominal pain, breast adenoma, leukopenia, left ventricular hypertrophy, nasopharyngitis, palpitations and ventricular extrasystoles) were reported for no more than 1 patient in each treatment group.

Table 31: Summary of study drug-related TEAEs (reported for ≥ 3% of patients in either treatment group) by SOC and PT in Study CT-P6 3.2 (Safety Analysis Set)

Period	Neoadjuvant Period		Adjuvant Period		Overall Period	
System Organ Class Preferred Term	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)
	Number (%) of Patients					
Number of Patients with ≥ 1 related TEAE	**112 (41.3)**	**129 (46.4)**	**50 (18.5)**	**63 (22.7)**	**130 (48.0)**	**145 (52.2)**
Blood and lymphatic system disorders	**17 (6.3)**	**38 (13.7)**	**10 (3.7)**	**18 (6.5)**	**24 (8.9)**	**46 (16.5)**
Anaemia	7 (2.6)	18 (6.5)	7 (2.6)	11 (4.0)	11 (4.1)	25 (9.0)
Leukopenia	4 (1.5)	10 (3.6)	2 (0.7)	4 (1.4)	6 (2.2)	14 (5.0)
Neutropenia	13 (4.8)	25 (9.0)	3 (1.1)	9 (3.2)	16 (5.9)	30 (10.8)
Eye disorders	**15 (5.5)**	**14 (5.0)**	**4 (1.5)**	**3 (1.1)**	**17 (6.3)**	**15 (5.4)**
Lacrimation increased	13 (4.8)	8 (2.9)	1 (0.4)	1 (0.4)	13 (4.8)	8 (2.9)
Gastrointestinal disorders	**33 (12.2)**	**32 (11.5)**	**3 (1.1)**	**1 (0.4)**	**35 (12.9)**	**33 (11.9)**
Constipation	8 (3.0)	4 (1.4)	1 (0.4)	0	8 (3.0)	4 (1.4)
Diarrhoea	14 (5.2)	12 (4.3)	0	0	14 (5.2)	12 (4.3)
Nausea	15 (5.5)	19 (6.8)	0	1 (0.4)	15 (5.5)	20 (7.2)
Stomatitis	8 (3.0)	7 (2.5)	0	0	8 (3.0)	7 (2.5)
General disorders and administration site conditions	**34 (12.5)**	**31 (11.2)**	**8 (3.0)**	**9 (3.2)**	**40 (14.8)**	**39 (14.0)**
Asthenia	9 (3.3)	5 (1.8)	2 (0.7)	1 (0.4)	11 (4.1)	6 (2.2)
Fatigue	8 (3.0)	13 (4.7)	6 (2.2)	4 (1.4)	13 (4.8)	17 (6.1)
Injury, poisoning and procedural complications	**14 (5.2)**	**14 (5.0)**	**11 (4.1)**	**5 (1.8)**	**22 (8.1)**	**18 (6.5)**
Infusion related reaction	14 (5.2)	14 (5.0)	11 (4.1)	5 (1.8)	22 (8.1)	18 (6.5)
Investigations	**18 (6.6)**	**30 (10.8)**	**15 (5.5)**	**20 (7.2)**	**30 (11.1)**	**40 (14.4)**
Alanine aminotransferase increased	4 (1.5)	10 (3.6)	0	9 (3.2)	4 (1.5)	16 (5.8)
Aspartate aminotransferase increased	2 (0.7)	10 (3.6)	0	9 (3.2)	2 (0.7)	15 (5.4)
Ejection fraction decreased	9 (3.3)	5 (1.8)	11 (4.1)	3 (1.1)	19 (7.0)	8 (2.9)
Musculoskeletal and connective tissue disorders	**15 (5.5)**	**16 (5.8)**	**2 (0.7)**	**3 (1.1)**	**17 (6.3)**	**18 (6.5)**
Arthralgia	4 (1.5)	11 (4.0)	1 (0.4)	3 (1.1)	5 (1.8)	13 (4.7)
Nervous system disorders	**12 (4.4)**	**12 (4.3)**	**3 (1.1)**	**5 (1.8)**	**14 (5.2)**	**17 (6.1)**
Headache	9 (3.3)	2 (0.7)	2 (0.7)	1 (0.4)	10 (3.7)	3 (1.1)
Peripheral sensory neuropathy	2 (0.7)	7 (2.5)	0	2 (0.7)	2 (0.7)	9 (3.2)
Skin and subcutaneous tissue disorders	**55 (20.3)**	**50 (18.0)**	**15 (5.5)**	**2 (0.7)**	**57 (21.0)**	**51 (18.3)**
Alopecia	21 (7.7)	25 (9.0)	6 (2.2)	0	21 (7.7)	25 (9.0)
Rash	9 (3.3)	5 (1.8)	1 (0.4)	0	10 (3.7)	5 (1.8)

Adverse events of special interest

Cardiac adverse events:

SAE that is related to heart failure is defined as follows: symptomatic left ventricular systolic dysfunction such as decreased LVEF.

In the Neoadjuvant Period of Study CT-P6 3.2 with EBC patients, 5 (1.8%) patients in the CT-P6 treatment group and 2 (0.7%) patients in the Herceptin treatment group had at least 1 TEAE due to heart failure. Of those, 4 (1.5%) patients and 2 (0.7%) patients had at least 1 study drug-related TEAE due to heart failure in the CT-P6 and Herceptin treatment groups, respectively. There were no Grade 4 or Grade 5 events in either group. No patients with fatal outcome were reported.

All cases of individual cases of heart failure and LVEF decline were asymptomatic and non-serious events. Four of 5 patients in the CT-P6 treatment group and 1 of 2 patients in the Herceptin treatment group reported cases resulted in recovery. Similarly, 4 of 5 patients in the CT-P6 treatment group and 1 of 2 patients in the Herceptin treatment group did not necessitate the treatment withdrawal because the LVEF decline was modest, documented only at a single time point and was not confirmed at subsequent re-evaluation. During the Adjuvant Period, 6 (2.2%) patients in the CT-P6 treatment group and 4 (1.4%) patients in the Herceptin treatment group had at least 1 TEAE due to heart failure. Overall during the study the incidences were similar and the majority of cases were Grade 1-2 and non-serious.

The overall number of patients experiencing at least 1 TEAE due to vascular disorders was similar between the 2 treatment groups with a similar proportion for severe events during the study including the Adjuvant and Overall Follow-up Periods. There was a slight trend towards higher hypertension related and unrelated TEAEs due to Vascular Disorders with CT-P6 during the Neoadjuvant Period, as TEAEs due to hypertension were reported for 16 (5.9%) patients in the CT-P6 group and 4 (1.4%) patients in the Herceptin group. During the Adjuvant Period, TEAEs due to hypertension were less frequently reported for patients in the CT-P6 group compared to the Herceptin group (3 patients, i.e.1.1%, vs. 7 patients, i.e., 2.5%). Thus there is no consistent trend in the rate of AEs due to hypertension in the two treatment groups.

Most patients with at least 1 TEAE due to hypertension had relevant medical history and baseline characteristics predisposing to hypertension, including higher BMI, age and baseline blood pressure. There were no clinically relevant differences between the treatment groups with respect to these factors. Also, no difference was observed between the groups regarding treatment and duration of hypertension.

Taken together, no clinically relevant differences between the groups were observed in the rate or the nature of hypertension reported as an AE.

Left Ventricular Systolic Dysfunction:

In clinical studies with CT-P6, cardiac ejection fraction was assessed by ECHO (or MUGA scan in Study CT-P6 3.2 only) at pre-defined time points. Mean LVEF values at baseline were 66.05% and 65.93% for the CT-P6 and Herceptin treatment groups respectively. Mean changes from baseline in LVEF value were - 1.11% and - 0.78% at Cycle 4 and - 2.66 and - 2.13 at EOT1 in the CT-P6 and Herceptin treatment groups, respectively. For the overall worst value (post baseline worst value), there were no notable differences between the 2 treatment groups. The median (range) for the post-baseline worst value were 62.00% (38.0% - 76.0%) and 62.75% (37.0% - 77.0%) in the CT-P6 and Herceptin treatment groups, respectively.

One patient in each treatment group was withdrawn from the treatment in concordance with the protocol-specified criteria for withdrawal. Thus, the number of patients with significant LVEF decrease

that met the protocol-defined criteria for withdrawal from treatment was the same in the 2 treatment groups.

The data on decreased ejection fraction and heart failure was updated and revealed that the mean LVEF values and the number of patients with significant decrease in ejection fraction (9 patients in the CT-P6 group and 7 patients in the Herceptin group) were similar between the treatment groups during the overall study. Three patients in each treatment group were withdrawn due to significant LVEF decrease. Among these patients, one in the Herceptin group had symptomatic LVEF decrease during the adjuvant period that was reported as a SAE.

TEAEs due to heart failure were reported for the above mentioned 16 patients and for one additional patient in the CT-P6 group (who had no significant LVEF decrease). Overall, the incidences were similar and the majority of cases were Grade 1-2 and non-serious (see above).

The Applicant has further looked at C_{max} values in three subgroups based on overall worst value for LVEF in the Neoadjuvant Period, as PK samples were collected during this period only. There was no correlation of LVEF and higher C_{max} throughout the 8 treatment cycles.

Overall, cardiac safety of CT-P6 and Herceptin appears similar based on the data available.

Infusion related reactions:

Treatment-emergent AEs due to IRRs were reported for 31 (11.4%) patients and 29 (10.4%) patients in the CT-P6 and Herceptin treatment groups, respectively.

The signs and symptoms most frequently reported for patients in the CT-P6 treatment group were related to cardiovascular (hypertension: 10 [3.7%] patients, Hypotension: 1 [0.4%] patient, palpitation: 1 [0.4%] patient, and tachycardia: 4 [1.5%] patients) and general disorders and administration site conditions (chest discomfort: 2 [0.7%] patients, chest pain: 1 [0.4%] patient, chills: 7 [2.6%] patients, feeling hot: 1 [0.4%] patient, injection site pain: 1 [0.4%] patient).

The signs and symptoms most frequently reported for patients in the Herceptin treatment group were related to cardiovascular (hypertension: 6 [2.2%] patients, Hypotension: 2 [0.7%] patients, and tachycardia: 1 [0.4%] patient) and skin and/or mucosal (angioedema: 1 [0.4%] patient, flushing: 8 [2.9%] patients, rash: 1 [0.4%] patient, and swollen lips: 3 [1.1%] patients).

Haematotoxicity

During the Overall Period, 143 (52.8%) patients in the CT-P6 treatment group and 163 (58.6%) patients in the Herceptin treatment group experienced at least 1 TEAE due to haematotoxicity. Of these, 26 (9.6%) patients in the CT-P6 treatment group and 51 (18.3%) patients in the Herceptin treatment group experienced at least 1 study drug-related TEAE due to haematotoxicity. Most of the patients (133/143 patients in the CT-P6 treatment group and 143/163 patients in the Herceptin treatment group) recovered. TEAE due to haematotoxicity leading to the treatment discontinuation was reported for 1 (0.4%) patient in the CT-P6 treatment group.

Oligohydramnios

There is no patient who had a pregnancy to term, and therefore no oligohydramnios was recorded throughout the Study CT-P6 3.2

Pulmonary Disorders

During the Overall Period, 2 (0.7%) patients in each treatment groups experienced a TEAE due to pulmonary disorders. All events were study drug-unrelated, non-serious and did not lead to treatment discontinuation from the study drug.

Infections

During the Overall Period, 78 (28.8%) patients in the CT-P6 treatment group and 65 (23.4%) patients in the Herceptin treatment group experienced at least 1 TEAE due to infection. Of these, 13 patients in each treatment group experienced at least 1 study drug-related TEAE due to infection. Most of the patients (73/78 patients in the CT-P6 treatment group and 60/65 patients in the Herceptin treatment group) recovered. TEAEs due to infection leading to the treatment discontinuation were reported for 2 (0.7%) patients in the Herceptin treatment group.

Vital signs and Hypersensitivity monitoring

The mean changes from baseline in vital signs (systolic and diastolic blood pressure, heart rate, body temperature and respiratory rate) were small and there were no apparent differences between the treatment groups during the Adjuvant Period. The most commonly reported abnormal vital sign result from the start of the study drug infusion occurring during hypersensitivity monitoring was high respiratory rate in up to 13.3% of patients).

Serious adverse event / deaths / adverse events leading to discontinuation

Safety summary Study CT-P6 1.4 and CT-P6 1.5

No serious TEAEs or TEAEs leading to study discontinuation or deaths occurred during these studies.

Safety summary Study CT-P6 3.2

Serious adverse events

Table 32: Summary of grade 3 or Higher TEAEs (reported for ≥ 1% of patients in either treatment group) by severity in study CT-P6 3.2 (Safety Analysis Set)

Period	Neoadjuvant Period		Adjuvant Period		Overall Period	
System Organ Class Preferred Term	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)
	Number (%) of patients					
Number of patients with ≥ 1 grade 3 or higher TEAE	**98 (36.2)**	**106 (38.1)**	**9 (3.3)**	**16 (5.8)**	**105 (38.7)**	**112 (40.3)**
Grade 3	67 (24.7)	61 (21.9)	9 (3.3)	14 (5.0)	73 (26.9)	66 (23.7)
Grade 4	29 (10.7)	44 (15.8)	0	1 (0.4)	30 (11.1)	44 (15.8)
Grade 5	2 (0.7)	1 (0.4)	0	1 (0.4)	2 (0.7)	2 (0.7)
Grade 3 or higher TEAEs by PT						
Blood and lymphatic system disorders	**77 (28.4)**	**84 (30.2)**	**0**	**2 (0.7)**	**78 (28.8)**	**84 (30.2)**
Febrile neutropenia	16 (5.9)	17 (6.1)	0	0	16 (5.9)	17 (6.1)
Leukopenia	7 (2.6)	8 (2.9)	0	0	7 (2.6)	8 (2.9)
Neutropenia	67 (24.7)	72 (25.9)	0	1 (0.4)	68 (25.1)	72 (25.9)
Investigations	**11 (4.1)**	**16 (5.8)**	**2 (0.7)**	**2 (0.7)**	**13 (4.8)**	**18 (6.5)**
Alanine aminotransferase increased	0	3 (1.1)	0	1 (0.4)	0	4 (1.4)
Neutrophil count decreased	7 (2.6)	9 (3.2)	0	0	7 (2.6)	9 (3.2)
White blood cell count decreased	5 (1.8)	6 (2.2)	0	0	5 (1.8)	6 (2.2)
Vascular disorders	**2 (0.7)**	**3 (1.1)**	**3 (1.1)**	**2 (0.7)**	**5 (1.8)**	**5 (1.8)**
Hypertension	2 (0.7)	2 (0.7)	2 (0.7)	1 (0.4)	4 (1.5)	3 (1.1)

Table 33: Summary TESAEs (reported for more than one patient in either treatment group) by SOC and PT in study CT-P6 3.2 (Safety Analysis Set)

Period	Neoadjuvant Period		Adjuvant Period		Overall Period	
System Organ Class Preferred Term	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)	CT-P6 (N=271)	Herceptin® (N=278)
	Number (%) of patients					
Total number of TESAEs	**23**	**32**	**3**	**14**	**27**	**46**
Number of patients with ≥ 1 TESAE	**19 (7.0)**	**22 (7.9)**	**3 (1.1)**	**12 (4.3)**	**21 (7.7)**	**33 (11.9)**
Related	5 (1.8)	7 (2.5)	1 (0.4)	1 (0.4)	6 (2.2)	8 (2.9)
Unrelated	15 (5.5)	17 (6.1)	2 (0.7)	11 (4.0)	16 (5.9)	27 (9.7)
Blood and lymphatic system disorders	**8 (3.0)**	**8 (2.9)**	**0**	**0**	**8 (3.0)**	**8 (2.9)**
Anaemia	1 (0.4)	3 (1.1)	0	0	1 (0.4)	3 (1.1)
Febrile neutropenia	6 (2.2)	3 (1.1)	0	0	6 (2.2)	3 (1.1)
Neutropenia	2 (0.7)	3 (1.1)	0	0	2 (0.7)	3 (1.1)
Infections and infestations	**4 (1.5)**	**4 (1.4)**	**0**	**2 (0.7)**	**4 (1.5)**	**6 (2.2)**
Device related infection	0	1 (0.4)	0	1 (0.4)	0	2 (0.7)
Pneumonia	2 (0.7)	1 (0.4)	0	0	2 (0.7)	1 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**0**	**1 (0.4)**	**0**	**2 (0.7)**	**0**	**3 (1.1)**
Breast cancer	0	0	0	2 (0.7)	0	2 (0.7)

Death

Treatment-emergent AEs leading to death were reported for 2 patients in each treatment, respectively.

- One patient who was treated with Neoadjuvant Period Cycle 3 of CT-P6 in combination with docetaxel, experienced dyspnoea and died on the same day. Pulmonary embolism could not be ruled out from the cause of sudden death due to medical history of deep vein thrombosis and pulmonary hypertension. The LVEF was 65% and ECG was normal at screening period and the case was considered unrelated to study drug by investigator
- One patient who was treated with Neoadjuvant Period Cycle 8 of CT-P6 in combination with FEC; was considered to be unrelated to study treatment by the investigator and the exact cause of death is unknown, potential role of metastases in fatal outcome cannot be completely ruled out.
- One patient who was treated with Neoadjuvant Period Cycle 1 of Herceptin in combination with docetaxel experienced an acute myocardial infarction and died on the next day. This is the only reported death considered to be possibly related to study drug was acute myocardial infarction (1 [0.4%] patient in the Herceptin treatment group). The LVEF was 70% and BP was 120/80 mmHg at screening. However, it is likely that background severe hypertension and underlying ischemic heart disease contributed to an acute coronary event
- One patient in the Herceptin treatment group who was treated with Adjuvant Period Cycle 9 treatment on 02 September 2016 experienced an aortic dissection on 23 September 2016, and died on the next day (Adjuvant Period Cycle 9 Day 23). The patient had ongoing medical histories of hypertension, uterine leiomyoma, and ovarian cyst, however, no concomitant medication was reported regarding treatment for hypertension. LVEF value was assessed as 71.6% at screening, and no significant LVEF decrease was reported until Adjuvant Period cycle 9. According to the autopsy report, the cause of death was confirmed as dissection of ascending aorta, and the investigator considered this event as unrelated to the study drug.

During the Post-treatment Follow-up Period, 5 deaths (due to progressive disease) in the CT-P6 treatment group and 3 deaths (2 deaths due to progressive disease and 1 death with unknown reason) in the Herceptin treatment group were reported.

Adverse events leading to discontinuation

During Overall Period, 11 (4.1%) patients in the CT-P6 treatment group and 13 (4.7%) patients in the Herceptin treatment group experienced a TEAE leading to treatment discontinuation.
The most frequently reported TEAEs leading to discontinuation was infusion related reaction (5 [1.8%] patients and 2 [0.7%] patients, respectively).

Immunological events

One of the secondary objectives of Study CT-P6 3.2 was to assess the immunogenicity of CT-P6 in comparison to Herceptin. Immunogenicity testing findings were assessed in the safety analysis set defined as all randomised subjects who received at least 1 dose (fully or partial) of either CT-P6 or Herceptin.

In Study CT-P6 3.2, blood samples for immunogenicity assessments of the Neoadjuvant Period (ADA and NAb) were obtained at baseline, after Cycle 4 and at EOT1. Blood samples for immunogenicity assessments of the Adjuvant Period were collected at Cycle 1, after Cycles 3 and 6, and at EOT2. In the Post-treatment Follow-up Period, immunogenicity was assessed every 3 months up to 1 year (maximum 4 times).

For the Neoadjuvant Period, a total of 4 patients in the CT-P6 treatment group and 8 patients in the Herceptin treatment group were ADA positive at pre-dose, however, NAb results were all negative for these patients. During the Adjuvant Period and Post-treatment Follow-up Period as of cut-off date (28 February 2017), none of the patients were ADA positive. It is noteworthy that Post-treatment Follow-up 1 was approximately 3 months after the last dose of study treatment in the Neoadjuvant or Adjuvant Periods, thus drug interference is not expected.

Laboratory findings

Most of laboratory parameters had no NCI CTCAE grade or were mild or moderate for each laboratory parameter and time point. There was no notable difference between the 2 treatment groups for patients with NCI CTCAE grade 3 or higher hematology and chemistry laboratory parameters.

2.6.1. Discussion on clinical safety

Key safety information is derived from 2 completed Phase 1 clinical studies in healthy subjects (Studies CT-P6 1.4 and CT-P6 1.5) and 1 ongoing Phase 3 study in patients with early breast cancer (EBC) (Study CT-P6 3.2).

The safety findings of Study CT-P6 1.4 and CT-P6 1.5 may be viewed as similar between both arms.

The main safety data is derived from study CT-P6 3.2 in patients with EBC/LABC that may be viewed as mature with a median follow up of 19.3 months in the CT-P6 treatment group and 19.6 months in the Herceptin treatment group.

The exposure of study treatment CT-P6 3.2 was comparable between the 2 treatment groups. The relative dose intensity of study drug was similar, indicating good tolerability of CT-P6 and Herceptin.

The overall safety profile in this study was consistent with the known safety profile of Herceptin with chemotherapy regimen used in the Neoadjuvant Period.

There were no new or unexpected safety findings observed in this study.

The proportion of patients who experienced at least 1 TEAE was similar between the 2 treatment groups While the emergence of TEAEs in the Neoadjuvant Period can be augmented by the effects of background chemotherapy regimens,docetaxel, fluorouracil, epirubicin and cyclophosphamide, the study drug was administered in the absence of concomitant chemotherapy and less events were recorded in the Adjuvant Period.

More than 90% of TEAEs in both treatment groups were of grade 1 or 2 in intensity.

Overall, the incidence of the most frequently reported TEAEs was similar between the 2 treatment groups.

The proportions of patients who experienced TEAEs considered to be related to the study drug were similar between the 2 treatment groups.

Treatment-emergent AEs considered related to study drug in the CT-P6 or Herceptin treatment groups were largely similar between treatment arms (or less in CT-P6 arm), and therefore currently of no concern. It is noteworthy that there are more than twice as many patients with blood and lymphatic system disorders considered related to study drug (5.5% versus 13.7% for CT-P6 and Herceptin, respectively) and liver enzyme elevations (2.2% versus 6.8% for CT-P6 and Herceptin, respectively) in the Herceptin arm.

The number of patients who experienced severe (Grade ≥3) TEAEs was similar between the 2 treatment groups and the distribution of patients was comparable across all SOCs.

The proportion of patients who experienced at least 1 TESAE was similar between 2 treatment groups. Treatment-emergent SAEs related to study drug reported were similar between the 2 treatment groups.

Overall the incidence and severity of TEAEs of special interest was comparable across the treatment groups.

There were 3 deaths reported during the Neoadjuvant Period and one in the adjuvant period.

Two cases of death were reported in the CT-P6 treatment group. One was sudden death with no causal relationship to study drug and the potential role of metastases in fatal outcome cannot be completely ruled out. The other was considered to be unrelated to study drug by the investigator. One death case with acute myocardial infarction was occurred in the Herceptin treatment group.

The proportion of patients who experienced at least 1 TEAEs leading to permanent study drug discontinuation was similar between the 2 treatment groups.

With regards to immunogenicity of CT-P6, it appears low and comparable to that of Herceptin, with both ADA methods used. Only samples from the Neoadjuvant Period have been tested with the new ADA method. The old assay is less drug tolerant and therefore the negative ADA samples of the treatment-free follow-up period are particularly relevant. As there is no clinical signal of increased immunogenicity, the data available are considered sufficient to exclude clinically relevant immunogenicity of CT-P6.

From the safety database of trastuzumab all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics of Herzuma which follows the one of Herceptin. Furthermore, the RMP of Herzuma adequately addresses the safety concerns of trastuzumab, in line with Herceptin.

The applicant claimed the same therapeutic indications for the biosimilar Herzuma as granted for Herceptin for intravenous administration in the EU. Herzuma showed similarity to Herceptin in terms of safety based on available data up to 20 months in EBC patients. The results are comparable to data published for the reference product. Overall, no clinically meaningful differences were observed between Herzuma and Herceptin in key trastuzumab adverse events that would preclude extrapolation of safety

outcomes obtained in the HER2-positive MBC indication. Furthermore, the mechanism of action of trastuzumab is the same in all three indications and results of the physico-chemical, structural, and biological characterization studies, as well as PK data support similarity between Herzuma and Herceptin. Therefore, extrapolation from safety perspective is considered acceptable.

2.6.2. Conclusions on the clinical safety

The main data relevant for comparability exercise in terms of safety comes from study CT-P6 3.2 in patients with HER-2 positive early breast cancer (EBC). The overall safety profile as reflected by the most frequently reported TEAEs, severity of the TEAEs and number reported as related, appears broadly similar between Herzuma and Herceptin and in line with those expected on the basis of the EU Herceptin SmPC. The immunogenicity profiles were also comparable.

To conclude, the available safety data support biosimilarity between Herzuma and Herceptin and since no clinically relevant differences in safety were observed in EBC between Herzuma and Herceptin, no differences in the safety of Herzuma is expected in the MBC and MGC indication and hence, extrapolation to other indications of the reference product is acceptable.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	- Cardiac dysfunction - Administration-Related Reactions (ARRs) - Haematotoxicity - Oligohydramnios - Pulmonary disorders
Important potential risks	- Infections - Medication errors (e.g. reduced efficacy due to SC administration of IV formulation)
Important missing information	- Treatment in male patients (breast cancer only) - Safety of 75 mg/m^2 v 100 mg/m^2 docetaxel dose

Pharmacovigilance plan

Routine pharmacovigilance is deemed sufficient to identify and characterize the risks of this medicinal product.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Identified risk- Cardiac dysfunction	Proposed text in SmPC: Recommendation for Cardiac dysfunction monitoring are	No additional risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	included in SmPC sections 4.4 Information on the overall understanding of the occurrence of Cardiac dysfunction, including the occurrence and frequency of Cardiac dysfunction, is contained in the SmPC section 4.8 Other routine risk minimisation measures: None proposed.	proposed.
Identified risk-Administration-Related Reactions (ARRs)	Proposed text in SmPC: Precautions to be taken prior to administration for the prevention of ARRs are included in SmPC section 4.2 and 4.3 Recommendation for ARRs monitoring are included in SmPC sections 4.4 Information on the overall understanding of the occurrence of ARRs, including the occurrence and frequency of ARRs, is contained in the SmPC section 4.8 Other routine risk minimisation measures None proposed.	No additional risk minimisation measures proposed.
Identified risk-Haematotoxicity	Proposed text in SmPC: Information on the overall understanding of the occurrence of Haematotoxicity, including the occurrence and frequency of Haematotoxicity, is contained in the SmPC section 4.8 Other routine risk minimisation measures: None proposed.	No additional risk minimisation measures proposed.
Identified risk-Oligohydramnios	Proposed text in SmPC: Information to be checked prior to administration for the prevention of Oligohydramnios are included in SmPC section 4.6 Other routine risk minimisation measures: None proposed.	No additional risk minimisation measures proposed.
Identified risk-Pulmonary disorders	Proposed text in SmPC: Precautions to be taken prior to administration for the prevention of Pulmonary disorders are included in SmPC section 4.3 Recommendation for Pulmonary disorders monitoring are included in SmPC sections 4.4 Information on the overall understanding of the occurrence of Pulmonary disorders, including the occurrence and frequency of Pulmonary disorders, is contained in the SmPC section 4.8 Other routine risk minimisation measures: None proposed.	No additional risk minimisation measures proposed.
Potential risk-Infections	Proposed text in SmPC: Information on the overall understanding of the occurrence of Infections, including the occurrence and frequency of Infections, is contained in the SmPC section 4.8 Other routine risk minimisation measures: None proposed.	No additional risk minimisation measures proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Potential risk-Medication errors (e.g. reduced efficacy due to SC administration of IV formulation)	Proposed text in SmPC: Precautions to be taken prior to administration for the prevention of Medication errors are included in SmPC section 4.2 Other routine risk minimisation measures: None proposed.	No additional risk minimisation measures proposed.
Missing information-Treatment in male patients (breast cancer only)	Proposed text in SmPC: Information on the overall understanding of Treatment in male patients (breast cancer only), is contained in the SmPC section 5.3 Other routine risk minimisation measures: None proposed.	None.
Missing information-Safety of 75 mg/m^2 v 100 mg/m^2 docetaxel dose	Proposed text in SmPC: Precautions to be taken prior to administration for the prevention of Safety of 75 mg/m^2 v 100 mg/m^2 docetaxel dose are included in SmPC section 4.2 Other routine risk minimisation measures: None proposed.	None

In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of this medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Herzuma (trastuzumab) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The therapeutic indications, dosage and route of administration proposed for CT-P6 are identical to those approved for Herceptin for IV use in HER2 positive; metastatic breast cancer, early breast cancer and metastatic gastric cancer.

3.1.2. Main clinical studies

Overall, the clinical development programme for CT-P6 includes 2 completed Phase 1 clinical studies in healthy subjects (Studies CT-P6 1.5 and CT-P6 1.4) and 1 ongoing Phase 3 study in patients with early breast cancer (EBC) (Study CT-P6 3.2) and safety data is reported for all three studies.

Studies CT-P6 1.5 and CT-P6 1.4 were designed to demonstrate the similarity between CT-P6 and Herceptin with respect to the Pharmacokinetics (PK) profile but also in terms of comparative safety and tolerability.

Study CT-P6 3.2 was designed to demonstrate the therapeutic equivalence in terms of pathological complete response (pCR) assessed during the surgery after the Neoadjuvant Period (24 weeks [8 cycles]) and to collect other comparative efficacy, PK/ Pharmacodynamics (PD), safety and immunogenicity data between CT-P6 and Herceptin in patients.

3.2. Favourable effects

From a quality perspective, CT-P6 has been developed as a similar biological medicinal product to the innovator product Herceptin (trastuzumab). Overall the data indicate that CT-P6 can be considered biosimilar to Herceptin.

The overall the non-clinical data on PD/PK and toxicology indicate that CT-P6 was comparable to the reference product Herceptin.

In terms of clinical pharmacokinetics, in trials, CT-P6 1.4 and 1.5 the comparison of the presented single dose PK results ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max}) and also of secondary PK endpoints (Tmax, Vz, λz, t1/2, CL) of CT-P6 versus US Herceptin in study CT-P6 1.4 and CT-P6 1.5 in healthy volunteers indicate biosimilarity. Likewise, the presented PK data (C troughs for cycle 1-8) in EBC patients (study CT-P6 3.2) is similar between the CT-P6 and Herceptin treatment groups.

Based on the efficacy results of the pivotal phase III clinical study CT-P6 3.2 in patients with HER2 positive EBC/LABC, The primary endpoint of the study was met. The number of responders in the CT-P6 and Herceptin treatment groups were 46.8% patients and 50.4% patients, respectively, leading to a minor difference of – 3.6% for CT-P6 treated patients. The 95% CI for the estimate of treatment difference was - 12.38%, 5.16% which is entirely contained within the equivalence range of -15% to 15% thus supporting biosimilarity.

The secondary endpoint pCR of breast and axillary nodes with absence of DCIS is comparable between the two arms with 39.9% CT-P6 patients and 41.4% Herceptin patients, respectively. The 95% CI for the estimate of treatment difference is (-10.22%, 7.31%) The results are confirmed in the ITT analysis.

Further, the secondary endpoint data for pCRB seem comparable between the two treatment arms at 4.8% versus 4.7%, respectively and the proportion of patients who achieved an overall response during the neoadjuvant period appeared the same in the two arms with CT-P6 (84.3%) and Herceptin (84.0%) patients and is in accordance with the literature thus supporting similarity

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties concerning the favourable effects.

3.4. Unfavourable effects

The safety data (data cut off: 28 February 2017) may be viewed as mature since 90% of patients completed the adjuvant period and patients have been followed up for a median duration of 19.3 months for CT-P6 and 19.6 months for the Herceptin treatment group. The type and incidence of ADRs of CT-P6 and Herceptin were broadly comparable and in line with those described in the Herceptin SmPC. No increased immunogenicity was observed for CT-P6.

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties concerning the unfavourable effects.

3.6. Benefit-risk assessment and discussion

3.6.1. Balance of benefits and risks

CT-P6 has been developed as a similar biological medicinal product to the innovator product Herceptin (trastuzumab). The overall non-clinical data has shown comparability of CT-P6 to Herceptin in terms of PD/PK and toxicology. Pharmacology studies have shown similarly where the presented single and multiple dose PK results of CT-P6 versus US Herceptin are comparable. The primary clinical efficacy endpoint for the phase III trial CT-P6 3.2 was met with the proportion of patients achieving pCR was 46.8% (95%CI 40.4%, 53.2%) for CT-P6 and 50.4% (95%CI 44.1. 56.7%) for the Herceptin arm and the confidence limits of the 95% CI of the difference in the proportions of responders were entirely bounded by the interval (-0.15 – 0.15), demonstrating similarity in terms of efficacy between the two products.

The safety database was mature with most safety data derived from study CT-P6 3.2 and a median follow up of 19.3 months in the CT-P6 treatment group and 19.6 months in the Herceptin treatment group. No new signals were identified and the safety data was supportive of biosimilarity.

The totality of the data on the comparability exercise indicate that CT-P6 can be considered a biosimilar of Herceptin.

3.6.2. Additional considerations on the benefit-risk balance

Herceptin is authorised in patients with HER2-positive MBC, early breast cancer, and metastatic gastric cancer. The mechanism of action of trastuzumab is the same in all three indications and the target receptor involved is also the same in early breast cancer, metastatic gastric cancer and MBC (i.e., HER2). The dosage is also similar for all 3 indications, and trastuzumab is administered by the same route in all indications. Hence, extrapolation in terms of efficacy is supported by the results of the physico-chemical, structural and biological characterization data, results from comparative preclinical studies (in vitro functional tests) together with PK comparability data. Extrapolation is also considered acceptable from a safety perspective since no difference in the safety risks have been identified. Overall, available data support the extrapolation to the other indications of the reference product.

The applicant claimed the same therapeutic indications for the biosimilar Herzuma as granted for Herceptin for intravenous administration in the EU. Considering Herceptin is also marketed for subcutaneous administration, a risk of medication error was identified as an important potential risk. Adequate risk minimisation measures to avoid the potential route of administration error have been included in the SmPC section 4.2 and in the RMP.

3.7. Conclusions

Herzuma is considered biosimilar to Herceptin and therefore the overall benefit risk balance of Herzuma is positive in the following indications:

"Breast cancer

Metastatic breast cancer

Herzuma is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer

Herzuma is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC):

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).

- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.

- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.

- in combination with neoadjuvant chemotherapy followed by adjuvant Herzuma therapy, for locally

advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Herzuma should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

Metastatic gastric cancer

Herzuma in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herzuma should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1)."

4. Recommendations

Outcome

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

"Breast cancer

Metastatic breast cancer

Herzuma is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer

Herzuma is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC):

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Herzuma therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Herzuma should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

Metastatic gastric cancer

Herzuma in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herzuma should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1)."

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.