25 April 2025
EMA/CHMP/86926/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dazublys

International non-proprietary name: trastuzumab

Procedure No. EMEA/H/C/006219/0000

Note

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

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List of abbreviations

Abbreviation	Definition
ADA	Anti-Drug Antibody
ADCC	Antibody Dependent Cell-mediated Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT (SGPT)	Alanine Aminotransferase
ASCO	American Society of Clinical Oncology
BMI	Body Mass Index
BSA	Body Surface Area
CAP	College of American Pathologists
CHMP	Committee for Medicinal Products for Human Use
CISH	Chromogenic In Situ Hybridization
CR	Complete Response
CRO	Clinical Research Organisation
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough serum Concentration
CV%	Coefficient of Variation
DISH	Dual In Situ Hybridization
EBC	Early Breast Cancer
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
ER	Estrogen Receptor
ERBB2	Erb-B2 receptor tyrosine kinase 2 (HER2 gene)
FAS	Full Analysis Set
FFPE	Formalin Fixed Paraffin Embedded
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HER2	Human Epidermal growth factor Receptor 2
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product

IRB	Institutional Review Board
ITT	Intent-To-Treat
i.v.	Intravenous
LHRH	Luteinizing Hormone-Releasing Hormone
LLOQ	Lower Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MGC	Metastatic Gastric Cancer
MUGA	Multiple Gated Acquisition
NAb	Neutralizing Antibody
N/A	Not Applicable
NE	Not Evaluable
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
pCR	pathological Complete Response
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response or Progesterone Receptor (depending on context)
PT	Preferred Term
Q	Quartile
QA	Quality Assurance
QC	Quality Control
RDI	Relative Dose Intensity
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease or Standard Deviation (depending on context)
SDMC	Safety Data Monitoring Committee
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
tpCR	total pathological Complete Response
ULN	Upper Limit of Normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant CuraTeQ Biologics s.r.o. submitted on 11 January 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Dazublys, 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 indication:

Breast cancer

Metastatic breast cancer (MBC)

Dazublys is indicated for the treatment of adult patients with HER2-positive 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 (EBC)

Dazublys is indicated for the treatment of adult patients with HER2-positive EBC.

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)

- 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 Dazublys therapy for locally advanced (including inflammatory) disease or tumors> 2 cm in diameter.

Dazublys 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.

Metastatic gastric cancer (MGC)

Dazublys 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.

Dazublys should only be used in patients with 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

The chosen reference product is: Herceptin.

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 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: 28-08-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/00/145/001

Medicinal product authorised in the Union/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: 28-08-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/00/145/001

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

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

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14 November 2019	EMEA/H/SA/4232/1/2019/III	Dieter Deforce (BE) Elena Wolff-Holz (DE)

The Scientific advice pertained to the following *quality*, non-clinical and clinical aspects:

-Sufficiency of the proposed analytical similarity exercise to support an MAA, including statistical approaches for different quality attribute criticality levels

-Adequacy of conducted toxicity study to support an MAA without the need for further studies.

-PK study design including study population, sample size, endpoints and immunogenicity assessment.

-Clinical safety and efficacy study design including study population, dose and treatment regimen and endpoints.

-Choice of reference product to be studied.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Karin Janssen van Doorn

The application was received by the EMA on	11 January 2024
The procedure started on	1 February 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 April 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	06 May 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	02 May 2024
The CHMP agreed on the consolidated List of Questions to be sent to	30 May 2024

the applicant during the meeting on	
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 November 2024
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: – A GCP inspection at 3 study sites in India in June 2024. The outcome of the inspection carried out was issued on.	06 September 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	06 January 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 January 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	30 January 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 April 2025
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 Dazublys on	25 April 2025

2. Scientific discussion

2.1. Problem statement

Not applicable.

2.2. About the product

BP02 (Trastuzumab) is being developed as a biosimilar to EU-Herceptin (Roche Registration Limited, hereafter referred to as Herceptin) by CuraTeQ Biologics Private Limited for the same indications for which they are approved.

Trastuzumab is a humanized immunoglobulin G1 (IgG1) kappa isotype monoclonal antibody directed against an epitope on the extracellular juxtamembrane domain of HER2.

Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. The 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 tumor cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro, trastuzumab-mediated ADCC is preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER.

BP02 is supplied in one presentation containing 150 mg per single-use vials. The finished product is intended for reconstitution with 7.2 mL of sterile water for Injection (SWI). Upon reconstitution, each vial contains approximately 21 mg/mL of trastuzumab, and the reconstituted product is intended for dilution in saline (0.9% sodium chloride) for intravenous administration.

The formulation, dosage, strength upon reconstitution, and administration are the same as for the reference product, Herceptin, and the same formulation of BP02 was used throughout the clinical development program. However, BP02 is intended only for intravenous use and the Applicant did not apply for the subcutaneous route of administration (authorised for Herceptin -600 mg strength, solution for injection pharmaceutical form).

BP02 is a powder for concentrate for solution for infusion containing 150 mg of trastuzumab per single-use vials.

2.3. Type of application and aspects on development

This application is submitted under Article 10(4) of Directive 2001/83/EC relating to applications for biosimilar medicinal products. The reference product is Herceptin (150 mg powder for concentrate for solution for infusion: Roche Registration Limited). Herceptin was authorised in the EU on 28 August 2000.

CHMP scientific advice was given on quality, nonclinical and clinical development.

2.4. Quality aspects

2.4.1. Introduction

Trastuzumab (BP02), is being developed as biosimilar to the reference product Herceptin (*trastuzumab*). The finished product (FP) is presented as powder for concentrate for solution for infusion containing 150 mg of Trastuzumab as active substance (AS).

Other ingredients are: L-Histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate and Polysorbate 20 (E432).

The product is available in 15 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film containing 150 mg of trastuzumab.

2.4.2. Active substance

2.4.2.1. General information

BP02 (Trastuzumab) is a glycosylated IgG1 kappa humanized antibody that contains human IgG1 framework regions inserted with the Complementarity-Determining Regions (CDRs) of a murine antibody (4D5) that binds to HER2.

2.4.2.2. Manufacture, characterisation and process controls

The AS is manufactured, tested and released by CuraTeQ Biologics Private Limited (Survey No. 77 and 78, Indrakaran Village, Kandi Mandal, Sangareddy District, 502329 Hyderabad, Telangana, India). A valid proof of EU GMP compliance was missing and during the assessment a Major Objection (MO) was raised. An adequate GMP certificate has been provided by the applicant, and the issue considered solved.

Description of manufacturing process and process controls

BP02 (Trastuzumab) is expressed in Chinese Hamster Ovary (CHO) cells, cultured in a production bioreactor, operated in fed batch mode at CuraTeQ Biologics Pvt. Ltd.

The upstream manufacturing stage consists of the following steps: ampoule thaw, inoculum preparation and expansion in shake flasks and seed bioreactors, final inoculum transfer into the production bioreactor, batch harvest, and clarification. The BP02 upstream manufacturing process begins with the thawing of one ampoule from the Cell Bank. After inoculation and several expansion steps the expanded seed culture is used to inoculate the production bioreactor. Parameters in the cell culture are monitored. A Major objection was raised regarding the testing of the unprocessed bulk harvest (UBH). The applicant later confirmed that the UBH will be tested before the release of the F. The respective tests were included in the dossier. This issue was considered solved.

The downstream manufacturing process consists of chromatography and filtration steps for AS preparation. The maximum hold times recommended for the BP02 in-process intermediates from development study are summarized. There are no reprocessing or rework steps foreseen in the BP02 AS commercial manufacturing process. For the manufacture of FP, the frozen BP02 AS bags are transferred to warehouse and thawed by keeping the bags at room temperature. Upon thawing, AS is transferred to the FP facility located in the same building. Since the transfer of the AS is carried out within the same building, no shipping validation is deemed necessary.

The active substance manufacturing process is considered acceptable.

Control of materials

Other than the mammalian cell line (i.e., CHO) expressing the product, no other animal or biological origin materials are used in the BP02 AS manufacturing process. All media components and feed additives are serum free; they do not contain materials of animal origin and are manufactured using materials devoid of animal/human origin components.

The raw/starting materials used in the BP02 AS manufacturing process and the certificates of Analysis (CoA) from the vendors for the raw/starting materials are provided. For the non-compendial raw materials used in the BP02 manufacturing process in-house specifications are defined.

Cell banks were tested in accordance with current GMPs and the requirements of the International Conference on Harmonization (ICH) 5QA and Q5D. One vial from this MCB was used to prepare WCB. The vials were then frozen and transferred to a liquid nitrogen. The MCB Clone was selected for generation of stability study and subjected to long-term culture. Cells at the end of the cell culture process were collected to prepare the End of Production Cell Bank (EPCB). EPCB characterisation and testing results showed compliance with the acceptance criteria.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted.

Control of critical steps and intermediates

The BP02 AS manufacturing process control strategy includes controls for operational parameters to ensure consistent and desired product output. At production bioreactor stage CPPs are defined.

Setpoints and Normal Operating Ranges (NOR) are deemed acceptable and supported by process characterisation (PC) studies. For downstream processing CPPs are defined for the individual stages. The identified CPPs and the applied setpoints/NORs are considered acceptable and supported by PC studies. The process is monitored by Performance parameter (PP) which serves as an indicator that the process performed as expected. Performance parameters are assigned to either in-process controls (IPCs) or in-process tests (IPTs). Results from IPCs for process intermediates must be met prior to forward processing or during processing before batch release. Throughout the process, IPCs and IPTs are defined and both categories have predefined acceptance limits. The defined categories and proposed limits together with their justification are considered suitable for monitoring of process performance. The maximum hold times established for the BP02 in-process intermediates are acceptable.

In conclusion, a comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. The actions taken, if limits are exceeded, are specified.

Process validation

The upstream process performance qualification (PPQ) results from at scale batches demonstrate that the batches were well operated within the pre-defined operational CPP ranges and the output quality attributes meet the acceptance criteria. Data obtained from consecutive PPQ batches from downstream manufacturing process demonstrated that the process performed well within the pre-defined NORs for the CPPs and delivers a consistent product quality as indicated by the IPC/IPT test results. Thus, the PPQ results show that the manufacturing process is suitable and can be considered adequately validated.

The proposed hold times for process intermediates seem acceptable and the Hold Time Study Protocol for Process Intermediates of BP02 is provided. The recommended maximum hold times for the BP02 in-process intermediates were established from the development scale but confirmed at-scale which is acknowledged. PPQ batches were used for evaluation of process time. The anticipated maximum re-use cycle number for commercial manufacturing scale for Chromatography methods is established and is considered acceptable.

A membrane lifetime study for reusability is being conducted to ensure that membrane functionality does not deteriorate over time, affecting the process and the product. The outcome of the study at development scale is reported and the data show compliance with the acceptance criteria. The retention capacity of the hydrophilic Durapore membrane of pore size of 0.22 µm was validated with a bacterial retention test.

The active substance manufacturing process has been validated adequately.

Manufacturing process development

The BP02 development program started with the establishment of a Quality Target Product Profile (QTPP), which served as the basis for manufacturing process development. Potential Critical Quality Attributes (CQAs) were derived from the QTPP and were confirmed and categorized for criticality through a risk assessment based on their impact on patient PK/PD, safety, efficacy, and potency. The QTPP ranges for the quality attributes were obtained from analysis of multiple lots of Herceptin, and the target ranges were used during process development with an aim of obtaining a product quality profile similar to the Reference Medicinal Product (RMP).

The upstream and downstream platform processes were optimized at laboratory scale at CuraTeQ Biologics by performing a series of experiments to achieve the desired product quality. The upstream and downstream processes were further optimized for process parameters and performance attributes. After optimization, the process was scaled up to the production bioreactor scale by performing batches in the cGMP manufacturing facility. Performance of these batches demonstrated process consistency at scale. The AS generated from these batches was used for clinical studies and analytical similarity. No major changes were made to the manufacturing process from scale up to the production bioreactor scale through manufacturing of clinical and process performance qualification (PPQ) batches, except for the change in final AS concentration.

The applicant declared that no significant changes were made to the AS manufacturing process throughout BP02 development from clinical to PPQ batches. However, changes were made to the protein concentration as well as to the UF/DF step. This was not acceptable and this issue was raised as a Major Objection (MO) during the assessment. In response to this MO, the Applicant performed a comparison between clinical and PPQ AS batches to establish comparability with respect to routine batch analysis, characterisation, and stability (real-time at -20 ± 5 °C; accelerated at 5 ± 3 °C; and stressed at 25 ± 2°C/60 ± 5% RH). Based on the data and justification presented by the Applicant, it can be concluded that clinical batches are to be considered worst case in terms of purity compared to PPQ batches, but that other quality attributes can be regarded as comparable. Also, results from additional post-PPQ batches showed that the commercial AS/FP manufacturing process does not lead to purity outliers as previously observed for some of the BP02 clinical batches. Hence, it is acknowledged that clinical batches can be considered comparable to PPQ/commercial batches (except for the few outliers regarding purity).

A control strategy was developed based on comprehensive understanding of product, manufacturing process and sources of variability to maintain CQAs of the product within acceptable limits. The operating ranges/targets for operational parameters were developed during process development and control strategy is designed in a way that the operational parameters when controlled will deliver a consistent output. Further, potential CPPs were identified based on FMEA and characterized into CPPs, key process parameters (KPPs) and non-CPPs (NCPPs) based on impact on critical quality attributes and process performance attributes. The control strategy also includes testing and monitoring the output process parameters (IPCs and IPTs) to ensure the product conforms to its specifications. Identified pCPPs were further characterized in process characterization studies using a qualified scaled-down model (SDM). For downstream SDM qualification, the CQAs and KPIs that were considered for the qualification of the model, along with the rationale, are provided. The overall process characterisation of the downstream process is considered adequate. It is concluded that CPP and non CPPs were confirmed in the individual unit operation and the corresponding PAR was established. The applicant refers to tables in the dossier that do indicate setpoints and NOR, which are acceptable.

Characterisation

Trastuzumab (BP02) is a proposed biosimilar candidate to the reference medicinal product, Herceptin. Characterisation of BP02 was done for the Internal Reference Standard (IRS) batch and the AS PPQ batches. BP02 was engineered to have a 100% identical amino acid sequence to trastuzumab heavy and light chains. BP02 shows one N-linked glycosylation site at the consensus asparagine (Asn) residue at position 300. The oligosaccharides are of complex bi-antennary structures, fucosylated with the two branches terminating mainly with zero (G0, G0F), one (G1, G1F), and/or two (G2, G2F) galactose residues. The G0F glycoform predominates. In addition to C-terminal heterogeneity and glycosylation modifications, trastuzumab is prone to other post-translational modifications such as deamidation, oxidation, and fragmentation. AS batches manufactured at scale were subjected to structural, physico-chemical and functional characterization. The test panel is considered sufficient for structural, physico-chemical characterisation. Regarding functional characterisation the test panel was initially considered

sparse. It was expected that Fc-mediated effector functions were completely characterized. This includes binding to the whole panel of Fcg-receptors including low and high affinity phenotypes, FcRn binding and functional assays such as ADCC and ADCP activity. Further, it was expected that the glycosylation/functional relationship was being investigated and during the assessment this issue was raised as a Major Objection. In response to this MO, multiple approaches were used by the Applicant to generate species with varying afucosylation levels and study the impact of afucosylation on biological functions and/or efficacy and safety. However, the Applicant experienced technical difficulties in obtaining fractions with higher and lower total afucosylation levels beyond the range observed for BP02 product in the initial similarity analysis. Hence, structure-function relationship studies to investigate the impact from different total afucosylation (%TAF) levels on FcyRIIIa binding and ADCC activity have not been performed. Instead, a statistical prediction model was used to prove the correlation between %TAF and ADCC activity/FcyRIIIa binding. Although the statistical prediction model cannot be fully endorsed, a slight linear correlation between %TAF and FcyRIIIa binding/ADCC activity could be observed from the actual data provided. Therefore, the current data and provided explanations can be accepted and this issue was not be further pursued.

Process-related impurities were identified. Based upon the risk assessment, risk mitigation was performed for the raw materials with high-risk to patient health, safety and product quality. Host Cell Protein (HCP), Host cell DNA and Protein A leachates are adequately cleared by the downstream process and these parameters, endotoxin and bioburden are also tested for release. Theoretical evaluation of the residual amount of Selenium and Antifoam C present in the final FP is presented indicating that values are less than maximum allowable limits based on PDE values. Regarding process-related impurities, impurity clearance data for residual Selenium and antifoam C are provided, which demonstrated sufficient clearance and no need for routine control at AS level. This is accepted.

Charged variants and size variants are identified as product-related impurities. Acidic and basic variants of BP02 were enriched using cation exchange chromatography and characterized. The content of product-related impurities is controlled by release specifications.

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a IgG1 humanized antibody. In summary, the characterization is considered appropriate for this type of molecule.

2.4.2.3. Specification

The AS specifications are set in accordance with ICH Q6B. The initial approach proposed by the Applicant for setting the specifications limits was not acceptable (e.g. only a subset of BP02 batches selected, arbitrary extension of BP02 min-max range) leading to wide acceptance criteria not considered justified. A MO was raised, and the Applicant was asked to revise the specification limits for the quality attributes. The proposed limits were revised during the assessment and considered adequately justified. All relevant characteristics of trastuzumab AS (general and molecular characteristics, identity, potency, purity, impurities and safety) are adequately covered.

For N-linked Oligosaccharide Profiling by normal phase chromatography the applicant proposes total fucosylation (%G0F, GIF, GIF' and G2F area) ≥ 80.0%. During the assessment, the afucosylation analysis and the proposed acceptance criteria for %TAF were not endorsed and a MO was raised. The Applicant responded satisfactorily to this question with additional data. The correlation between afucosylated structures and FcgRIIIa binding/ADCC activity has been established and structure-function relationship studies with representative BP02 product to investigate the impact from different total afucosylation (%TAF) levels on FcyRIIIa binding and ADCC activity have been performed. Based on that and considering the batch data from the RMP EU-Herceptin and the BP02 batch data from

batches used in the clinical efficacy study, %TAF limits are set. Additional batch analysis data for total sialylation have been provided for both BP02 batches and RMP EU-Herceptin batches. Based on the BP02 batch data, batch-to-batch consistency can be acknowledged for the commercial BP02 AS batches. In addition, levels of total sialylation are comparable between BP02 and RMP EU-Herceptin, with slightly higher NANA and lower NGNA levels in BP02 compared to EU-Herceptin. Based on the totality of BP02 batch data and biosimilarity data presented for total sialylation, the omission of a specification for total sialylation at the AS level can now be agreed and is considered justified. For biological activity, the omission of a routine HER-2 binding assay from the AS and FP specifications (in addition to the anti-proliferation assay) has been properly justified and is acceptable. The HER-2 binding assay (by SPR) will be kept as characterisation test, which is endorsed.

Analytical methods

All the in-house analytical procedures listed are verified and/or validated as applicable and as per ICH Q2(R1) guidelines. The compendial methods are based on the European Pharmacopeia (Ph. Eur.). Protein concentration is determined by UV absorbance at 280 nm. The experimentally determined extinction coefficient of trastuzumab is used for calculations. Potency is determined by in-vitro inhibition of cell proliferation. The CHO HCP content in the BP02 in-process samples and AS were determined using a kit-based ELISA method. Effective removal of residual HCPs by the manufacturing process is demonstrated. Upon request, the use of a commercial kit has been justified by generating process-specific antibodies and demonstrating almost 100% coverage to the commercial kit. The Bacterial Endotoxin Test is a procedure to detect or quantify endotoxins from Gram-negative bacteria using amoebocyte lysate horseshoe crab (*Limulus Polyphemus* or *Tachypleus tridentatus*). This test is based on the procedure described in Ph. Eur., Bacterial Endotoxins 2.6.14. Regarding the icIEF method for charge heterogeneity, the method was re-validated and found suitable. The CE-SDS (NR) method was not validated for LMW species because, according to the applicant, "thermal stress sample did not generate expected/sufficient amount of LMW species to enrich validation standard for spiking study. Upon request, the Applicant included validation results with respect to %LMW species, including spike linearity, accuracy and LOQ. The HILIC method for total afucosylation is sufficiently validated for repeatability, intermediate precision, reproducibility and robustness.

Batch analysis

Batch analysis data of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference standards or materials

Internal reference standards (IRS) and Primary reference standards (PRS) are stated to be prepared from lot(s) representative of at-scale proposed commercial process and clinical process batches. Secondary Reference standards (SRS) will be prepared from the commercial material and will be qualified against the Primary reference standards. The internal reference standard of BP02 was used for the characterization, comparability/biosimilarity studies, in-process, lot release, and stability testing of BP02 AS and FP. The IRS was qualified to enable its use as a system suitability (SS) standard in the analytical tests and calibrated as an IRS for estimating relative potency in the in vitro potency assay. The primary reference standard (PRS) was established from the clinical batches produced at scale using the manufacturing process that is representative of the proposed commercial scale. The Reference Standards were established based on a BP02 developmental batch (for Internal Reference Standard) and a BP02 clinical batch (for Primary Reference Standard) at different protein concentration (i.e. 25 mg/mL). Given the doubts raised regarding the representativeness of BP02 clinical batches to the commercial product, the use of non-commercial process materials for establishment of the Reference Standards was questioned. The Applicant was asked to demonstrate that IRS and PRS can be considered representative of the commercial process and recommended to establish as soon as

possible a new Primary Reference Standard derived from a commercial process batch and to qualify this PRS against the RMP EU-Herceptin. This issue was raised as a Major Objection during the assessment. Instead of establishing a new PRS derived from a commercial process batch (and qualifying against the RMP EU-Herceptin), the Applicant provided further clarifications on the establishment and usage of the different Reference Standards (IRS and PRS). Given that the PRS is qualified against both EU-Herceptin and WHO IS (and bridged against IRS) and that the provided results are acceptable, it was agreed that the PRS (established from the clinical batch) can be used until the new SRS is established. The newly established secondary reference standard was thoroughly evaluated and is comparable to the primary reference standard. The issue was considered solved.

Container closure

The AS is filled into bags These bags are single-use, USP class VI compliant, sterilized by gamma-irradiation, ready to-use containers that have been specifically designed for long-term frozen storage of biopharmaceuticals. The bags comply with USP <85>, USP <87>, USP <88>, and USP <661> and are classified USP Class VI. The contact layer of the film passes current Ph. Eur. 3.1.7 requirements and complies with U.S. FDA 21CFR 177.1350 and European Guidance EMA 1410/01 rev 3 and Ph. Eur. 5.2.8. Even though the risk of potential for migration of leachables into frozen AS during long term storage is low, a simulated in-use leachable study was conducted on the storage bags and no compounds were detected above the calculated Analytical Evaluation Threshold (AET) thresholds.

2.4.2.4. Stability

BP02 performance qualification (PPQ) was performed. The test methods and specification for PPQ batches stability studies are provided. Although it was initially claimed that no notable differences were observed between the clinical and PPQ batch process nor in the AS quality attributes, and that the primary batches and the clinical batches are considered representative for PPQ respective commercial batches, this was not fully endorsed, given the important differences observed in purity between clinical and PPQ batches. Upon request, additionally available stability data at real-time conditions for the PPQ AS batches have been submitted. It was also argued that PPQ batches yield product with enhanced product quality as a consequence of the implemented tightened process controls at the CEX unit operation. It can be concluded that clinical batches are to be considered worst case in terms of purity compared to PPQ batches, but that other quality attributes can be regarded as comparable. Furthermore, as the AS remains stable with no obvious trends observed during storage, it is agreed that the BP02 clinical AS batches can be used to support the AS shelf-life claim.

Overall, the claimed AS shelf-life is adequately supported by real-time stability data from clinical and PPQ AS batches, for which long-term stability data were provided.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The finished product (FP) is presented as a white to pale yellow lyophilized powder for concentrate for solution for infusion containing 150 mg of Trastuzumab as active substance (AS). The product is available in 15 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film containing 150 mg of trastuzumab.

After reconstitution the FP is a clear, colourless to pale yellow solution and practically free from particles in a sterile, preservative-free, non-pyrogenic, single-dose vial. The excipients used in the formulation of the FP are L-Histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate and Polysorbate 20 (E432). A volume overage of 4 % ensures that the labelled dose of 150 mg can be withdrawn from each vial.

Regarding the AS content, it seemed that this product is formulated at a strength of 22 mg/mL, whereas the RMP EU-Herceptin is formulated at 21 mg/mL. According to the Guideline on similar biological medicinal products (CHMP/437/04 Rev 1), deviations from the RMP as regards strength require justification and, if needed, additional data showing that any difference does not compromise safety. Therefore, this issue was raised as a Major Objection during the assessment.

The clarifications and calculations provided by the Applicant, justifying the target protein concentration for the formulated bulk AS of 22 mg/mL, but 21 mg/mL at FP level, were found reasonable and the issue was solved.

The quality target product profile (QTPP) for BP02 was derived from the characterization of the reference medicinal product, Herceptin. The QTPP served as the basis for defining the manufacturing process, selecting appropriate in-process tests and acceptance criteria for monitoring process performance, and delineating the control strategies to ensure that the manufacturing process consistently delivers a desired product quality meeting the defined specifications. A risk assessment was performed, as per ICH guideline Q8 (R2), to derive the Critical Quality Attributes (CQAs) from the QTTP by linking the quality attributes to the PK, PD, patient safety, efficacy based on published information and prior knowledge. The criticality of each process step and the operational parameter was estimated using an effective risk management tool, failure modes and effects analysis (FMEA). Thawed AS hold time was performed as a one-time study based on risk assessment, and the ranges were established during process development.

The clinical batches of BP02 FP were manufactured. No substantial changes were made to the manufacturing process parameters, process controls, sterilization procedures, and process equipment during the transition from clinical to PPQ proposed commercial process. The clinical and PPQ batches meet the release specifications, and the results for product quality attributes are comparable. Changes were made to the protein concentration as well as to the UF/DF step in the AS manufacturing process. Likewise, the dilution step in the FP manufacturing process was also changed. QC results from BP02 clinical FP batches show a wide data distribution compared to EU-Herceptin with several outliers/inconsistent results regarding purity, clearly showing important differences between BP02 clinical and PPQ batches, and between BP02 clinical FP batches and EU-Herceptin. This was not acceptable and this issue was raised as a Major Objection (MO) during the assessment. In response to this MO, the Applicant provided, apart from comparability at AS level, an overview of the revisions made for the FP manufacturing process. Comparative data between 3 clinical and 3 PPQ FP batches were presented with respect to routine batch analysis, characterisation, and stability. In addition, 2 clinical and 2 PPQ FP batches were subjected to forced degradation conditions. Comparability between BP02 clinical and PPQ batches can be agreed for all quality attributes, except for the outliers regarding purity, which should be regarded as worst-case batches in terms of purity.

The FP primary packaging materials consist of a 15 mL clear Type I glass vial with a 20 mm Lyophilization bromobutyl rubber stopper sealed with a 20 mm flip-off seal made of aluminium and a coloured plastic cap. An extractable study and a simulated in-use leachable study were conducted and the primary packing material for FP was considered suitable. Container closure integrity for BP02 FP vials has been demonstrated as part of PPQ and stability testing.

BP02 FP manufacturing is performed under aseptic conditions. The BP02 formulated bulk AS that is used in the FP manufacturing is manufactured with stringent controls for microbial attributes during in-process and batch release and the excipients used in the formulated bulk AS are tested as per the compendial specification and there are no excipients that are of animal and human origin are used.

All the excipients used in formulation of FP are compendial grade and are tested as per the monograph of the current version of pharmacopoeia. Representative certificate of analysis of the excipients are provided. No excipients of human or animal origin nor novel excipients are used. The information on excipients is sufficient.

To demonstrate the compatibility of the FP with the materials used for administration to patients, the in-use stability study was tested in infusion bags. Following the dilutions with 0.9% saline physicochemical in-use stability has been demonstrated for up to 48 hours. It is emphasized that in accordance with the guideline on in-use stability, from a microbiological point of view, the reconstituted solution and BP02 (trastuzumab) infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2°C to 8°C unless reconstitution and dilution have taken place under controlled and validated aseptic conditions. This has been properly included in SmPC section.

2.4.3.2. Manufacture of the product and process controls

Manufacture

For the FP manufacturer, a valid proof of EU GMP compliance was missing during the assessment, and a Major Objection (MO) was raised. An adequate GMP certificate has been provided by the applicant, and the issue considered solved.

The FP manufacturing process consists of thawing of the AS, preparation of formulated bulk, formulated bulk 0.22µm first filtration (bioburden reduction), formulated bulk sterile 0.22µm second filtration (aseptic filtration), vial filling and half-stoppering, lyophilization and full stoppering, vial sealing, visual inspection, and storage of lyophilized vials in the validated cold rooms. BP02 AS stored in a bag is transferred for thawing.

The vials are filled with a set fill volume in 15 mL vials. The applicant has performed the fill volume accuracy for the PPQ batches from start to end of the filling process. The fill volume data from PPQ batches were found within the predefined acceptance limit which demonstrates the reliability of current controls in place to ensure the fill volume accuracy from start to end of the batch filling process.

The finished product-filled vials are half-stoppered with bromo-butyl rubber stoppers, moved to the lyophilizer loading area, and loaded onto the lyophilizer shelves. The filling, half-stoppering and lyophilizer loading is a continuous process. Formulated bulk batches were used in the lyophilisation characterisation studies.

Aluminium seals are crimped onto the stoppered vials to maintain the integrity of the container closure system and then transferred for visual inspection. The lyophilized vials are checked for any critical, major, or minor defects. All PPQ batches visual inspection results are found to be within the defined acceptance limit. After visual inspection, good vials are transferred to a validated cold room for storage at 2-8ºC until labelling and secondary packaging are required. Reprocessing is not performed during the manufacturing of the FP.

Controls of critical steps and intermediates

Process parameters used during the manufacturing of FP are categorized into operational parameters (CPPs/NCPPs) and performance parameters (IPCs/IPTs). The overall control strategy is based on a planned set of controls derived from current product and process understanding, ensuring process performance and product quality. The operational parameters are reflected in detail in the description of the manufacturing process. The classification of output parameters together with the defined acceptance limits is considered adequate.

Process validation

For the PPQ, full-scale production batches (150 mg/vial) were manufactured in the same facility, using the same process and equipment as for the batches intended for commercial manufacturing. Process performance qualification was carried out using FP batches. Fill volume verification in 15 mL USP Type-1 glass vial with different speeds using qualified vial filling machine was performed. The fill volume was within the acceptance criterion. The execution of PPQ batches revealed that in-process controls and in-process test parameters were with ranges and acceptance criteria. The uniformity of protein content across the filling process was confirmed as all investigated vials met the acceptance criteria. After lyophilisation sealed vials (lyophilized cakes) are subjected to 100% visual inspection.

Aseptic process simulations were conducted by performing successful media fill runs. Media-filled vials were examined for microbiological contamination at the end of the incubation period and no growth was observed. The FP manufacturing process includes different manufacturing options which are associated with different process parameters (all categorised as critical) and limits. These different manufacturing options, and their potential combinations, were not appropriately challenged during PPQ process validation. The different manufacturing options were applied for manufacturing of the clinical batches, which were found to be compliant with their acceptance criteria. PPQ batches were then manufactured using worst-case conditions (e.g. duration of thawing, mixing time, contact area, handling at the time of batch manufacturing) and no impact on FP quality is anticipated. The manufacture of the commercial batches will be performed according to the manufacturing conditions that have been validated during PPQ batches.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

2.4.3.1. Product specification

Similar to the AS, the initial approach proposed by the Applicant for setting the specifications limits was not acceptable leading to wide acceptance criteria not considered justified. A MO was raised, and the Applicant was asked to revise the specification limits for the quality attributes. The proposed limits were revised during the assessment and considered adequately justified.

The specifications for FP release testing are defined in accordance with ICH Q6B. All relevant characteristics of trastuzumab FP (general characteristics, identity, potency, purity, excipients and safety) are adequately covered. The proposed specification acceptance criteria were established based on compendial guidelines for safety and impurity tests, including bacterial endotoxin, sterility, and sub visible particles, Herceptin information and SmPC and data generated from in-house FP batches. The proposed acceptance criteria are acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities and Ph. Eur. 2.4.20. FP batches were assessed to determine the possible elemental impurities (at 30 % of the PDE limit) through ICP-MS (inductively coupled plasma-mass-spectrometry) analysis. Based on the results obtained, all the elemental impurities analysed in BP02 FP batches were below LOD and it was confirmed that the batches do not have any risk from elemental impurities, which can impact patient safety. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). A detailed risk assessment considering the AS and FP manufacturing process, the quality of materials, media and buffer and CCSs was conducted and no risk of presence of nitrosamines was identified and thus, also no specific extractable studies were conducted, which is accepted. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

For the majority of in-house analytical methods, it is referred to the AS section. Only for determination of PS20 (E432) in the FP, a specific non-compendial method is utilized, namely RP-HPLC and has demonstrated to be suitable. The compendial methods are based on the European Pharmacopoeia. Analytical procedures including physical appearance, visible particles, sub-visible particles, osmolality, pH, and extractable volume are performed using the compendial methods as described in Ph. Eur, and thus verification is performed. The analytical methodologies used for testing of bacterial endotoxin and sterility are based on the European Pharmacopeia and these methods have been validated to establish suitability during routine analysis. The applicant is encouraged to consider the feasibility of transitioning to Ph. Eur. 2.6.32. Test for bacterial endotoxins using recombinant factor C, eliminating the need for horseshoe crab derived material.

Batch analysis

Batch analysis data for FP (150 mg/Vial presentation) manufactured at the commercial scale in the GMP facility of CuraTeQ Biologics Private Limited, India, was provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference Standards

The reference standards or reference materials used for release and stability testing of the FP are the same as for AS.

2.4.3.2. Stability of the product

A shelf-life of 36 months is proposed. During the assessment, all available stability data have been updated. This results in real-time (5±3°C) stability data up to 36 months for clinical FP batches and up to 12 months for PPQ FP batches. Accelerated (25±2°C/60±5% RH) stability data are available for up to 6 months for the same clinical and PPQ FP batches. Stress (40±2°C/75±5% RH) stability data are available for up to 1 month for one clinical FP batch and one PPQ FP batch. Furthermore, the pre-PPQ batch was also placed on stability and real-time and accelerated stability data are available. Moreover, this batch was also subject to thermal cycling studies and the results are also submitted.

Similar to AS, further discussion was provided regarding representativeness of the clinical batches compared to the PPQ (commercial scale) batches. It is agreed that the BP02 clinical FP batches can be used to support the FP shelf-life claim.

Overall, the claimed FP shelf-life of 36 months at 5±3°C is adequately supported by real-time stability data from clinical and PPQ FP batches, for which long-term stability data up to 36 and 12 months respectively, were provided.

2.4.3.3. Adventitious agents

The general strategy of viral safety of the manufacturing process follows the requirements of ICH Q5A. This includes the selection of raw materials devoid of animal or human origin, the testing of the cell banks and the bioreactor harvest for a suitable panel of viruses, the design of the purification process to include two dedicated virus inactivation/removal steps and the validation of selected steps of the manufacturing process to reduce a broad panel of viruses including retrovirus-like particles, a contaminant present in the cell line.

With regard to TSE, the manufacturing process of BP02 was shown to be in compliance with the TSE guideline EMA/410/01 rev3, because of the avoidance of any material of animal or human origin except the production cell line. CHO cells are hamster-derived and as such not derived from a TSE-relevant species. Furthermore, no human- and animal-origin material was used during cell bank preparation and cell line development.

The BP02 cell banks (MCB and WCB) have been tested sufficiently for endogenous and adventitious viruses. The testing panel and strategy is in line with ICH Q5A requirements. Test results for virus testing are provided and demonstrate no viral contamination, except for the presence of retrovirus-like particles which is expected for CHO cells, and the manufacturing process provides sufficient capacity to remove / inactivate these viruses. This is considered sufficient.

Future WCBs will be tested as described for the current WCB in the MAA and in accordance with relevant guidelines.

Testing has been done in accordance with ICH Q5A on bulk harvests (clinical batches and PPQ batches) by an in vitro assay for the detection of adventitious viruses as well as a qPCR for the detection of MMV showing absence of viral contamination.

Four steps in the manufacturing process have been validated for virus reduction. Details on the materials used, the down scaling and the spiking studies are presented in the dossier and the study report has been provided. The down scaling is performed adequately. The virus reduction capacity of the downstream purification process has been investigated. The process steps were potent to effectively remove enveloped as well as small, non-enveloped viruses. Virus carry-over studies also demonstrated appropriate cleaning between column cycles. With this purification process, the retrovirus load in the bulk harvest can be reduced to an acceptable limit and has shown to be suitable for reducing potential viral contaminants with different physicochemical attributes from the process.

2.4.3.4. GMO

Not applicable.

2.4.3.5. Biosimilarity

FP batches generated at the proposed commercial scale were used for analytical similarity assessment. During the assessment, the inclusion of more FP batches in the head-to-head analytical assessment was considered required as data from BP02 PPQ batches was too limited to allow a meaningful conclusion on biosimilarity and a Major Objection was raised. Additional data from representative batches was provided. The Applicant added 5 commercial FP batches, as well as 1 EU-Herceptin and 4 US-Herceptin batches, resulting in at least 12 batches from each product to be considered in the biosimilarity analysis. The 5 added FP batches are manufactured from independent AS batches, which is endorsed. Hence, the 12 included FP batches represent 5 clinical, 1 pre-PPQ, 3 PPQ, and 3 post-PPQ batches. The following additional similarity analyses have been performed:

- Physicochemical parameters: protein concentration; primary structure (intact and reduced molecular mass and deglycosylated molecular mass by ESI LC-MS); secondary structure (far-UV CD, FTIR); tertiary structure (near-UV CD, FLR, Tm by DSC, molar mass/hydrodynamic radii/polydispersity by SEC-MALS, free thiol by Ellman's assay); %monomer, %HMW, %LMW by SE-HPLC; %Intact IgG, %LMW by CE-SDS (NR); %HC+LC, %NGHC by CE-SDS (R); %acidic, %main, %basic peaks by CEX-HPLC and by icIEF; pI by icIEF; and glycosylation by HILIC (afucosylation, high mannose, total fucosylation).
- Functional parameters: anti-proliferation activity (by cell-based assay), HER2 binding (by ELISA and SPR), FcRn binding (by SPR), FcγRIa binding (by SPR), FcγRIIa binding (both isoforms; by BLI), FcγRIIb binding (by BLI), FcγRIIIa binding (both isoforms; by SPR), FcγRIIIb binding (by BLI), C1q binding (by BLI), ADCC binding (both isoforms; by RGA and PBMC assay), and ADCP assay (high isoform; by RGA).

The analytical methods used to study the structural, physicochemical, and functional attributes of trastuzumab for the assessment of analytical similarity seem adequate. It is noted that no qualification data is presented for the method for determination of CDC activity. As CDC activity is not a mechanism of action of trastuzumab, this can be accepted. The level of details provided in the qualification/suitability reports (e.g. method execution, samples used, qualification acceptance criteria, system suitability criteria, results, etc.) is considered sufficient to confirm the suitability of the analytical methods used for the biosimilarity exercise.

Analytical Similarity Assessment

It is noted that a risk ranking was performed by the applicant to determine the criticality score for each quality attribute. Upon request, the criticality score for glycan heterogeneity was amended. In general, the approach for determination of the criticality score is acceptable. It is noted that (apart from the basic species) differences seem to be present for acidic and main variants (measured by CEX-HPLC) with the BP02 PPQ batches outside the quality range of EU-Herceptin for all three species (acidic, main, basic). Based on the consistency of data presented for the BP02 PPQ and post-PPQ batches, the additional biosimilarity analyses for BP02 showed comparable results with EU-Herceptin for all physicochemical parameters, except for some minor differences. The Applicant justified the differences by stating that these are minor and not clinically meaningful, since all endpoints in the Phase I (PK) and Phase III clinical studies have been met. Furthermore, an additional comparative forced degradation study between PPQ FP batches and EU-Herceptin/ US-Herceptin batches has been performed. The results from this additional study did not reveal significant differences between BP02 and EU/US-Herceptin under the conditions tested. Also trends in degradation were comparable and no new impurities have been observed.

Functional analytical similarity

Equivalence testing was performed for relative potency data of proliferation inhibition assay for EU-approved Herceptin, US-licensed Herceptin and BP02 samples. On performing pairwise comparison, the observed difference in means along with the upper and lower 95% confidence intervals using TOST analysis were well within the defined equivalence acceptance criteria.

Trastuzumab binds to extracellular domain IV of the HER2 receptor. This was demonstrated by cell-based ELISA. Surface plasmon resonance (SPR) technology was used to determine the binding affinity of trastuzumab to FcRn. Slightly higher binding of BP02 to the FcRn was observed. It is argued that no significant effect was observed in the half-life during clinical pharmacokinetic study compared to EU-approved Herceptin.

All BP02 batches, except for one batch binding affinity to FcγRIIA (R167) and to FcγRIIB fall within the range of EU-approved Herceptin. Nevertheless, a slight trend can be seen for BP02, which indicates

that the values are closer to the upper limit of the similarity range. BP02 binding affinity to FcγRIIIA (V176) and (F176) receptors and to FcγRIIIB receptor can be considered similar to EU-approved Herceptin.

BP02 binding affinity to C1q can be considered similar to EU-approved Herceptin. Absence of CDC activity of trastuzumab was demonstrated using a positive control.

As described above, during the assessment, a MO was raised regarding the afucosylation strategy and in the responses submitted, the Applicant addressed the assay's capability to discriminate between batches displaying different afucosylation levels. The Applicant used a statistical prediction model to discriminate between batches displaying different afucosylation levels, which are known to impact FcyRIIIa binding and ADCC activity. Although the statistical prediction model is the sole information provided, it could predict a correlation between total afucosylation and FcyRIIIa binding/ADCC activity. Therefore, the explanations can be accepted and the issue will not be further pursued.

With regard to ADCP activity, data of BP02 batches were outside of the 3σ quality range for EU-approved Herceptin but it is agreed that there is no evidence from the clinical studies that there is a functional impact.

The lack of CDC activity is known for trastuzumab and is confirmed herein and does not need to be addressed further.

BP02 and EU-approved Herceptin were tested in a comparative mode using a panel of recombinant HEK-293 cell lines for assessing the test product-induced activation of Toll-like receptors (TLRs). These cell lines functionally overexpress a given TLR protein as well as a reporter gene which is a secreted alkaline phosphatase. The production of this reporter gene is driven by an NF-kB inducible promoter. TLR activation results are given as optical density values (OD). Results indicate that the absolute level of each cytokine induced after treatment were very similar across all EU-approved Herceptin.

Comparative Forced Degradation and Stability Study

Results obtained in comparative thermal stress stability, comparative accelerated stability and force degradation studies revealed that BP02 FP, US Herceptin and EU Herceptin showed a similar degradation profile and there are no significant differences in their trends over time with respect to the changes in quality attributes studied when subjected to accelerated stability conditions (25°C± 2°C/60% ± 5% RH) and stress stability conditions (40 ± 2°C/75 ± 5% RH) for up to 6 months and of 3 months respectively.

Two batches of BP02 FP, US-licensed Herceptin and EU-approved Herceptin were investigated in a head-to-head study to compare the degradation pathways and degradant product profiles when exposed to thermal stress, photo stress, pH stress, and white light stress. As the BP02 clinical FP batches are at present not considered representative of the commercial BP02 product, upon request, the Applicant performed an additional comparative forced degradation study including additional batches from representative BP02 FP batches, EU-Herceptin and US-Herceptin. The results showed no statistically significant differences between BP02 and EU/US-Herceptin under the conditions tested. Also trends in degradation were comparable and no new impurities have been observed. The presented additional comparative forced degradation study is accepted.

Summary of the results are provided below.

Table 1 - Analytical Similarity Assessment of Dazublys and EU approved Herceptin

Category	Product Characteristic	Analytical methodology	Conclusion/Justification
Protein Content/Dose	Protein Concentration	UV Spectroscopy (OD280)	Protein concentration of BP02 is within ranges of EU approved Herceptin
Primary Structure and Identity	Product Molecular mass (Intact and Reduced), Deglycosylated molecular mass (Intact)	ESI LC-MS	Intact molecular weights of BP02 batches are identical to EU approved Herceptin Additionally, both deglycosylated and LC, HC molecular weights of BP02 are comparable to Herceptin.
	Protein (Amino Acid) sequence, N-Terminal and C-Terminal Sequence and amino acid composition	ESI LC-MS/MS	The N-terminal and C-terminal amino acid sequence are identical for BP02, EU-approved Herceptin.
	Amino acid composition	RP-HPLC	Amino acid composition for BP02 is similar to EU-approved Herceptin.
	Extinction Coefficient	UV-Spectroscopy	Extinction coefficient of BP02 batches is comparable to EU-approved Herceptin.
	Peptide Mapping	RP-HPLC	The profiles of BP02 batches are comparable to EU-approved Herceptin
Conformation and Size Heterogeneity	Monomer/ HMWs/ LMWs	SE-HPLC	BP02 is comparable to EU-approved Herceptin.
	Aggregates	SV-AUC	The aggregates/HMWs and monomer % and molecular weight are comparable.
	Intact/Clips/ Fragments/LMWs	CE-SDS (NR)	LMW levels in BP02 batches are comparable with EU approved Herceptin
	Purity (LC/HC/NGHC)	CE-SDS (R)	The cumulative LC+HC % of BP02 batches are comparable to EU- approved Herceptin.
Charge Heterogeneity (with and without CpB digestion)	Acidic, main and basic peaks (Isoforms)	icIEF, CEX-HPLC	The acidic, basic and main peak % areas are comparable between BP02 and EU-approved Herceptin
	Isoelectric Point	icIEF	The pI is similar between BP02 and EU-approved Herceptin batches.
Glycan Heterogeneity	Glycosylation or Oligosaccharide profile (Afucosylation, Fucosylation)	HILIC	The N-glycan profiles are comparable between BP02 and EU-approved Herceptin.

Category	Product Characteristic	Analytical methodology	Conclusion/Justification
	Terminal Sialylation	RP-UPLC	Percentage of sialylation are comparable between BP02 and EU-approved Herceptin.
	Monosaccharide composition	GC-MS	Molar ratio of mannose, galactose and GlcNAc are comparable for BP02 and EU-approved Herceptin.
PTMs	Deamidation	Tryptic peptide mapping LC-MS/MS (ESI LC-MS/MS)	The percentage levels of Deamidation and Oxidation are comparable between BP02 and EU-approved Herceptin.
	Oxidation		
	N-terminal pyroglutamate,		N-terminal pyroglutamate and C-terminal lysine for HC and LC are comparable between BP02 and EU-approved Herceptin.
	C-terminal Lysine variants		
Higher-Order Structure	Secondary Structure	Far-UV CD, FTIR,	Secondary structure by FTIR, Far-UV,and CD of BP02 batches are comparable to EU-approved Herceptin.
		1D 1H-NMR	Tertiary structure by NMR for BP02, and EU-approved Herceptin batches are similar indicating the identity of BP02.
	Tertiary Structure	Near-UV CD, Intrinsic fluorescence (FLR)	Tertiary structures in BP02 and EU-approved Herceptin is highly similar.
	Melting Temperature (Tm)	DSC	Thermal unfolding transition midpoints are comparable for BP02 and EU-approved Herceptin batches.
	Molar Mass/ Hydrodynamic Radii/ polydispersity	SEC-MALS	The molar mass, hydrodynamic radii and polydispersity are similar for BP02 and EU-approved Herceptin
	Disulfide Bond Assignment	Non-reduced RP-UPLC (ESI LC-MS/MS)	All the disulphide bonds were mapped and are similar between BP02 and EU-approved Herceptin
	Ellman assay (Free Thiol)	Ellman's Assay	The free thiol content in BP02 and EU-approved Herceptin batches are observed to be comparable.

Product Characteristic	Product Quality Attribute	Analytical Methodology	Conclusion and Key findings
Functional Characterization	Inhibition of Proliferation	Potency Estimation by BT474 Proliferation Inhibition Assay	The relative potency values of BP02 and EU-approved Herceptin are similar and within the equivalence margin.
	HER2 Binding	Target Binding Activity-HER2 binding ELISA	HER2 binding activity of BP02 and EU-approved Herceptin by ELISA and SPR are similar
		HER2 Binding by SPR	
	FcRn Binding	FcRn binding by SPR	

Product Characteristic	Product Quality Attribute	Analytical Methodology	Conclusion and Key findings
	FcγRI Binding	FcγRI binding by SPR	FcRn, FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, FcγRIIIB binding affinities of BP02 and EU-approved Herceptin are similar
	FcγRIIA Binding	FcγRIIA binding by BLI	
	FcγRIIB Binding	FcγRIIB binding by BLI	
	FcγRIIIA Binding	FcγRIIIA binding by SPR	
	FcγRIIIB Binding	FcγRIIIB binding by BLI	
	C1q Binding	C1q binding by BLI	C1q binding affinity of BP02 and EU-approved Herceptin are similar
	ADCC	ADCC activity by RGA	The relative potency values of BP02 and EU-approved Herceptin are similar
		ADCC activity by PBMC	
	ADCP	ADCP activity by RGA	
	CDC	CDC activity	BP02 and EU-approved Herceptin did not show any CDC activity and are similar.
Immunogenicity	Innate Immune Response	TLR Mediated Reporter Assay	TLR activating components are absent in the BP02 finished product, indicating no potential to induce innate immunity.
	Systemic Inflammatory Response	PBMC based Cytokine/Chemokine Production assay	Similar levels of cytokine levels were induced by BP02 and EU-approved Herceptin batches.
	Adaptive Immune Response	DC-CD4+ T cell Mediated Proliferation	TOST analysis showed BP02 and EU-approved Herceptin batches are equivalent.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Dazublys (BP02) is developed as a trastuzumab biosimilar to the reference medicinal product EU-Herceptin.

The finished product (FP) is presented as a white to pale yellow lyophilized powder for concentrate for solution for infusion containing 150 mg of Trastuzumab as active substance (AS). The product is available in 15 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film containing 150 mg of trastuzumab.

The manufacturing processes for the active substance and finished product reflects a standard manufacture of trastuzumab products. During the assessment several MO were raised: on the GMP compliance of AS/FP manufacturer site, on the testing of UBH, on structure-function relationship between glycosylation and Fc-mediated effector functions, on the manufacturing process changes made from clinical to PPQ batches, on the Reference standards and on the AS/FP specifications limits. Also regarding biosimilarity, two MO were raised on the target protein content differences from EU-Herceptin and on the relevance of the clinical FP batches used in the biosimilarity analysis (due to a shift in purity between clinical and PPQ batches). All of these MOs were adequately addressed during the assessment and considered resolved.

The AS and FP manufacturing processes, process controls, process development and process validations as well as raw and starting materials used for the manufacture have, overall, been appropriately described. The results of tests carried out indicate consistency and uniformity of

important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Analytical methods have been appropriately validated.

Reference standards are sufficiently described and characterised. A comprehensive risk assessment on impurities has been provided and found acceptable. Adventitious agents safety evaluation has been satisfactorily performed.

BP02 FP batches generated at the proposed commercial scale were used for analytical similarity assessment. Supported by the inclusion of additional, representative BP02 FP batches in the head-to-head analytical assessment, Dazublys showed comparable results with EU-Herceptin and the currently available data are sufficient to conclude that the commercial BP02 product can be considered biosimilar to EU-Herceptin.

To conclude, the quality part of the dossier is sufficient and adequate.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.5. Non-clinical aspects

2.5.1. Introduction

BP02 (Trastuzumab) is being developed as a biosimilar to EU-Herceptin by CuraTeQ Biologics Private Limited for the same indications for which they are approved.

According to the CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1): to support biosimilarity, relevant non-clinical studies should be performed before initiating clinical trials. A stepwise approach is recommended for evaluation of the similarity of the biosimilar and the reference product. Analytical studies (see Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues (EMA/CHMP/BWP/247713/2012) and in vitro pharmaco- toxicological studies should be conducted first and a decision then made as to the extent of what, if any, in vivo work in animal studies will be required.

Non-clinical pharmacology studies comprised in vitro studies to evaluate potency and functionality. The in vitro studies are more appropriately addressed alongside the related quality data in the biosimilar comparability evaluation .

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Non-clinical pharmacology comprised in vitro studies to evaluate potency and functionality. These were presented in Module 3 of the dossier and discussed in the quality report.

Briefly, BP02 (Trastuzumab) is a proposed biosimilar candidate to the reference medicinal product, Herceptin and thus, was engineered to have a 100% identical amino acid sequence to trastuzumab heavy and light chains. BP02 DP batches generated at the proposed commercial scale were used for analytical similarity assessment.

The following in-vitro functional assays assessing functions mediated by the Fab domain, the Fc domain, and Fab-Fc domains were performed to demonstrate the nonclinical pharmacological (PD) comparability.

Fab domain mediated functions:

1. Binding to the HER-2 was assessed using SPR

2. Binding to the HER-2 expressed cells, was assessed using ELISA

3. Inhibition of HER-2 mediated cell proliferation, was assessed using BT474 cells.

Fab-Fc mediated functions:

4. ADCC was assessed using BT474 cells expressing membrane-bound HER2 as target cells and engineered Jurkat cells with FcγRIIIa V158/V158 and FcγRIIIa V158/F158 phenotype as effector cells. An additional ADCC assay using CHO cells as target cells and PBMC with FcγRIIIa as effector cells was also conducted.

5. ADCP was assessed using BT474 cells and Jurkat cells with FcγRIIa (H allelic form) was performed.

Fc mediated functions:

6. Binding to Fc gamma receptors - FcγRIa, FcγRIIa, FcγRIIb, FcγRia (V158), FcγRiya (F158), FcγRIIIb, FcRn and the first subcomponent of the C1 complex of the classical pathway of complement activation (C1q) protein was also assessed. In addition to this negative CDC activity was assessed

The analytical biosimilarity study showed good comparability between the proposed biosimilar and its reference medicinal product and further data is presented in the quality report

2.5.3. Pharmacokinetics

Not applicable.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Not applicable.

2.5.4.2. Repeat dose toxicity

The applicant has conducted a repeat dose toxicity study in mice. Results showed that BP02 and the reference medicinal product, EU-Herceptin, are similar with respect to the incidence and severity of the observations recorded in this study as well as their toxicokinetic and immunogenicity profiles in mice.

Genotoxicity, carcinogenicity, and reproductive and developmental toxicological studies have not been conducted with BP02 which is acknowledged.

2.5.4.3. Other toxicity studies

BP02 and EU-approved Herceptin were tested in a comparative mode in several assays to address immunotoxicity. Both BP02 and EU-approved Herceptin do not activate the hTLR2, hTLR3, hTLR4, hTLR5, hTLR7, hTLR8, or hTLR9 reporter cell lines. The absolute level of each cytokine induced after treatment were very similar across all EU-approved Herceptin. The data indicate that there is no difference in the adaptive immune response between BP02 and EU-approved Herceptin

2.5.4.4. Ecotoxicity/environmental risk assessment

The applicant submitted a justification for not providing an environmental risk assessment. According to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr. 2*) certain types of products such as proteins are exempted from providing ERA studies because they are unlikely to result in significant risk to the environment due to their nature. The absence of a formal environmental risk assessment studies is considered justified and trastuzumab is not expected to pose a risk to the environment due to its nature.

2.5.5. Discussion on non-clinical aspects

The non-clinical program for the development of BP02 as a biosimilar to EU Herceptin is sufficient. Non-clinical pharmacology studies comprised in vitro studies to evaluate potency and functionality:

The in vitro studies are more appropriately addressed alongside the related quality data in the biosimilar comparability evaluation (further details are included in the quality section above).

Fab characterization was performed by BT474 proliferation inhibition assay, cell based HER2 binding ELISA and HER2 binding by SPR. BT474 proliferation inhibition assay showed that BP02 and EU-Herceptin have similar potency to inhibit cell proliferation and passed the equivalence test. Moreover, HER2 binding by ELISA and SPR showed that the binding activity and affinity of BP02 and EU-Herceptin are similar. Fc characterization was performed for several Fcγ receptors and C1q. FcRn, FcγRI, FcγRIIA/B, FcγRIIIA/B and C1q binding affinities were assessed using SPR and BLI technology. Results showed that BP02 and EU-Herceptin have similar binding affinities across all receptors. Additionally, Fc effector functions were estimated using ADCC by RGA and PBMC, ADCP by RGA. Both assessments showed that BP02 and EU-Herceptin have similar potency to exhibit ADCC and ADCP activities. Furthermore, CDC activity assay was performed which showed the BP02 and EU-Herceptin have not induced any CDC activity.

The currently available data are sufficient to conclude that the commercial BP02 product can be considered biosimilar to EU-Herceptin from a non-clinical perspective.

PK drug interactions studies are not considered necessary in the evaluation of biosimilars as the established safety profile of the reference product is considered as more relevant, and in accordance with the Guideline on similar biological medicinal products containing monoclonal antibodies, non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

Toxicity studies are not considered necessary in the evaluation of biosimilars as the established safety profile of the reference product is considered as more relevant, and in accordance with the Guideline on similar biological medicinal products containing monoclonal antibodies, non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

In line with the current Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1), and the Guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals

(EMA/CHMP/ICH/731268/1998), no additional non-clinical studies were included in this application, which is considered acceptable.

2.5.6. Conclusion on the non-clinical aspects

From non-clinical point of view, no further in vivo data are required and the marketing authorisation application for Dazublys can be considered approvable. The assessment of the non-clinical data indicated similar activity between BP02 and the reference product Herceptin.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Protocol	Design	Objective(s)	Treatment	Status
BP02-101 (PK similarity)	A randomized, double-blind, single-dose, 3-way, parallel-group, comparator-controlled study to evaluate the pharmacokinetic, safety, tolerability, and immunogenicity of BP02 (trastuzumab) compared to Herceptin® (EU-approved and US-licensed) in healthy adult male N=111 (37 in each treatment arm)	**Primary objective**: The primary objective is to establish pairwise PK similarity between BP02, EU-Herceptin and US-Herceptin in healthy adult male subjects. **Secondary Objectives:** The secondary objectives are to evaluate the safety, tolerability, and immunogenicity, and to further characterize the PK of BP02, EU-Herceptin and US-Herceptin in healthy adult male subjects.	Subjects received single IV infusion of 6 mg/kg of either BP 02 or EU-Herceptin or US- Herceptin on Day 1	Completed
CR201-18	A Multicenter, Double-Blind, Randomized, Parallel-Group, Active-Controlled, Phase III Study to evaluate the Efficacy, Safety, Immunogenicity and Pharmacokinetics of BP02 (Trastuzumab) in comparison with Herceptin®-EU in Patients with HER2-Positive Metastatic Breast Cancer (MBC) N=690 (345 in each treatment arm)	**Primary objective:** To compare the Objective Response Rate (ORR) at end of cycle 8 of BP02 (Trastuzumab) and Herceptin®- EU when administered in combination with Docetaxel in patients with HER2-Positive MBC at the end of Induction Phase. **Secondary Objectives:** • To assess the Progression Free Survival (PFS) and Overall Survival (OS) of BP02 (Trastuzumab) as compared to Herceptin® EU in patients with HER2-Positive MBC.	The order of administration was BP02 (Trastuzumab) or Herceptin® EU followed by Docetaxel. A loading dose 8 mg/kg of body weight Trastuzumab over 90 minutes was provided in Cycle 1 and a maintenance dose of 6 mg/kg of body weight Trastuzumab for subsequent cycles (Cycle 2-8), up to Cycle 8 as an intravenous (IV) infusion.	Completed
		•To assess the safety profile of BP02 (Trastuzumab) as compared to Herceptin®-EU. To assess the potential immunogenicity of BP02 (Trastuzumab) as compared to Herceptin®-EU. • To compare the Ctrough of BP02(Trastuzumab) and Herceptin®-EU when administered in combination with Docetaxel in Induction Phase.		

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The results described in this PK section were obtained from two pivotal clinical studies included in this Marketing Authorisation Application (MAA) for BP02, a similar biological medicinal product to the reference medicinal product, Herceptin (Roche Registration Limited).

To support the demonstration of biosimilarity of BP02 to EU-authorised Herceptin (hereinafter referred to as EU-Herceptin), data from one completed Phase 1 study in healthy male volunteers (BP02-101) and one Phase 3 study (induction part completed, maintenance part completed during the MA procedure) in patients with Human epidermal growth factor receptor-2 (HER2)-positive breast cancer (CR201-18) are presented. These are summarised in the following table:

Table 2 - Phase 1 study (PK similarity) and Phase 3 study

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
BP02-101 (PK similarity)	A randomized, doubleblind, single-dose, 3-way, parallel-group, comparator-controlled study to evaluate the pharmacokinetic, safety, tolerability, and immunogenicity of BP02 (trastuzumab) compared to Herceptin® (EUapproved and USlicensed)	Healthy adult male N=111 (37 in each treatment arm)	Subjects received single IV infusion of 6 mg/kg of either BP 02 or EU-Herceptin or US- Herceptin on Day 1	**Primary objective:** to establish pairwise PK similarity between BP02, EU-Herceptin and US-Herceptin in healthy adult male subjects. ($AUC_{0-\infty}$, AUC_{0-t}, and C_{max}) **Secondary Objectives:** to evaluate the safety, tolerability, and immunogenicity, and to further characterize the PK of BP02, EUHerceptin and USHerceptin in healthy adult male subjects.
CR201-18	A Multicenter, Double-Blind, Randomized, Parallel-Group, Active-Controlled, Phase III Study to evaluate the Efficacy, Safety, Immunogenicity and Pharmacokinetics of BP02 (trastuzumab) in comparison with Herceptin®-EU	Patients with HER2-Positive Metastatic Breast Cancer (MBC) N=690 (345 in each treatment arm)	The order of administration was BP02 (trastuzumab) or Herceptin® EU followed by docetaxel. A loading dose 8 mg/kg of body weight trastuzumab over 90 minutes was provided in Cycle 1 and a maintenance dose of 6 mg/kg of body weight trastuzumab for subsequent cycles (Cycle 2-8), up to Cycle 8 as an intravenous (IV) infusion.	**Primary objective:** To compare the Objective Response Rate (ORR) at end of cycle 8 of BP02 (trastuzumab) and Herceptin®- EU when administered in combination with docetaxel in patients with HER2-Positive MBC at the end of Induction Phase. **Secondary Objectives:** To assess the Progression Free Survival (PFS) and Overall Survival (OS) of BP02 (trastuzumab) as compared to Herceptin® EU in patients with

				HER2-Positive MBC. To assess the potential immunogenicity of BP02 (trastuzumab) as compared to Herceptin®-EU. To compare the Ctrough of BP02 (trastuzumab) and Herceptin when administered in combination with docetaxel in Induction Phase.

2.6.2.2. Pharmacokinetic data analysis

The bioanalytical methods used for the clinical study sample testing were developed and validated at Central laboratory.

The approach of single validation was followed for both phase I and phase III clinical trials due to the difficulty in getting a large amount of diseased matrix. Within the same validation study, both healthy and diseased matrices were used to check the assay performance, and the same methodology was applied.

An enzyme-linked immunosorbent assay (ELISA) for the determination of BP02 (Trastuzumab) in human serum was validated at Central laboratory according to test method SOP and validation plan, over an analytical range of 100 to 2500 ng/mL.

The molecule BP02 (Trastuzumab, Test Product (T)) was validated in parallel with US-Herceptin and EU-Herceptin reference standards. As per SOP, the method consists of indirect sandwich ELISA. Human serum study samples, calibration standards and QC/validation samples were diluted at least 20-fold with aqueous buffer (MRD, minimum required dilution). The determination of trastuzumab in human serum was carried out over a calibration range of 100 ng/mL (LLOQ) – 2500 ng/mL (ULOQ). The diluted samples were analysed by a three-step indirect sandwich ELISA using an analyte-specific capture antibody, a biotinylated analyte-specific detection antibody and streptavidin-peroxidase tracer visualized by 3,3',5,5' Tetramethylbenzidine (TMB) substrate. The quantification was performed using the optical density (OD) values at 450 nm (reference wavelength 620 nm subtracted). The calibration curve was fit using 4-PL (4-parameter logistic function) with weighting 1/y.

Validation Study

ELISA analytical method to quantify the concentration of BP02 and Herceptin in human serum has been adequately validated. This ELISA method is suitable for the quantification of BP02 and Herceptin in human serum. The analyses were within the pre-defined run acceptance criteria and in accordance with the current Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

The validation of the method included assessment of precision and accuracy of the standard curve, the assay range (defined by the LLOQ and ULOQ), intra-assay and inter-assay precision and accuracy (BP02 and Herceptin), selectivity (BP02 and Herceptin), dilution linearity, minimum required dilution, hook effect (BP02 and Herceptin), assay robustness and short-term, long-term and freeze/thaw stability (BP02 and Herceptin).

5 QC samples [100.0.00 (LLOQ), 300.0 (LQC), 1000 (MQC), 1875 (HQC) and 2500 (ULOQ) ng/mL] were used to assess accuracy and precision of the method. Inter and intra-precision and accuracy of calibration standards and QC samples were within the criteria. Intra-assay and inter-assay precision and accuracy

for BP02 and Herceptin are met, except intra-run accuracy and precision for 2/8 runs for Herceptin EU due to inappropriate QC preparation and one failure at one of five QC levels.

The minimum required dilution (MRD) is described: human serum study samples, calibration standards and QC/validation samples are diluted at least 20-fold with aqueous buffer. As per SOP (submitted with responses) 2 dilution steps are applied, first a pre-dilution by 5-fold, 25-fold or 125-fold in matrix (i.e. human serum pool) then 20-fold in PBS buffer (MRD). This is performed manually or automatically. For high concentrations, a manual, 500-fold dilution step was included.

All assays were selective in human plasma. Selectivity in individual matrix from healthy and disease donors was evaluated separately for BP02, Herceptin EU and Herceptin US. 10 individual matrix lots were used from healthy donors and 10 individual matrix lots were used from breast cancer patients.

The data suggested that there was dilutional linearity up to 500-fold dilution.

No high dose Hook effect was observed up to BP02 and Herceptin concentrations of 200 000 ng/mL

As a part of validation, assay robustness, haemolysis and hyperlipidemia were also tested on selectivity and met acceptance criteria.

For specificity, no co-administered compounds were foreseen.

Study samples for parallelism testing are taken from the phase III study. The samples are received and managed in Central laboratory. The method validation was performed and long-term stability is extended.

Stability was tested on multiple occasions, starting with combined stability testing (freeze/thaw, short-term and initial frozen storage). BP02 concentrations in human serum were stable through six cycles of freeze (-80°C) /thaw cycles and in short term at room temperature. Long-term stability report VCA31919-02 submitted with the response demonstrated stability of LQC (300 ng/mL), HQC (1880 ng/mL) und DQC (200 µg/mL) for Herceptin and BP02in human serum for up to 1052 days at 20°C and -80°C.

Regarding the validation of the bioanalytical method for the determination of BP02 and Herceptin in human serum, there was assessment of carry-over for the robotic method performed in the form of a stress test.

Deviations and event observations are described in method validation study.

Bioanalytical Study

The analytical method was developed in-house and is described in the method standard operating procedure SOP. Long-term stability and parallelism are evaluated separately.

A total of 1927 samples were analysed and reported with a valid result within the study report. Of the 1927 reported samples analysed, 376 samples (19.5%) had to be re-assayed for analytical reasons (mainly dilution QC sample out of range).

The incurred sample analysis (ISR) has been correctly carried out. The concentrations obtained for the initial analysis and the concentrations obtained by reanalysis are within 30% of their mean for at least 67% of the repeats.

Electrochemiluminescence immunoassays to detect and confirm the presence of anti-drug antibodies and neutralizing anti-drug antibodies against BP02 (trastuzumab) human serum was validated at Central laboratory according to test methods and validations plan and to test method and validation plan respectively.

Study Design & Methods

Study BP02-101

BP02-101 was a Phase 1 randomized, double-blind, single-dose, 3-way, parallel-group trial in healthy volunteers to evaluate pharmacokinetic, safety, and immunogenicity of BP02 compared to EU- and US-Herceptin in New Zealand (majority Caucasian population).

Subjects received a single dose of either BP02 or EU-Herceptin or US-Herceptin at a dose of 6 mg/kg as a single IV infusion over 90 minutes in the arm on Day 1 of the study. Six mg/kg is the recommended maintenance dose in patients receiving the 3-weekly treatment schedule for Herceptin, after an initial 8 mg/kg loading dose.

Table 3 - Subject Disposition and Analysis Set - BP02-101

Categories	BP02	EU-Herceptin	US-Herceptin	Overall
Number of subjects screened				241
Number of subjects screen failure				129 (53.5)
• Subject did not meet eligibility criteria				83 (64.3)
• Subject withdrew consent				24 (18.6)
• Other				22 (17.1)
Number of subjects randomized[#]	37	38	37	112
Number of subject dosed	37	37	37	111
Number of subjects completed study	36 (97.3)	37 (97.4)	33 (89.2)	106 (94.6)
Number of subjects prematurely withdrawn	1 (2.7)	1 (2.6)	4 (10.8)	6 (5.4)
• Adverse event	1 (100.0)	0	3 (75.0)	4 (66.7)
• Withdrawal of consent	0	1 (100.0)	1 (25.0)	2 (33.3)
Safety Analysis Set	37 (100.0)	37 (97.4)	37 (100.0)	111 (99.1)
Pharmacokinetic Analysis Set	36 (97.3)	37 (97.4)	31 (83.8)	104 (92.9)

Note(s): Percentages for the screen failure subjects are based on the number of subjects enrolled. Percentages for the reasons for screen failure are based on the number of subjects who failed screening. Percentages for the reasons for discontinuation are based on the number of subjects who prematurely withdrew from the study. All other percentages are based on the number of subjects randomised.

#One subject was randomised but not administered with study drug due to withdrawn the consent

The difference in the assayed content (protein concentrations) between the bio-batches of test and EU-reference products does not differ more than 5% (21.2 mg/mL and 21.8 mg/mL respectively). No dose-correction/adjustment is needed.

PK blood samples were collected at pre infusion (or 0 hours, collected within 1 hour prior to the start of the infusion and at the end of the infusion) 0.5, 1, 4, and 6 hours after the end of infusion, 24, 48, 72, and 96 hours, Day 8 (168 hours), Day 15 (336 hours), Day 22 (504 hours), Day 29 (672 hours), Day 36 (840 hours), Day 50 (1176 hours), Day 64 (1512 hours), and Day 78.

Overall, 86 subjects (77.5%) had protocol deviations in the study. Of these, 24 subjects had major deviations and 70 subjects had minor deviations (see Table 4).

There were two major protocol deviations in the BP02 group regarding PK/PD. One of the major protocol deviations regarding PK/PD was one missing day 50 visit of subject 101-028. Subject 102-057 had post

end of infusion PK samples taken out of the protocol specified windows on day 1, 2, 3, 4, 5, and 8 and did not attend day 15, 22, 29, 36, 50 and 64. This subject was excluded from pharmacokinetic analysis set.

No subject was excluded in the EU-Herceptin group. No major protocol deviations were reported for the EU-Herceptin group.

Table 4: Overview of protocol deviations (overall, major, minor) - BP02-101

Classification Type	BP02 (N=37)	EU-Herceptin (N=37)	US-Herceptin (N=37)	All Subjects (N=111)
Overall	**29 (78.4)**	**23 (62.2)**	**34 (91.9)**	**86 (77.5)**
Major	**7 (18.9)**	**3 (8.1)**	**14 (37.8)**	**24 (21.6)**
Study procedures	4 (10.8)	2 (5.4)	10 (27.0)	16 (14.4)
PK/PD	2 (5.4)	0	2 (5.4)	4 (3.6)
Exclusion criteria	0	0	2 (5.4)	2 (1.8)
Informed consent and process	0	1 (2.7)	1 (2.7)	2 (1.8)
Laboratory assessment	1 (2.7)	0	0	1 (0.9)
Minor	**25 (67.6)**	**20 (54.1)**	**25 (67.6)**	**70 (63.1)**
Study procedures	17 (45.9)	13 (35.1)	11 (29.7)	41 (36.9)
PK/PD	10 (27.0)	8 (21.6)	12 (32.4)	30 (27.0)
Laboratory assessment	4 (10.8)	2 (5.4)	5 (13.5)	11 (9.9)
Administrative	2 (5.4)	1 (2.7)	4 (10.8)	7 (6.3)
Source document criteria	1 (2.7)	3 (8.1)	1 (2.7)	5 (4.5)
Conmed criteria	0	0	1 (2.7)	1 (0.9)

Abbreviations: N = number of subjects meeting the criteria.
Note: Only the most severe deviation class within classification type for each subject was counted.
Source: Table 14.1.2

Overall, 51 subjects (45.9%) had at least one prior medication in the study. The prior medications received by >5% of subjects were paracetamol (16.2%), whey protein (8.1%), ibuprofen (6.3%), and vitamin C (5.4%).

Overall, 69 subjects (62.2%) had at least one concomitant medications in the study. The concomitant medication received by >5% of subjects were paracetamol (52.3%), ibuprofen (25.2%), cetirizine (9.0%), and Pfizer Biontech Covid-19 Vaccine (7.2%).

Table 5 - Study treatment details - BP02-101

Study Treatment Name:	BP02 (trastuzumab) (proposed biosimilar), concentrate for solution for infusion in vials	EU-Herceptin	US-Herceptin
Dosage Formulation:	α,α trehalose dihydrate, L-histidine hydrochloride monohydrate, L-histidine, and polysorbate-20. pH 6.0		
Unit Dose Strength/Dosage Level:	Strength: 150 mg vial. Dose: 6 mg/kg.		
Route of Administration:	IV infusion.		
Dosing Instructions:	Subjects received one dose of either BP02 or EU-Herceptin or US-Herceptin at a dose of 6 mg/kg as a single IV infusion over 90 minutes in the arm on Day 1 of the study.		
Packaging and Labeling:	All clinical study material was packaged and labeled to comply with applicable regulations.		
Manufacturer:	CuraTeQ Biologics Private Limited. Plot No.2, Maitrivihar, Ameerpet, Hyderabad, Telangana, India, 500 038	Roche Pharma AG Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 USA

2.6.2.3. Pharmacokinetic results

The table summarizes the serum PK parameters after single IV infusion of trastuzumab (BP02, EU-Herceptin, and US-Herceptin) and the bioequivalence assessment results.

Table 6 - Summary of Single-dose trastuzumab Serum Pharmacokinetic Parameters (Pharmacokinetic Analysis Set) – BP02-101

Treatment/ Statistic	AUC_{0-inf} (ng*h/mL)	AUC_{0-t} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	λ_z (1/h)	CL/F (L/h)
BP02, (N=36)							
n	36	36	36	36	36	36	36
Mean	31791595.75	31603914.38	150722	-	139.711	0.0052	0.015
SD	5162676.024	5128363.456	24614.3	-	32.1455	0.00099	0.0023
CV%	16.2	16.2	16.3	-	23	19.2	15.6
Minimum	21682918.99	21484921.01	107000	0.25	98.85	0.0029	0.011
Median	32042158.85	31747733.95	151000	0.52	129.132	0.0054	0.014
Maximum	46364458.65	46042943.45	228000	6.13	239.931	0.007	0.021
Geo mean	31382214.22	31198207.81	148842	-	136.608	0.0051	0.015
GCV%	16.5	16.5	16.1	-	21.1	21.1	15.4
EU-Herceptin, (N=37)							
n	37	37	37	37	37	37	37
Mean	29542711.08	29454764.09	148108	-	129.135	0.0056	0.016
SD	4061285.268	4062270.99	19899.4	-	30.1557	0.0013	0.0027
CV%	13.7	13.8	13.4	-	23.4	22.3	16.5
Minimum	21746421.33	21171256	115000	0.25	83.048	0.0034	0.012
Median	29117827	29095532.52	146000	0.25	123.297	0.0056	0.016
Maximum	41148310.15	40834917.68	188000	1.05	205.598	0.0083	0.025
Geo mean	29271598.37	29181125.95	146821	-	125.886	0.0055	0.016
GCV%	13.9	14.0	13.4	-	23.0	23.0	15.8
US-Herceptin, (N=31)							
n	31	31	31	31	31	31	31
Mean	29578379.96	29328296.45	144516	-	140.443	0.0052	0.016
SD	3920605.634	3875478.431	22812.1	-	37.8818	0.0011	0.0023
CV%	13.3	13.2	15.8	-	27	21.4	14.5
Minimum	22066928.03	22019112.87	101000	0.25	97.685	0.0029	0.012
Median	29628474.58	29493534.64	138000	0.5	124.357	0.0056	0.015
Maximum	37536216.04	37261750.76	218000	4	239.684	0.0071	0.02
Geo mean	29320414.3	29074949.07	142886	-	136.279	0.0051	0.015
GCV%	13.6	13.6	15.2	-	24.4	24.4	14.7

For T_{max}, only n, median, minimum, and maximum are presented
0.25 hours time point is the PK blood sample collected at the end of infusion.

Table 7 - Bioequivalence Assessment (BP02-101)

Treatment Comparison/ Parameter	Cmax (ng/mL)	AUC(0-inf) (ng*h/mL)	AUC(0-t) (ng*h/mL)	Bioequivalence Criteria (Yes/No)*
BP02 Vs US-Herceptin (N=67) [Geometric LS Means (CV%)]				
BP02	148841.5 (16.1)	31382214.2 (16.5)	31198207.8 (16.5)	
US-Herceptin	142885.9 (15.2)	29320414.3 (13.6)	29074949.1 (13.6)	Yes
Total-Subject CV (%)	15.7	15.3	15.2	
(%)Ratio[90% CI]	104.17 [97.73, 111.03]	107.03 [100.59, 113.88]	107.30 [100.87, 114.15]	
BP02 Vs EU-Herceptin, (N=73) [Geometric LS Means (CV%)]				
BP02	148841.5 (16.1)	31382214.2 (16.5)	31198207.8 (16.5)	
EU-Herceptin	146821.2 (13.4)	29271598.4 (13.9)	29181126 (14.0)	Yes
Total-Subject CV (%)	14.8	15.2	15.3	
(%)Ratio[90% CI]	101.38 [95.71, 107.37]	107.21 [101.05, 113.74]	106.91 [100.76, 113.44]	
EU-Herceptin Vs US-Herceptin, (N=68) Geometric LS Means (CV%)				
EU-Herceptin	146821.2 (13.4)	29271598.4 (13.9)	29181126 (14.0)	
US-Herceptin	142885.9 (15.2)	29320414.3 (13.6)	29074949.1 (13.6)	Yes
Total-Subject CV (%)	14.3	13.8	13.8	
(%) Ratio [90% CI]	102.75 [96.99, 108.86]	99.83 [94.43, 105.55]	100.37 [94.92, 106.17]	

For Tmax, only n, median, minimum, and maximum are presented. 0.25 hours time point is the PK blood sample collected at the end of infusion.

Arithmetic mean (± SD) serum concentration time data for BP02 (trastuzumab), EU-Herceptin (trastuzumab), and US-Herceptin (trastuzumab) in both linear and semilogarithmic scale (PK analysis set) are presented in the figures below.

Figure 1 - Mean (SD) BP02 Serum Concentration-time Profiles by Scheduled Time on Linear Scale (Pharmacokinetic Analysis Set) - BP02-101

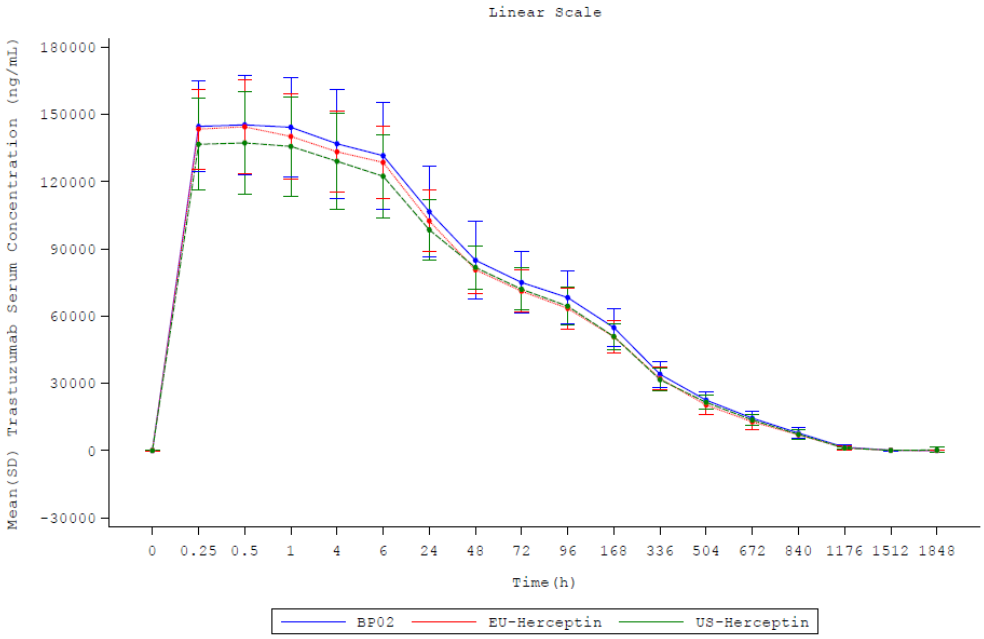
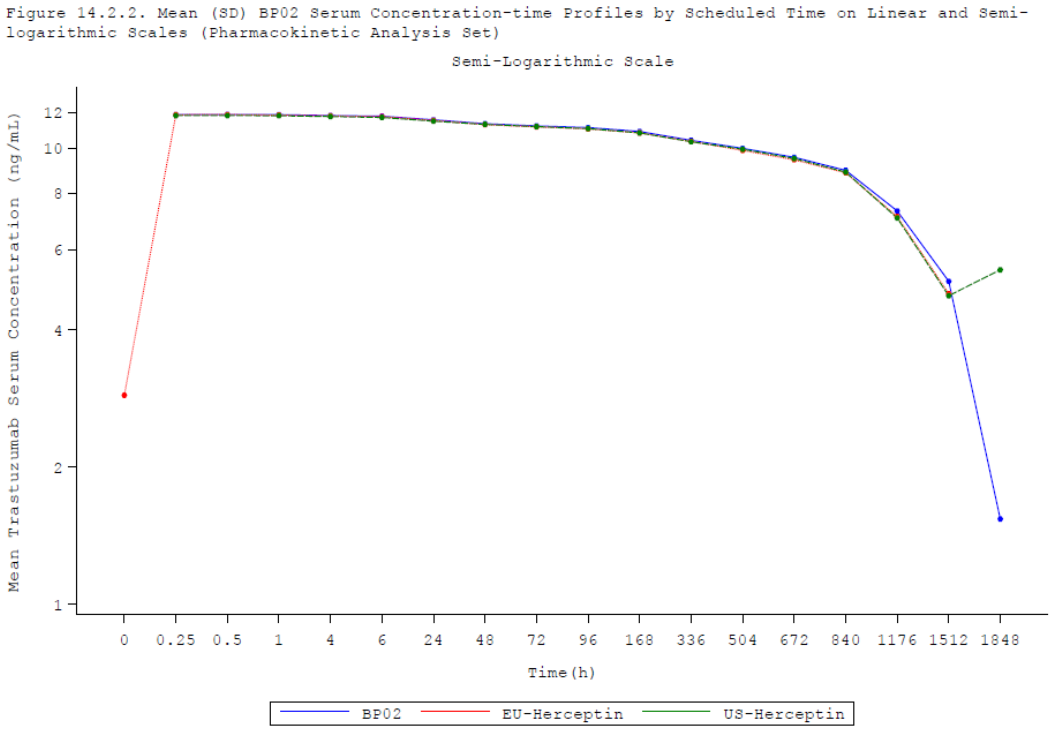


Figure 2 - Mean (SD) BP02 Serum Concentration-time Profiles by Scheduled Time on Semi-logarithmic Scale (Pharmacokinetic Analysis Set) – BP02-101



Scatter plots of AUC0-inf and Cmax of trastuzumab comparing treatment group and sites are provided below.

Figure 3 - Scotter plot for Cmax (ng/mL) by Center - BP02-101

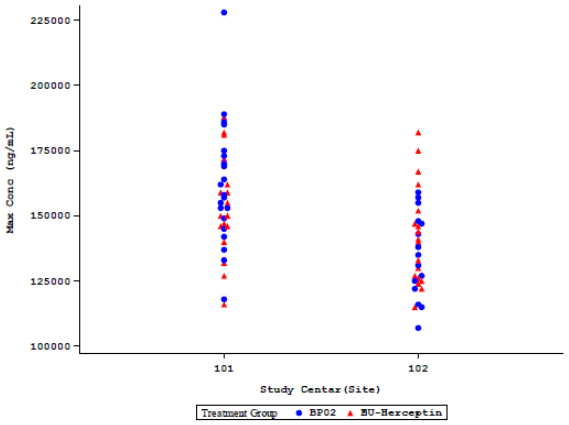
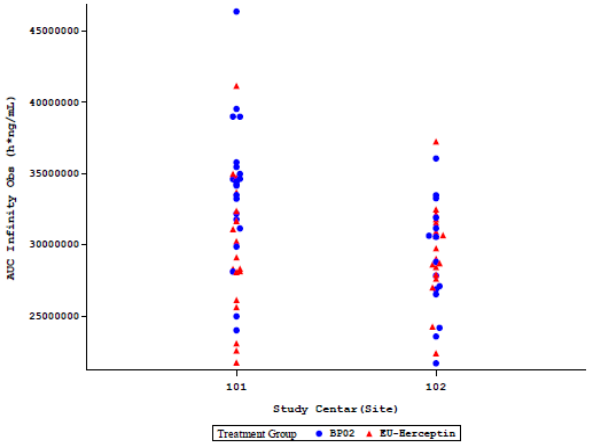


Figure 4 - Scotter plot for AUC0-inf (ng/mL) by Center - BP02-101



The applicant has performed an analysis including site as factor in the analysis model which provided in below table.

Table 8 - Biosimilarity Assessment including Site as Factor in the Analysis Model (Pharmacokinetic Analysis Set) -BP02-101

Treatment Comparison/ Parameter	Cmax (ng/mL)	AUC(0-inf) (ng*h/mL)	AUC(0-t) (ng*h/mL)	Biosimilarity Criteria (Yes/No)*
BP02(N=36) Vs EU-Herceptin(N=37)				
Geometric LS Means (CV%)				
BP02	148841.5 (16.1)	31382214.2 (16.5)	31198207.8 (16.5)	Yes
EU-Herceptin	146821.2 (13.4)	29271598.4 (13.9)	29181126 (14.0)	
Total-Subject CV (%)	13.2	14.4	14.5	
(%) Ratio [90% CI]	99.76 [94.73, 105.05]	105.83 [100.04, 111.96]	105.57 [99.76, 111.72]	
#P-value	0.136	0.016	0.018	

Note: *yes,if the 90% CI for geometric LSM ratios of ln-transformed parameters AUC(0-inf), AUC(0-t) and Cmax and falls within the acceptance range of 80.00% to 125.00% else No.; N = number of subjects; CV% = coefficient of variation; CI=Confidence Interval.

#P-value is evaluated to interaction effect Treatment Group*Center by using ANOVA model with Treatment Group, Center and Center*Treatment group at 5% level of significance, the P-values of Treatment Group*Center is found less than 0.05, hence Center and Center*Treatment group is retained as factors in the ANOVA model to evaluate 90% CI of GMR.

Table 9 - Biosimilarity Assessment by Site (Pharmacokinetic Analysis Set; BP02 vs EU-Herceptin) - BP02-101

Site	Parameter	BP02	EU-Herceptin	Total-Subject CV (%)	(%) Ratio	90% CI		Meet Biosimilarity Criteria
		GeoLSM (CV%)	GeoLSM (CV%)			Lower	Upper	
101 (N=39)	$AUC_{(0\text{-}inf)}$	33503891.8 (15.0)	29128789.1 (16.7)	15.8	115.02	105.65	125.22	No
	$AUC_{(0\text{-}t)}$	33260486.6 (15.0)	29015413.6 (16.8)	15.9	114.63	105.25	124.85	Yes
	C_{max}	160384.8 (14.3)	153427.2 (12.9)	13.7	104.53	97.11	112.53	Yes
102 (N=34)	$AUC_{(0\text{-}inf)}$	28635662.7 (14.3)	29407537.2 (11.1)	12.6	97.38	90.47	104.81	Yes
	$AUC_{(0\text{-}t)}$	28524045.1 (14.5)	29338989.5 (11.1)	12.7	97.22	90.29	104.69	Yes
	C_{max}	134063.1 (12.3)	140825.4 (12.9)	12.6	95.20	88.44	102.47	Yes

Note: *yes,if the 90% CI for geometric LSM ratios of ln-transformed parameters AUC(0-inf), AUC(0-t) and Cmax falls within the acceptance range of 80.00% to 125.00% else No.; N = number of subjects; CV% = coefficient of variation; CI=Confidence Interval; LS Means, Ratio and CI calculated using ANOVA model with treatment as fixed effect for Site 101 and Site 102.

Pharmacokinetics in the target population.

The Ctrough levels presented are from CR201-18 study, the pivotal phase III, multicentre, double-blind, 1:1 randomized, parallel-group, active-controlled study to compare the pharmacokinetics, efficacy, and safety of BP02 and EU-Herceptin in combination with docetaxel in induction phase and trastuzumab during maintenance phase in Asian-Indian patients only with HER2 positive metastatic breast cancer (MBC)

The Pharmacokinetic (PK) Population included patients who were randomized to the study treatment (ITT Set) and had at least one post dose drug concentration measurement, leading to 658 patients PK analysis was performed based on induction phase data. Measured concentration at the end of a dosing interval and prior to next dose administration (C_{trough}) data were descriptively summarized by visit and treatment group. No complete PK profile in the target population was obtained.

The following sampling time points were set: Sampling at Day 22 (cycle 2), Day 64 (cycle 4), Day 106 (cycle 6), Day 148 (cycle 8) and Day 169 (end of induction phase) within 5 minutes before infusion of each cycle were considered to report the trough concentrations. According to clinical study report Amendment 01, section 7.4, a time window of +3 days was allowed for blood drawl of C_{trough} concentrations.

Table 10 - Summary of Analysis Set - CR201-18

	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patients	**n (%)**	**n (%)**	**n (%)**
Intent-to Treat (ITT) Population	345 (100.0)	345 (100.0)	690 (100.0)
Per Protocol (PP) Population	314 (91.0)	323 (93.6)	637 (92.3)
Safety population (SAF)	345 (100.0)	345 (100.0)	690 (100.0)
Pharmacokinetic (PK) Population	327 (94.8)	331 (95.9)	658 (95.4)

C_{trough} data were descriptively summarized by visit and treatment group in Table 11 below.

Table 11: Summary of pharmacokinetic (PK) concentrations (ng/mL) - PK Population - CR201-18

Visit	Statistics	BP02 (N=327)	Herceptin (N=331)
Cycle 2 Day 22	n	310	313
	Arithmetic mean	14830.3	18323.6
	SD	20643.77	41899.84
	Arithmetic mean CV%	139.2	228.7
	Median	11450.0	11500.0
	Min, max	128, 193000	124, 616000
	Geometric mean	9427.9	9851.1
	Geometric mean CV%	142.8	163.9
Cycle 4 Day 64	n	277	293
	Arithmetic mean	15185.0	16061.5

	SD	14962.83	15614.26
	Arithmetic mean CV%	98.5	97.2
	Median	13100.0	13300.0
	Min, max	121, 151000	222, 137000
	Geometric mean	11308.3	12096.7
	Geometric mean CV%	108.5	97.6
Cycle 6 Day 106	n	252	273
	Arithmetic mean	15935.8	17755.1
	SD	22341.05	24292.17
	Arithmetic mean CV%	140.2	136.8
	Median	11250.0	13100.0
	Min, max	101, 204000	190, 198000
	Geometric mean	10076.7	11426.7
	Geometric mean CV%	133.2	127.1
Cycle 8 Day 148	n	236	263
	Arithmetic mean	16369.1	19183.9
	SD	12283.09	17874.73
	Arithmetic mean CV%	75.0	93.2
	Median	13800.0	16000.0
	Min, max	406, 117000	334, 137000
	Geometric mean	12938.6	14469.8
	Geometric mean CV%	90.2	94.4
End of Induction	n	253	265
	Arithmetic mean	17482.8	17467.7
	SD	14523.05	10376.85
	Arithmetic mean CV%	83.1	59.4
	Median	15000.0	16300.0
	Min, max	126, 133000	122, 56700
	Geometric mean	12328.9	13568.5
	Geometric mean CV%	138.3	105.3

The C_{trough} concentrations showed a very high variability (e.g., cycle 2, day 22; geometric mean CV% values ranging from 142.8% (BP02) to 163.9% (EU-Herceptin) with ranges of up to >1000-fold.

Analysis of variance (ANOVA) was performed on the log-transformed C_{trough} and geometric least-square means was calculated at each visit to evaluate the PK similarity and results are presented in Table below. The geometric mean ratios (GMR) and the 90% confidence intervals for GMR obtained for most of the visits were within the equivalence range of 0.80 to 1.25 except for the lower limit of 90%CI at Cycle 6 Day 106 and end of induction visit.

Table 12 - Analysis of Variance of Pharmacokinetic (PK) C_{trough}(ng/mL) Concentrations by Visit- PK Analysis Population – CR201-18

Visit	BP02 (N=327)		Herceptin (N=331)		GMR (BP02/Herceptin)	90% CI for GMR
	n	GLSM	n	GLSM		
Cycle 2 Day 22	310	9427.92	313	9851.12	0.96	0.83, 1.11
Cycle 4 Day 64	277	11308.33	293	12096.71	0.93	0.83, 1.05
Cycle 6 Day 106	252	10076.73	273	11426.72	0.88	0.76, 1.02
Cycle 8 Day 148	236	12938.58	263	14469.77	0.89	0.80, 1.00
End of Induction	253	12328.90	265	13568.46	0.91	0.79, 1.04
Note: Geometric LS Means (GLSM) are the exponentiated least-squares (LS) mean from the ANOVA. GMR (Geometric Mean Ratio) = (BP02/Herceptin).						

2.6.2.4. Pharmacodynamics

BP02 has been developed as a biosimilar product to the reference drug Herceptin (trastuzumab). BP02 is a humanized IgG1 monoclonal antibody directed against the human epidermal growth factor receptor-2 (HER2).

The Applicant provided an adequate justification for the absence of clinical PD studies, stating that PD studies were not performed as no PD markers have been validated for prediction of clinical efficacy of trastuzumab.

2.6.3. Discussion on clinical pharmacology

Two studies, a phase I study BP02-01 with the aim to demonstrate bioequivalence between the test- and reference product EU-Herceptin and used as the main study for establishing biosimilarity, and a phase III study CR201-18 in the target population aiming to confirm similarity in clinical efficacy, safety, and immunogenicity between BP02 and EU-Herceptin have been presented in support of this application

The primary PK endpoints selected to demonstrate PK similarity of BP02 to Herceptin in Study BP02-101 were AUC_{0-t}, AUC_{0-inf} and C_{max} in order to characterise the overall rate and extent. These proposed primary PK parameters are in accordance with the EMA/CHMP/BMWP/403543/2010 guideline. In the case of a monoclonal antibody using a long blood sampling, the residual area is very low and AUC_{0-inf} is very close to AUC_{0-t} parameter.

The bioanalytical methods used for the clinical study sample testing were developed and validated at Central laboratory and overall the methods were found to be fit for intended purpose.

The statistical methods are the standard methods and evaluation criteria recommended in the guideline on the Investigation of bioequivalence.

The reference product Herceptin is EU-sourced and is appropriate. The applied dose of 6 mg/kg is the recommended maintenance dose of trastuzumab at three-weekly intervals after an initial 8 mg/kg loading dose. A single dose is sufficient to detect any difference in clearance. Given that the clearance is independent of dose in the therapeutic dose range, any dose in this range is suitable for the study. This dose is therefore accepted and to establish PK similarity and is appropriate also from safety point of view.

The difference in the assayed content (protein concentrations) between the bio-batches of test and EU-reference products does not differ more than 5% (21.2 mg/mL and 21.8 mg/mL respectively). No dose-correction/adjustment is needed.

The method of administration is in line with reference product. Enough samples to adequately characterise the whole PK profile and estimate PK parameters of trastuzumab were collected, with sufficient sampling around predicted T_{max} to provide reliable estimate of peak exposure. The duration of study of 78 days is considered sufficient to reliably estimate PK parameters ($t_{1/2}$ is approximately 6 days). The sampling schedule covers the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure which is achieved as $AUC_{(0-t)}$ covers at least 80% of $AUC_{(0-\infty)}$. In the case of a monoclonal antibody with a long half-life and a potential for immunogenicity, a parallel design is adequate.

From an immunogenicity perspective (anti-drug antibodies in phase I studies), additional late blood samples could have been proposed to determine the presence of ADA against the product. However, given the low risk of immunogenicity of trastuzumab, the healthy population enrolled, the single dose administration and given the absence of positive ADA results in the available data, this is considered acceptable.

The selection of healthy male volunteers as population for the PK trial and the exclusion of female subjects is considered justified. The subject population has been selected with the aim of minimizing variability and permitting detection of differences between pharmaceutical products. This healthy population is the most sensitive population since there are fewer factors that could cause major inter-individual variability compared to patients (disease, age, treatments, co-morbidities). Target-mediated clearance is less important than in patients.

The sample size is adequate and has been selected to account for potential dropouts and provided 90% power overall and a true geometric mean ratio between 95 and 105%. The power calculation is for a 90% CI around the GMR to be in the 80-125% range with an alpha=0.05. It has been calculated taking into account the inter-subject coefficient of variation in both healthy volunteers and in patients. This is considered a conservative approach and is thus endorsed.

Both treatment groups were comparable with regards to demographic characteristics (race, age, weight, height) except a small difference in mean age.

Overall, 86 subjects (77.5%) had protocol deviations in the study. Of these, 24 subjects had major deviations and 70 subjects had minor deviations. The reported deviations were unlikely to have affected the results and conclusions of the study and safety of the subjects was not considered to be at risk.

For AUC_{0-t}, AUC_{0-inf} and C_{max}, the 90% confidence interval for the ratio of the test and reference product fell within the conventional bioequivalence acceptance range of 80.00-125.00% when comparing BP02 to the reference product from EU.

Since not only similarity in terms of absorption/bioavailability is of interest for monoclonal antibodies and since the risk of differences in elimination rate may be more likely, demonstration of comparability on clearance and/or half-life is encouraged as well. In this context, it is observed that T_{max}, the

terminal half-life, λz, and CL parameters were also similar across the groups. Additional statistical analysis is not requested for the secondary PK parameters (CL and t1/2). The volume of distribution is not evaluated. However, it is known that trastuzumab has a very small volume of distribution approaching that of the plasma (Levêque D et al. 2008). Vd data are not reported neither in the Dazublys SmPC nor in the Herceptin SmPC. Additionally, the applicant compared the secondary endpoints between treatment groups, and the results showed that the secondary PK parameters (T1/2, λz, CL/F) were all within the predefined bioequivalence interval of 80–125%.

Therefore, PK similarity and bioequivalence is considered to be adequately demonstrated being part of the step-wise biosimilarity exercise between BP02 and the EU reference product with respect to rate and extent of absorption following administration of a 6 mg/kg dose to healthy subjects in study BP02-101.

For the BP02-101 study, two GCP inspections were performed at both sites (New Zealand Clinical Research) by the US FDA in May 2017 and May 2021. The applicant has provided the outcome of GCP inspections carried out by FDA at study sites involved in the BP02-101 study after 2021 together with the inspection reports. In addition, the applicant adequately informed about the routine systems in place to ensure GCP compliance.

Using two sites for a PK study is unusual and revealed differences between centres. The Applicant conducted an analysis of the PK data and was unable to identify a difference in baseline demographic, or product quality imbalances that might explain the observed differences between sites. The parameters that could impact PK were balanced across the sites and treatment arms and no differences were found between the sites that could reasonably explain the observed differences in PK. The bioequivalence assessment demonstrated that BP02 was biosimilar to EU-Herceptin for the main parameters $AUC_{(0\text{-}t)}$ and C_{max} across both sites, except for AUC(0-inf) at Site 101. The $AUC_{(0\text{-}inf)}$ parameter at Site 101 showed a ratio of 115.02% with a 90% CI of 105.65% to 125.22%, which is outside the accepted biosimilarity range of 80% to 125%. No clear factors explained the differences between centres (baseline demographic, or product quality imbalances) and after these further evaluations the significant difference observed between centres is considered acceptable as the confidence intervals of the main parameters are within the acceptable range.

For the target population, in the pivotal phase III study CR201-18, only C_{trough} levels are presented from the induction phase.

It is noted that there were no pre-dose samples taken before cycle 1. Possible carry-over effects due to trastuzumab pre-dose concentrations would not be detected. From the exclusion criterion *"Patients received prior trastuzumab for adjuvant/ neoadjuvant therapy for breast cancer within 1 year prior to randomization"* it would be assumed, that there would be none.

The geometric mean concentration at the end of a dosing interval and prior to next dose administration (C_{trough}) at all visits were found to be comparable between both the arms, e.g., cycle 8 day 148, the geometric mean values are 12938.6 ng/mL (BP02) and 14469.8 ng/mL (EU-Herceptin) with corresponding geometric mean CV% values of 90.2% and 94.4%, respectively. As supportive evidence of PK similarity in patients to claim that these values are comparable, the applicant provided a statistical comparison of the geometric mean serum concentrations of each sampling time point and the calculable PK parameters (C_{min}). As a result, the geometric mean ratios (GMR) and the 90% confidence intervals for GMR obtained for most of the visits were within the equivalence range of 0.80 to 1.25 except for the lower limit of 90%CI at Cycle 6 Day 106 and end of induction visit.

The C_{trough} concentrations showed a very high inter-subject variability [e.g., cycle 2, day 22; geometric mean CV% values ranging from 142.8% (BP02) to 163.9% (EU-Herceptin)] up to 229% with ranges of up to >1000-fold, hampering adequate assessment. The variability might possibly result from, e.g.,

the number of different study sites or incorrect time points of blood draws for the measurement of C_{min}. The applicant provided a discussion on the high inter-subject variability observed in the CR201-18 study. Baseline characteristics known to serve as covariate for trastuzumab PK profile were compared, i.e. bodyweight of subjects and disease burden as evaluated by metastatic sites. Additionally, regarding the other covariate, the baseline disease burden with metastasis involvement was found slightly higher compared to the other approved trastuzumab biosimilar. The applicant regarded the higher disease burden as the reason for the high variability observed in the metastatic breast cancer population. The higher inter-subject variability due to a less homogenous population in patients compared to healthy volunteers can be followed.

Based on descriptive statistics, despite the very high variability, it could be observed that for both treatment groups, the (arithmetic) mean trough concentrations obtained at the subsequent cycles increased slightly with time (from 14830 ng/mL in cycle 2 to 17483 ng/mL at the end of induction), suggesting achievement of steady state.

After excluding the outliers from C_{trough} values geometric mean CV% values were lower Compared to other conducted biosimilarity studies in patients the arithmetic CV% values were overall comparable after excluding the outliers.

Taking into account the population predicted steady state PK exposure values of Herceptin IV dosing regimens in MBC, there is a clear discrepancy compared with the presented values. In the originator's published data for Herceptin, C_{min} at steady state shows 44.2 µg/mL (~44200 ng/mL) compared to significantly lower values in study CR201-18 of 12938.6 ng/mL for the test product and for the reference product (which is in case the same product, EU-Herceptin) 14469.8 ng/mL, as well. The applicant assumed that the difference of C_{min} values in the present study might be due to the low body weight in the Asian-Indian patient population in the present study. As the applicant stated, a published study of population PK and covariate analysis for IV Trastuzumab in solid tumours showed that weight is the covariate with largest influence on Trastuzumab PK. This argumentation can be followed.

The mechanism of action has been briefly described by the Applicant and no clinical PD studies were conducted using BP02.

Even though no PD markers were studied during the clinical studies, the approach to PD is in general acceptable as the medicinal product has been developed as a biosimilar. As the mechanism of action is similar across the target patient populations (HER2+ early breast cancer, metastatic breast cancer and metastatic gastric cancer) extrapolation to the other indications "HER2+ early breast cancer" or "gastric cancer" of the reference product (not investigated with BP02) is considered acceptable.

Formal studies to assess the potential drug-drug interaction have not been carried out. This is acceptable for a biosimilar application.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology package proposed for supporting this submission is the standard package provided for a trastuzumab biosimilar application and is acceptable.

From a clinical pharmacology point of view biosimilarity between BP02 and EU-Herceptin can be concluded and the application is approvable based on the current data.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

No dose response study was conducted.

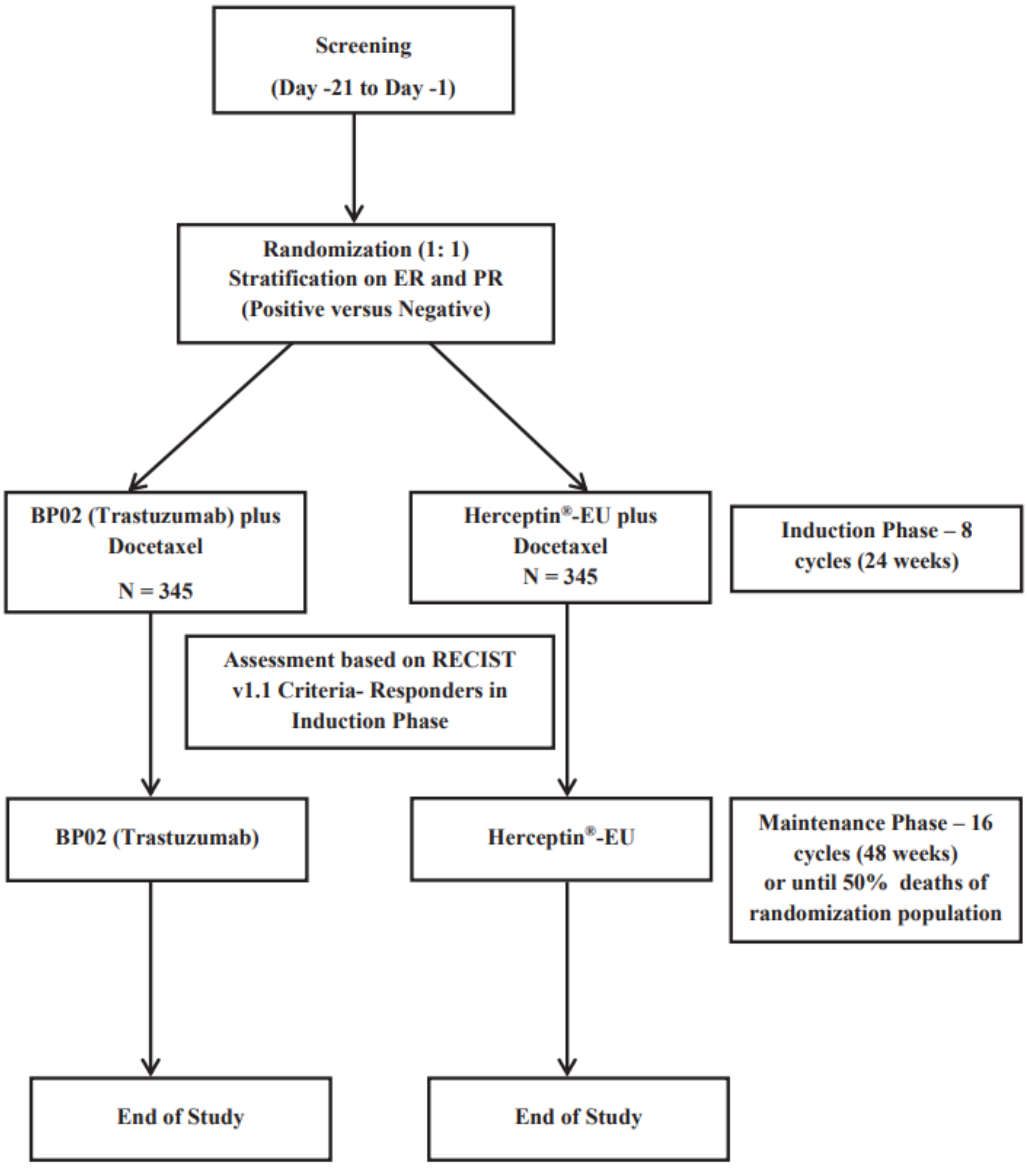
2.6.5.2. Main study(ies)

Study CR201-18

Phase III equivalence study CR201-18 is a double-blind, 1:1 randomized-controlled, multicentre, single–country study to compare the pharmacokinetics, efficacy and safety of BP02 (trastuzumab) and EU-Herceptin in combination with docetaxel in induction phase and BP02 or EU-Herceptin during maintenance phase in 690 Indian female patients with HER2 positive metastatic breast cancer (MBC) without previous systemic treatment for metastatic disease.

The study consists of two treatment periods: induction phase (Period I) and maintenance phase (Period II). Primary endpoint is best overall response rate in the induction phase (24 weeks), aiming at a predefined equivalence margin of 95% CI for BP02 of +/- 13 % from EU-Herceptin in 59 investigational sites in India from 23 September 2020 (first patient randomized) to 16 September 2022 (last patient randomized). The maintenance phase of the study was completed on 6 April 2024.

Figure 5 - Study design - CR201-18



Abbreviations: N = number of subjects; EU = European approved, Source: Summary of Safety, page 87.

Methods

Study Participants

Key Inclusion Criteria

Inclusion criteria included the following.

Cancer Related:

1. Locally recurrent or MBC with systemic metastasis that is not amenable to curative surgery and/or radiation.

2. Patients had histologically/ cytologically confirmed HER2+ metastatic breast cancer by immunohistochemistry (IHC 3+ or IHC 2+). When the IHC result is equivocal (defined > as 2+ score), patient with a positive FISH or CISH result at screening based on either a local or central laboratory report available before randomisation.

3. Patients had at least one measurable lesion as per Response Evaluation Criteria in Solid Tumors (RECIST) guideline v1.1 at screening. 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.

4. Patients who had received adjuvant radiotherapy or chemotherapy as part of treatment of EBC and LABC are eligible, if the last fraction of radiotherapy was administered ≥ 04 weeks prior to randomization provided target lesions are outside the irradiated field and have recovered from radiation toxicity and last dose of chemotherapy was administered at least 3 months prior to randomization.

5. Patient who had received radiotherapy ≥ 4 weeks prior to randomization should also be considered as eligible for the study provided the study target lesions must be outside the irradiated field and patients must have recovered from the radiation toxicity.6. Patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (both inclusive) at screening.

7. Patients had life expectancy of more than 18 months in the opinion of the investigator.

8. Prior treatment with hormonal agents or bisphosphonates/denosumab are allowed. Bisphosphonates/denosumab was given simultaneously with study treatment but cannot start after randomisation and was considered an indication of progressive disease (PD). Hormonal agents are discontinued prior to beginning study therapy.

9. Patients had not received blood transfusion within 2 weeks prior to randomisation.

General Inclusion Criteria:

10. Female patients aged between18 to 75 years (both inclusive) at the time of screening.

11. Signed informed consent obtained prior to initiation of any study specific procedures and treatment as confirmation of the patient’s awareness and willingness to comply with study requirements.

12. Women of child-bearing potential were non-lactating and had a negative pregnancy test at screening. 11. Patients of childbearing potential agreed to pregnancy prevention throughout the duration of the study.

13. Females used acceptable and effective methods of contraception.

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

15. Adaequate renal and hepatic function (Serum Creatinine ≤ 1.5 times X ULN; Serum Bilirubin ≤ 1.5 times X ULN). Haematology: ANC t 1500/µL; Platelet count 100,000/µL; Haemoglobin ≥ 8.5 g/dL.

16. Patient who has liver metastasis must have adequate organ function defined as: bilirubin ≤ 3 x upper limit of normal (ULN), alkaline phosphatase, alanine transaminase and aspartate transaminase ≤ 5 x ULN.

Exclusion Criteria

Patients who met any of the following criteria were excluded from this study:

Prior, Current, or Planned Treatment:

1. Patients who had history of exposure to the following cumulative doses of anthracyclines during their lifecycle: doxorubicin/ liposomal doxorubicin > 400 mg/m2, epirubicin > 800 mg/m2, mitoxantrone > 120 mg/m2

2. Patients received prior trastuzumab for adjuvant/ neoadjuvant therapy for breast cancer *within 1 year prior to randomisation*.

3. Patients received any therapy prior for metastatic disease except hormonal therapy, bisphosphonates therapy for bony metastasis/ osteoporosis and palliative radiotherapy for alleviating bony metastasis.

Cancer Related:

4. Patients had metastases to brain and spinal cord

5 Patients with any other cancer (i.e., contralateral breast cancer, within 5 years prior to screening-exception of treated ductal cancer or cervical cancer or basal or squamous cell cancer of skin)

Trastuzumab Exclusion Criteria:

6. Patients with history of symptomatic chronic heart failure (New York Heart Association [NYHA] Classes II−IV) or serious cardiac arrhythmia requiring treatment.

7. Patients with history of myocardial infarction or unstable angina within 6 months prior to enrolment.

8. Patients with uncontrolled hypertension as per investigator's discretion.

Treatments and trial intervention

Period I: Induction Phase (combination therapy): Patients received either study drug BP02 (trastuzumab) in combination with docetaxel 75 mg/m² or Herceptin in combination with docetaxel 75 mg/m² every 3 weeks (1 cycle) for a maximum of 8 cycles (24 weeks of combination treatment). In cycle 1, a loading dose of 8 mg/ kg on the first day of treatment was administered. From cycles 2 to 8, 6 mg/ kg doses of trastuzumab were administered.

Again, a reloading dose of trastuzumab (8 mg/kg) was given if the patient has missed a dose of trastuzumab by more than one week. If the patient has missed a dose of trastuzumab by one week or less, then the usual maintenance dose (6 mg/kg) was administered every 3 weeks.

Period II: Maintenance phase (monotherapy): Patients with at least stable disease after induction (CR or PR or stable disease as assessed by RECIST 1.1) were eligible to continue blinded medication (BP02 or Herceptin) until disease progression or discontinuation. If there was no evidence of disease progression, patients could continue treatment with BP02 (trastuzumab) or Herceptin q3W for a maximum of 16 cycles (48 weeks) or until 50% of the randomised population had died, whichever came first.

Palliative radiotherapy for bone metastatic pain was allowed during this phase if deemed necessary by the investigator and if disease progression was completely excluded. Tumour assessments were performed at cycle 13, cycle 17, cycle 21 and at the end of the study or in case of patient withdrawal from the study, withdrawal of consent, unacceptable toxicity, or loss to follow-up.

Concomitant medication and adverse event monitoring were to be performed throughout the maintenance phase. ADA assessments, laboratory investigations, ECG, ECOG performance status and

2D ECHO/MUGA tests, physical examination, vital signs and body weight/body surface area measurements were performed at all visits.

ECG (12-lead) and 2D ECHO/MUGA: A 12-lead ECG was recorded at the screening visit and this was interpreted by the PI to confirm the normal or abnormal result. Abnormalities were recorded in the patient's medical record, and these formed the baseline assessments and other specified visits according to the schedule of events or at the time of withdrawal. LVEF assessments were performed by 2D ECHO/MUGA measurement at screening and as specified in the schedule of events or at the time of withdrawal. If the LVEF percentage fell ≥10 points from baseline to below 50%, treatment was discontinued and a repeat LVEF assessment was performed within approximately 3 weeks. If LVEF did not improve or declined further, or if symptomatic CHF developed, discontinuation of trastuzumab was strongly considered, unless the benefits to the individual patient were deemed to outweigh the risks at the discretion of the investigator. All such patients were referred to a cardiologist for follow-up. If symptomatic heart failure developed during trastuzumab therapy, it was treated with standard heart failure medications.

Concomitant and rescue therapies

During the trial, corticosteroids were allowed as pre-medication, topical applications (e.g. for rash), inhaled sprays for obstructive airways disease and GCSF as prophylaxis for neutropenia, and bisphosphonates or denosumab (if started before randomisation). In addition, any other nonprohibited medication or treatment deemed necessary. Hormonal therapy for HR+MBC subjects was only allowed in the maintenance phase if indicated by the investigator. No other chemotherapy, immunotherapy, or experimental drug, including alternative drug regimens, was allowed while patients were enrolled in the trial. Caution was advised if docetaxel was administered concomitantly with cytochrome P450-3A inhibitors such as cyclosporine, ketoconazole and erythromycin and a strong CYP3A4 inhibitor.

Objectives

Primary:

To compare the Objective Response Rate (ORR) at end of cycle 8 of BP02 (Dazublys) and EU-Herceptin when administered in combination with docetaxel in patients with HER2-Positive MBC at week 24.

Secondary:

To assess the Progression Free Survival (PFS) and Overall Survival (OS) of BP02 (Dazublys) as compared to Herceptin EU in patients with HER2-positive MBC and to assess the safety profile of BP02 (Dazublys) as compared to EU- Herceptin

Table 13 - Estimands for primary objective - CR201-18

Population	**Patients with HER2 Positive Metastatic Breast Cancer (MBC) (for further details see in/exclusion criteria)**
Treatment condition	Assignment to BP02 (trastuzumab) in combination with docetaxel, regardless of temporarily pausing or missed doses of BP02 and docetaxel delay/discontinuation vs Assignment to Herceptin in combination with docetaxel, regardless of temporarily pausing or missed doses of Herceptin and docetaxel delay/discontinuation
Endpoint (variable)	Objective Response (OR) at week 24 Phase
Population-level summary	Difference in Objective Response Rate (ORR) at the week 24
Intercurrent events and strategy to handle them	
Temporary discontinuation of Trastuzumab	Treatment policy
Permanent discontinuation of Trastuzumab	While-on-treatment
Docetaxel delay/discontinuation	Treatment policy

The targeted estimand is the difference in best ORR at week 24 between BP02 (trastuzumab) combined with docetaxel and Herceptin combined with docetaxel in patients with HER2+ Metastatic Breast Cancer, while being on treatment with trastuzumab, regardless of temporary discontinuation of trastuzumab and docetaxel delay or discontinuation.

Outcomes/endpoints

Primary endpoint

Best Objective Response Rate (ORR) by BICR at week 24 of BP02 (Dazublys) and Herceptin when administered in combination with docetaxel in patients with HER2-positive MBC. A predefined equivalence margin of [-13%, +13%] was deemed to represent a clinically acceptable difference with respect to the ORR. Confirmation of response was not planned.

Secondary Endpoints

Progression Free Survival (PFS)

PFS was defined as the time from the date of first dose to subsequent confirmed progression according to RECIST 1.1, derived in months. Patients without progression were censored at the date of last tumour assessment. Patients were administratively censored at the end of induction if no progression or other censoring occurred before the end of induction. The Kaplan-Meier (KM) method was used to assess PFS, estimate the PFS rate and 95% confidence intervals (CI) of the PFS rate. A two-sided log-rank test was used to compare PFS between the two treatment groups. Kaplan-Meier figures were presented stratified by treatment group. The estimate of median PFS (in months) was reported along with the p-value from the log-rank test at the 5% significance level comparing the PFS distributions of the two treatments.

Cox's proportional hazards model with treatment group and stratification factor of estrogen and progesterone receptor status (positive versus negative) was used to estimate the hazard ratio and its 95% CIs of BP02 (trastuzumab) versus Herceptin at week 24.

Overall Survival (OS)

OS was defined as the time from the date of the first dose to subsequent death, derived in months. Patients alive during the trial were censored at the date of last contact. The KM method was used to assess the OS rate and confidence intervals of the OS rate. A two-sided log-rank test was used to compare OS between the two treatments. Kaplan-Meier figures stratified by treatment group were presented. The estimate of median OS time was reported along with the p-value from the log-rank test at the 5% significance level comparing the OS distributions of the two treatment groups. This analysis was performed at the end of the induction phase and included all patients who were ongoing and censored at that time. Patients were administratively censored at the end of induction if no death was documented prior to this time point. Cox's proportional hazards model with treatment group and stratification factor of estrogen and progesterone receptor status (positive versus negative) was used to estimate the hazard ratio and its 95% CIs between BP02 (Dazublys) and Herceptin at week 24.

3. To assess the safety profile of BP02 (Dazublys) as compared to Herceptin.

4. To assess the potential immunogenicity of BP02 (Dazublys) as compared to Herceptin.

5. To compare the Ctrough of BP02 (Dazublys) and Herceptin when administered in combination with docetaxel in induction phase.

Sample size

The sample size is assessed based on the following estimates considered from the Trazimera European Public Assessment Report: Power = ≥ 85 %; Significance Level = 2.5%; ORR of 60 %; Equivalence Margin (0.80-1.25) for risk ratio and (-13%, +13%) for risk difference. Based on above estimates, a sample size of 630 patients (315 in each arm) would be sufficient to establish equivalence between the formulations. However, considering the 10% dropout / withdrawals due to adverse events or noncompliance or due to personal reasons, a sample size of 690 patients (345 in each arm) were enrolled.

Randomisation and blinding (masking)

All eligible patients were centrally randomized in a 1:1 fashion through IWRS based on stratification estrogen and progesterone receptor status (positive versus negative) to receive either BP02 (trastuzumab) in combination with docetaxel or Herceptin in combination with docetaxel every 3 weeks (1 cycle) for a maximum of 8 cycles (24 weeks of combination treatment) after completion of all screening procedures. ER+PR+, ER+PR- and PR+ER- were considered as hormonal positive cases and ER-PR- was considered as hormonal negative cases. Site of metastases and disease-free interval after adjuvant therapy were not used as stratification factors despite recommendation in the advice.

Since this is a double-blind study, it was ensured that the patient and investigator/ research team could not differentiate between test, reference, and placebo. Blinding of investigational products was done by the third-party vendor, as per their standard procedures and the procedure was detailed in batch packing record. No study staff were identified as being unblinded.

Statistical methods

Intent-to Treat (ITT) Population: The ITT population is defined as the patients who are randomized to the study treatment. The ITT set was used for primary efficacy conclusion and other efficacy analysis.

Per Protocol (PP) Population: The PP set is defined as the patients who are randomized and have at least one post baseline tumour assessment with no major protocol deviations. The list of protocol deviations was determined based on blinded data review prior to data base lock. Efficacy analysis were presented on PP population as well.

Per Protocol 2 Population: Post hoc defined as a reaction on comments in the routine GCP inspection. The PP2 is defined as the randomised patients without dosing delay of more than 7 days and without a potential re-loading dose of 8 mg/kg. Sensitivity primary endpoint analysis was performed using this population.

Pharmacokinetic Population: Patient who are randomized and have completed the study (PP set) and have at least one post dose drug concentration measurement will be considered for population PK analysis.

Safety Population: All the patients who are randomized and have received at least one dose of the study treatment will be considered as safety population. Safety population will be considered for safety analysis including immunogenicity testing.

The risk ratio of ORRs (BP02 (trastuzumab)/ Herceptin-EU) and risk difference of the ORRs was used to determine if BP02 is equivalent to Herceptin-EU. These analyses were performed using ITT population. Sensitivity analysis was performed using PP population.

No imputation was done in this study for missing data for efficacy endpoints evaluation. If a patient qualifies for inclusion into an efficacy analysis population (i.e., ITT population) but has no post randomization independent radiologist reviewed evaluation, then the patient was categorized as a non-responder for the primary endpoint analysis.

Approach using Risk Difference:

A two one-sided test procedure was used to test this hypothesis. This analysis used was the ITT population. The 95% CI for ORR difference between BP02 (trastuzumab) and Herceptin was estimated and compared to the margin [-13%, +13%], which is deemed to represent a clinically acceptable difference with respect to the ORR.

The risk difference in objective response rate between two treatment arms and associated 95% confidence intervals was provided with the use of Hauck-Anderson method. Risk difference and associated 95% confidence intervals was also provided using the test for the common risk difference by using the stratified Mantel-Haenszel method, stratified by the stratification factor of oestrogen and progesterone receptor status (positive versus negative).

Approach using Risk Ratio:

A two one-sided test procedure was used to test this hypothesis. This analysis used the ITT population. The 90% CI for the ORR ratio between BP02 (trastuzumab) and Herceptin was estimated and compared to the margin [0.80, 1.25], which is deemed to represent a clinically acceptable difference with respect to the ORR.

The two-sided Cochran-Mantel-Haenszel test stratified by oestrogen and progesterone receptor status (positive versus negative) was used to compare the objective response rate between two treatment arms.

The two-sided 95%CI of ORR difference between BP02 (trastuzumab) and Herceptin is

equivalent to the two one sided test (TOST) at 2.5% significance level. One primary efficacy variable is defined in this study, which is being analysed at week 24 database lock and there is no multiplicity adjustment required.

Progression free survival (PFS) is defined as the time from the date of first dose to subsequent confirmed progression per RECIST 1.1, derived in months. Subjects that did not experience the progression were censored at the date of last tumour assessment. Patients were administratively censored at week 24 if no progression or other censoring appeared prior to week 24. The Kaplan-Meier (KM) method was used to assess the PFS, to estimate the PFS rate, and the confidence intervals of PFS rate. A two-sided log-rank test was used to compare the PFS between the two treatment groups.

Cox's proportional hazards model with treatment group and stratification factor of oestrogen and progesterone receptor status (positive versus negative) were used to estimate the hazard ratio and its 95% CI of BP02 (Dazublys) compared to Herceptin at week 24 phase and end of study.

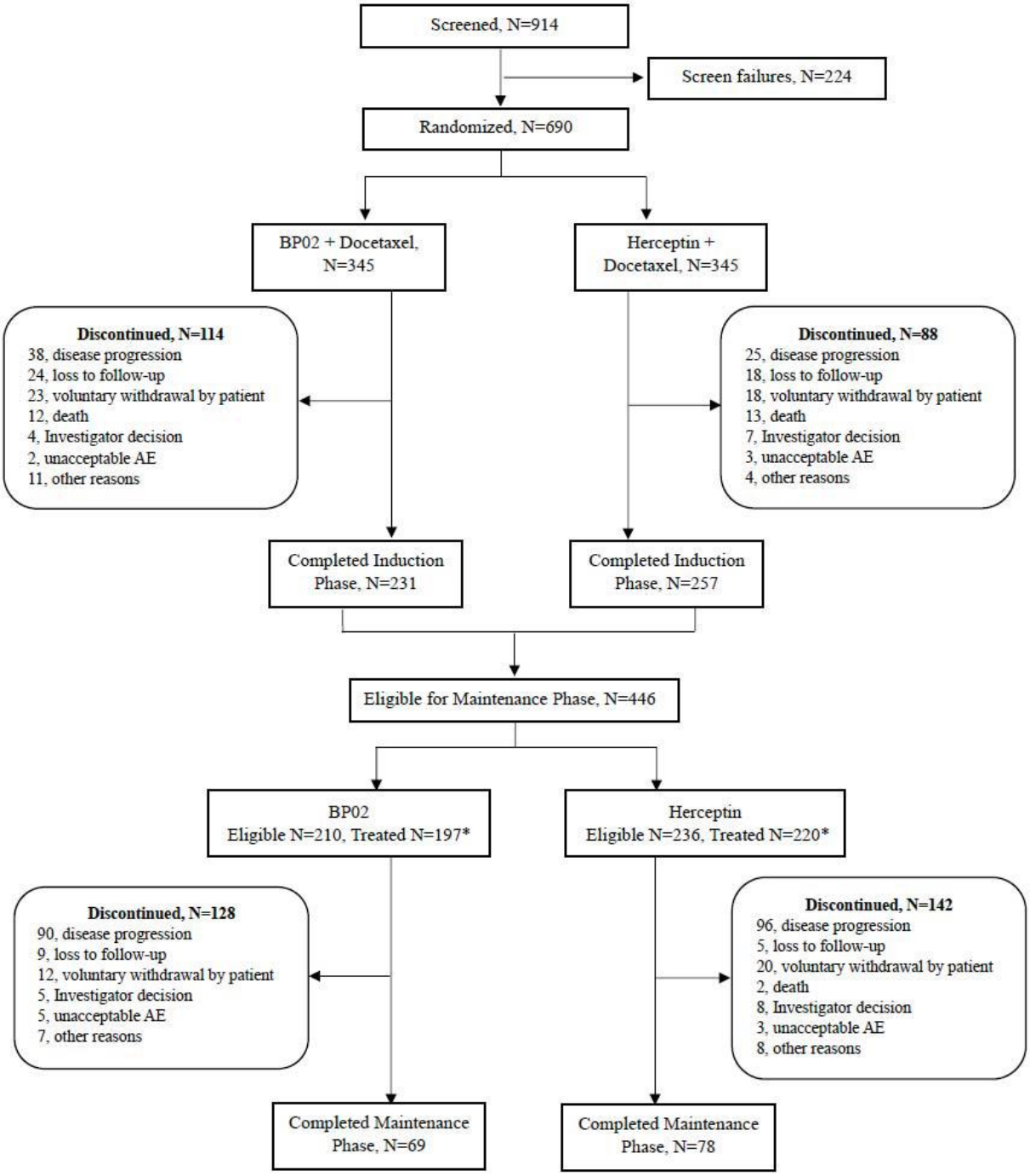
Overall survival (OS) is defined as the time from date of first dose to subsequent death, derived in months. Subjects that do not die during the study were censored at the date of last contact. Patients were administratively censored at week 24 if no death appeared prior to this time point. OS was analysed in the same way as PFS.

Results

Participant flow

A total of 914 patients were screened at 59 study sites, of which 224 were screen failures, with failure to meet criteria being the main reason (94.2%). A total of 488 (70.7%) patients completed the induction phase of the study, with 202 (29.3%) patients discontinuing treatment: 114 (33%) patients in the test arm and 88 (25.5%) patients in the reference arm discontinued treatment, leaving 231 (67%) and 257 (74.5%) patients who completed the induction phase.

Figure 6 - Participant flow – CR201-18



Protocol deviations reported in study CR201-18 were categorized into minor and major, see table below:

Table 14 - Protocol Deviations (Induction period) – CR201-18

Number of patients (%)	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
	n (%)	n (%)	n (%)
Patients with Minor Protocol Deviations	250 (72.5)	246 (71.3)	496 (71.9)
Patients with Major Protocol Deviations	5 (1.4)	1 (0.3)	6 (0.9)
Patients with Major Protocol Deviations that exclude them from PPS	5 (1.4)	1 (0.3)	6 (0.9)
Minor Protocol Deviations	**250 (72.5)**	**246 (71.3)**	**496 (71.9)**
Assessment Related	100 (29.0)	88 (25.5)	188 (27.2)
IMP Related	1 (0.3)	0	1 (0.1)
Procedure Related	21 (6.1)	20 (5.8)	41 (5.9)
Visit Related	215 (62.3)	216 (62.6)	431 (62.5)
Visit Related and Procedure Related	7 (2.0)	3 (0.9)	10 (1.4)
Visit Related and Assessment Related	1 (0.3)	2 (0.6)	3 (0.4)
Major Protocol Deviations	**5 (1.4)**	**1 (0.3)**	**6 (0.9)**
Visit Related	5 (1.4)	1 (0.3)	6 (0.9)

Table 15 - Summary of Out of Window Tumour Assessments (ITT Population) – Subset Analysis – CR201-18

Parameter, n (%)	BP02 (N = 345)	EU-Herceptin (N = 345)
At least 1 to 6 Out of Window Tumour Assessment		
At least 1 Out of Window Tumour Assessment	99 (28.7)	115 (33.3)
< -3 days	59 (17.1)	75 (21.7)
≥ 3 days	48 (13.9)	52 (15.1)
At least 2 Out of Window Tumour Assessments	29 (8.4)	35 (10.1)
< -3 days	18 (5.2)	22 (6.4)
≥ 3 days	5 (1.4)	4 (1.2)
At least 3 Out of Window Tumour Assessments	4 (1.2)	11 (3.2)
< -3 days	1 (0.3)	8 (2.3)
≥ 3 days	1 (0.3)	1 (0.3)
At least 4 Out of Window Tumour Assessments	0	1 (0.3)
< -3 days	0	1 (0.3)
At least 5 Tumor Assessment Delay	0	1 (0.3)
< -3	0	1 (0.3)
At least 6 Out of Window Tumour Assessments	0	1 (0.3)
< -3 days	0	1 (0.3)

Recruitment

The study was conducted from 23 September 2020 (first patient randomised) to 16 September 2022 (last patient randomised). The soft-lock date for the end of the induction phase was 06 June 2023. The maintenance phase was completed on 6 April 2024.

Conduct of the study

Initially in a "Part A", 176 patients with HER-2-positive early breast cancer were to receive BP02 (Dazublys) in a Phase III study in the neoadjuvant setting with tpCR rate as the endpoint. Following the clinical study report, a separate part of the CR201-18 study was suspended with amendment-from 01 09.09.21 and no patients with EBC were enrolled.

Baseline data

The Phase III CR201-18 study included only Asian Indian women and was conducted at 59 sites in India.

Table 16 - Summary of demographic details ITT population – CR201-18

Demographic Variable	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Age (years)			
n	345	345	690
Mean	51.2	50.2	50.7
SD	10.24	10.29	10.27
Minimum	22	24	22
Median	52.0	50.0	51.0
Maximum	74	74	74
Age Group			
n	345	345	690
<= 65 years	311 (90.1)	311 (90.1)	622 (90.1)
> 65 years	34 (9.9)	34 (9.9)	68 (9.9)
Gender			
Female	345 (100)	345 (100)	690 (100)
Race			
n	345	345	690
Asian Indian	345 (100)	345 (100)	690 (100)
Asian	0	0	0
American Indian	0	0	0
Caucasian or White	0	0	0
Black or African American	0	0	0
Other	0	0	0
Weight (kg)			
n	345	345	690
Mean	56.51	57.57	57.04
SD	11.762	12.824	12.307
Minimum	32.9	29.0	29.0
Median	55.00	56.00	55.05
Maximum	96.0	118.0	118.0
Height (m)			
n	345	345	690
Mean	1.513	1.521	1.517
SD	0.0643	0.0654	0.0649
Minimum	1.30	1.22	1.22
Median	1.510	1.520	1.520
Maximum	1.69	1.72	1.72

BMI (kg/m²)			
n	345	345	690
Mean	24.679	24.855	24.767
SD	4.9569	5.1520	5.0525
Minimum	13.22	11.05	11.05
Median	24.240	24.350	24.300
Maximum	41.01	46.09	46.09

Table 17 - Summary of baseline disease characteristics-ITT population – CR201-18

Disease Characteristics	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Diagnosis of HER2+breast cancer n (%)			
Yes	345 (100)	345 (100)	690 (100)
No	0	0	0
Time (days) duration since diagnosis to screening in the study			
n	345	345	690
Mean	220.1	243.6	231.8
SD	424.85	461.53	443.40
Minimum	1	-6	-6
Median	32.0	26.0	29.0
Maximum	3114	3108	3114
Last HER2 IHC Score			
n	345	345	690
Mean	2.9	2.9	2.9
SD	0.29	0.30	0.30
Minimum	2	2	2
Median	3.0	3.0	3.0
Maximum	3	3	3
HER2 FISH/CISH Status n (%)			
Positive	31 (9.0)	35 (10.1)	66 (9.6)
Negative	0	0	0
Not Applicable	314 (91.0)	310 (89.9)	624 (90.4)
ER & PR Status n (%)			
ER/PR Positive	95 (54.3)	96 (51.6)	191 (52.9)
ER/PR Negative	79 (45.1)	89 (47.8)	168 (46.5)
ER Low Positive	1 (0.6)	1 (0.5)	2 (0.6)
ECOG Performance Status			
0	97 (28.1)	84 (24.3)	181 (26.2)
1	239 (69.3)	246 (71.3)	485 (70.3)
2	9 (2.6)	15 (4.3)	24 (3.5)
History of Tumor Excision			
Yes	153 (44.3)	142 (41.2)	295 (42.8)
No	192 (55.7)	203 (58.8)	395 (57.2)
Site of disease			
Liver Metastases	182 (52.8)	174 (50.4)	356 (51.6)
Bone Metastases	164 (47.5)	158 (45.8)	322 (46.7)
Visceral Metastases	331 (95.9)	326 (94.5)	657 (95.2)
Prior anti-cancer therapy			

Treatment Naïve MBC Patients	175 (50.7)	187 (54.2)	362 2.5)
Patients with at least one anti-cancer treatment	98 (28.4%)	109 (31.6%)	207 (30.0%)
Patients with at least one chemotherapy	92 (26.7%)	99 (28.7%)	191 (27.7%)
Patients with at least one radiotherapy	41 (11.8%)	46 (13.3%)	87 (12.6%)
Patients with at least one hormonal therapy	18 (5.2%)	22 (6.4%)	40 (5.7%)
Patients with at least one biological therapy	3 (0,9%)	1 (0.3%)	4 (0,6%)

Table 18 - Summary of Medical History and Current Co-morbid Medical Conditions – CR201-18

System Organ Class	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patient's	**n (%) #E**	**n (%) #E**	**n (%) #E**
Overall	215 (62.3) 347	224 (64.9) 345	439 (63.6) 692
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	160 (46.4) 163	156 (45.2) 157	316 (45.8) 320
Vascular disorders	51 (14.8) 51	57 (16.5) 58	108 (15.7) 109
Metabolism and nutrition disorders	46 (13.3) 50	47 (13.6) 50	93 (13.5) 100
Blood and lymphatic system disorders	13 (3.8) 15	22 (6.4) 23	35 (5.1) 38
General disorders and administration site conditions	10 (2.9) 11	13 (3.8) 13	23 (3.3) 24
Endocrine disorders	10 (2.9) 10	9 (2.6) 9	19 (2.8) 19
Respiratory, thoracic and mediastinal disorders	7 (2.0) 8	7 (2.0) 10	14 (2.0) 18
Infections and infestations	6 (1.7) 6	6 (1.7) 6	12 (1.7) 12
Reproductive system and breast disorders	9 (2.6) 9	3 (0.9) 3	12 (1.7) 12
Gastrointestinal disorders	5 (1.4) 5	5 (1.4) 6	10 (1.4) 11
Musculoskeletal and connective tissue disorders	5 (1.4) 5	3 (0.9) 3	8 (1.2) 8
Nervous system disorders	3 (0.9) 3	2 (0.6) 2	5 (0.7) 5
Eye disorders	2 (0.6) 2	1 (0.3) 1	3 (0.4) 3
Hepatobiliary disorders	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Renal and urinary disorders	2 (0.6) 2	0	2 (0.3) 2
Social circumstances	2 (0.6) 2	0	2 (0.3) 2
Cardiac disorders	1 (0.3) 2	0	1 (0.1) 2
Ear and labyrinth disorders	1 (0.3) 1	0	1 (0.1) 1
Investigations	0	1 (0.3) 3	1 (0.1) 3
Skin and subcutaneous tissue disorders	1 (0.3) 1	0	1 (0.1) 1
N: Number of patients in safety population; n: Number of patients with non-missing assessment; E: Number of events.			

Table 19 - Prior anti cancer therapy – CR201-18

	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Patients with at least one anti-cancer treatment	**98 (28.4%)**	**109 (31.6%)**	**207 (30.0%)**
Patients with at least one chemotherapy	92 (26.7%)	99 (28.7%)	191 (27.7%)
Patients with at least one radiotherapy	41 (11.8%)	46 (13.3%)	87 (12.6%)
Patients with at least one hormonal therapy	18 (5.2%)	22 (6.4%)	40 (5.7%)
Patients with at least one biological therapy	3 (0,9%)	1 (0.3%)	4 (0,6%)

Numbers analysed

The per protocol (PP2) population includes randomised patients with at least one tumour assessment and no major protocol deviation but deviation in the dosing window of more than 7 days. That population was retrospectively defined to explore the impact of dosing delay on the primary endpoint.

Table 20 - Summary of analysis sets – CR201-18

	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patients	**n (%)**	**n (%)**	**n (%)**
Intent-to Treat (ITT) Population	345 (100.0)	345 (100.0)	690 (100.0)
Per Protocol (PP) Population	314 (91.0)	323 (93.6)	637 (92.3)
Per Protocol 2 (PP2) Population	194 (56.2)	202 (58.6)	396 (57.4)
Safety population (SAF)	345 (100.0)	345 (100.0)	690 (100.0)
Pharmacokinetic (PK) Population	327 (94.8)	331 (95.9)	658 (95.4)

Outcomes and estimation

Primary endpoint

Table 21 - Objective response rate (ORR) at week 24-risk difference - CR201-18

	BP02 (N=345)	**Herceptin (N=345)**	**Total (N=690)**
ITT population			
Proportion of patients achieving ORR (CR + PR), n (%) (95% CIs)	231 (67.0) (62.0, 71.9)	238 (69.0) (64.1, 73.9)	469 (68.0) (64.5, 71.5)
Risk difference (95% CIs) #	**-2.03 (-9.15, 5.09)**		
PP Population			
	BP02 (N=314)	**Herceptin (N=323)**	**Total (N=637)**
Proportion of patients achieving ORR (CR + PR), n (%) (95% CIs)	229 (72.9) (68.0, 77.8)	238 (73.7) (68.9, 78.5)	467 (73.3) (69.9, 76.7)
Risk difference (95% CIs) #	**-0.75 (-7.80, 6.29)**		
Note: #95% CIs for risk difference (of BP02 - Herceptin) are derived based on Hauck-Anderson method. 95% CIs of individual proportions are calculated using Wald method.			

Table 22 - Objective response rate (ORR) at week 24 - risk difference with 95% CIs from stratified Mantel-Haenszel method-ITT Population - CR201-18

	BP02 (N=345)	**Herceptin (N=345)**	**Total (N=690)**
Proportion of patients achieving ORR (CR + PR), n (%) (95% CIs)	231 (67.0) (62.0, 71.9)	238 (69.0) (64.1, 73.9)	469 (68.0) (64.5, 71.5)
Risk difference (95% CIs) #	**-2.03 (-8.99, 4.92)**		

Secondary Efficacy Analysis:

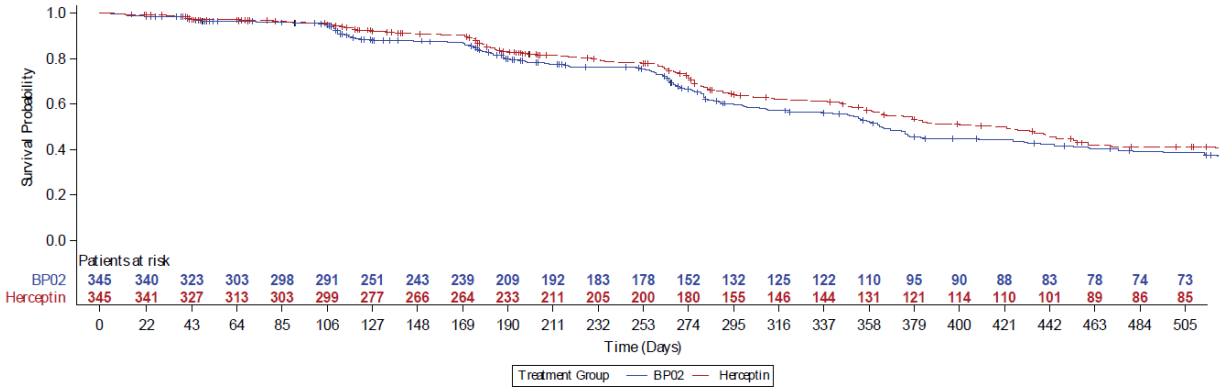
Progression free survival (PFS):

Table 23 - Secondary efficacy outcomes: Progression-free survival - CR201-18

	BP02 (N=345)	Herceptin (N=345)	Total (N=690)	P-value
End of Induction				
Number of patients with PD or death, n (%)	66 (19.1)	60 (17.4)	126 (18.3)	
Number of patients censored n (%)	279 (80.9)	285 (82.6)	564 (81.7)	
Median (95% CI), months	7.2	7.5	7.5	
Min, max	0.2, 7.4	0.2, 8.3	0.2, 8.3	
Log-rank test p-value	0.2984			
Hazard ratio* (95% CI)	1.2 (0.8, 1.7)			0.2924
Hazard ratio# (95% CI)	1.2 (0.8, 1.7)			0.3000
Estimated progression free survival rate at**				
Cycle 3 Day 43 (95% CI)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.96, 0.98)	
Cycle 6 Day 106 (95% CI)	0.95 (0.93, 0.97)	0.95 (0.93, 0.98)	0.95 (0.94, 0.97)	
EOI Day 169 (95% CI)	0.87 (0.83, 0.90)	0.90 (0.87, 0.93)	0.88 (0.86, 0.91)	
End of Study				
	BP02 (N=345)	**Herceptin (N=345)**	**Total (N=690)**	**P-value**
Number of patients with PD or death, n (%)	163 (47.2)	166 (48.1)	329 (47.7)	
Number of patients censored n (%)	182 (52.8)	179 (51.9)	361 (52.3)	
Median	11.9	13.7	12.4	
Min, Max	0.2, 20.6	0.2, 20.3	0.2, 20.6	
Log-rank test p-value	0.3739			
Hazard ratio* (95% CI)	1.1 (0.9, 1.4)			0.3623
Hazard ratio# (95% CI)	1.1 (0.9, 1.4)			0.3738
Estimated progression free survival rate* at				
Cycle 3 Day 43 (95% CI)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.96, 0.98)	
Cycle 6 Day 106 (95% CI)	0.95 (0.93, 0.97)	0.95 (0.93, 0.98)	0.95 (0.94, 0.97)	
EOI Day 169 (95% CI)	0.87 (0.83, 0.90)	0.90 (0.87, 0.93)	0.88 (0.86, 0.91)	
Cycle 13 Day 253 (95% CI)	0.75 (0.70, 0.81)	0.78 (0.73, 0.83)	0.77 (0.73, 0.80)	
Cycle 17 Day 337 (95% CI)	0.56 (0.50, 0.62)	0.61 (0.55, 0.67)	0.59 (0.54, 0.63)	
Cycle 21 Day 421 (95% CI)	0.44 (0.38, 0.51)	0.50 (0.44, 0.56)	0.47 (0.43, 0.52)	
EOS Day 505 (95% CI)	0.39 (0.32, 0.45)	0.41 (0.35, 0.47)	0.40 (0.35, 0.44)	

*From a Cox regression adjusted for the randomization stratum (estrogen and progesterone receptor status (positive versus negative)) as stratum and treatment as factor.
#From a Cox regression adjusted for the treatment as factor.
**Denominator is number of patients with an event till defined time.

Figure 7 - Kaplan–Meier plot for Progression Free Survival (PFS) until end of study – ITT population - CR201-18



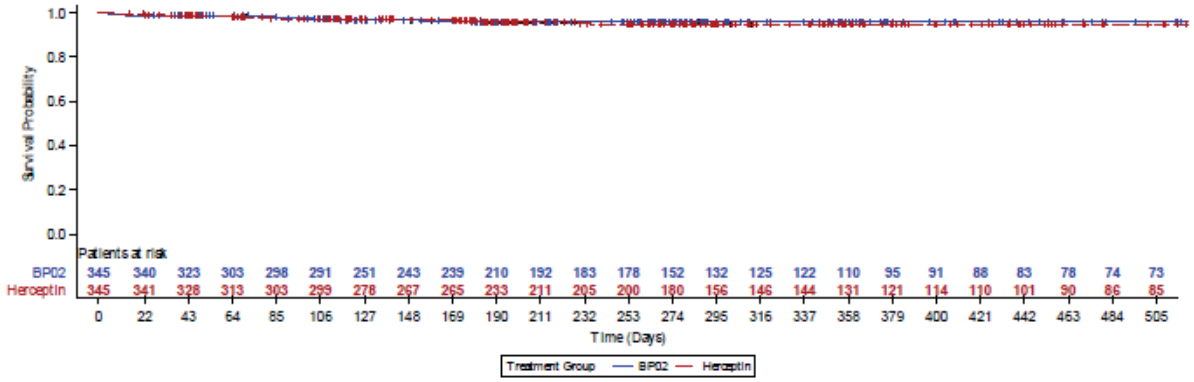
Overall survival (OS):

Table 24 - Secondary efficacy outcomes: Overall survival - CR201-18

End of Induction				
	BP02 (N=345)	**Herceptin (N=345)**	**Total (N=690)**	**P-value**
Number of patients with death, n (%)	11 (3.2)	10 (2.9)	21 (3.0)	
Number of patients censored, n (%)	334 (96.8)	335 (97.1)	669 (97.0)	
Median (95% CI), months	NE	NE	NE	
Min, max	0.2, 7.4	0.2, 8.3	0.2, 8.3	
Log-rank test p-value	0.7857			
Hazard ratio* (95% CI)	1.1 (0.5, 2.7)			0.7744
Hazard ratio# (95% CI)	1.1 (0.5, 2.7)			0.7859
Estimated overall survival rate** at				
Cycle 3 Day 43 (95% CI)	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	0.99 (0.98, 0.99)	
Cycle 6 Day 106 (95% CI)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.96, 0.99)	
EOI Day 169 (95% CI)	0.96 (0.94, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.98)	
End of Study				
Number of patients with death, n (%)	12 (3.5)	15 (4.3)	27 (3.9)	
Number of patients censored, n (%)	333 (96.5)	330 (95.7)	663 (96.1)	
Median	NE	NE	NE	
Min, max	0.2, 20.6	0.2, 20.3	0.2, 20.6	
Log-rank test p-value	0.6397			
Hazard ratio* (95% CI)	0.8 (0.4, 1.8)			0.6562
Hazard ratio# (95% CI)	0.81 (0.4, 1.8)			0.6402

Estimated overall survival rate at**				
Cycle 3 Day 43 (95% CI)	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	0.99 (0.98, 0.99)	
Cycle 6 Day 106 (95% CI)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.96, 0.99)	
EOI Day 169 (95% CI)	0.96 (0.94, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.98)	
Cycle 13 Day 253 (95% CI)	0.96 (0.94, 0.98)	0.95 (0.92, 0.97)	0.95 (0.94, 0.97)	
Cycle 17 Day 337 (95% CI)	0.96 (0.94, 0.98)	0.95 (0.92, 0.97)	0.95 (0.94, 0.97)	
Cycle 21 Day 421 (95% CI)	0.96 (0.94, 0.98)	0.95 (0.92, 0.97)	0.95 (0.94, 0.97)	
EOS Day 505 (95% CI)	0.96 (0.94, 0.98)	0.95 (0.92, 0.97)	0.95 (0.94, 0.97)	
*From a Cox regression adjusted for the randomization stratum (estrogen and progesterone receptor status (positive versus negative)) as stratum and treatment as factor. #From a Cox regression adjusted for the treatment as factor. **Denominator is number of patients with an event till defined time.				

Figure 8 - Kaplan-Meier-plot for Overall Survival (OS) until end of study – ITT population - CR201-18



Ancillary analyses

Subgroup analyses of the best ORR were performed by stratification factor (HR+ vs HR-) and ECOG performance status (0, 1 and 2) in the ITT population.

Table 25 - Primary Analysis in Subgroups Modified ER/PR Status- Objective response rate (ORR) at week 24 by ER/PR status - CR201-18

	BP02 (N=168)	Herceptin (N=171)	Total (N=339)
Modified ER/PR status (as per ASCO/CAP Guideline): ER/PR Positive			
Proportion of patients achieving ORR (CR + PR), n (%) (95% CI)	114 (67.9) (60.8, 74.9)	119 (69.6) (62.7, 76.5)	233 (68.7) (63.8, 73.7)
Risk difference (95% CI)	-1.73 (-11.93, 8.46)		
Modified ER/PR status (as per ASCO/CAP Guideline): ER/PR Negative			
	(N=172)	**(N=173)**	**(N=345)**
Proportion of patients achieving	113 (65.7) (58.6, 72.8)	118 (68.2) (61.3, 75.1)	231 (67.0) (62.0, 71.9)

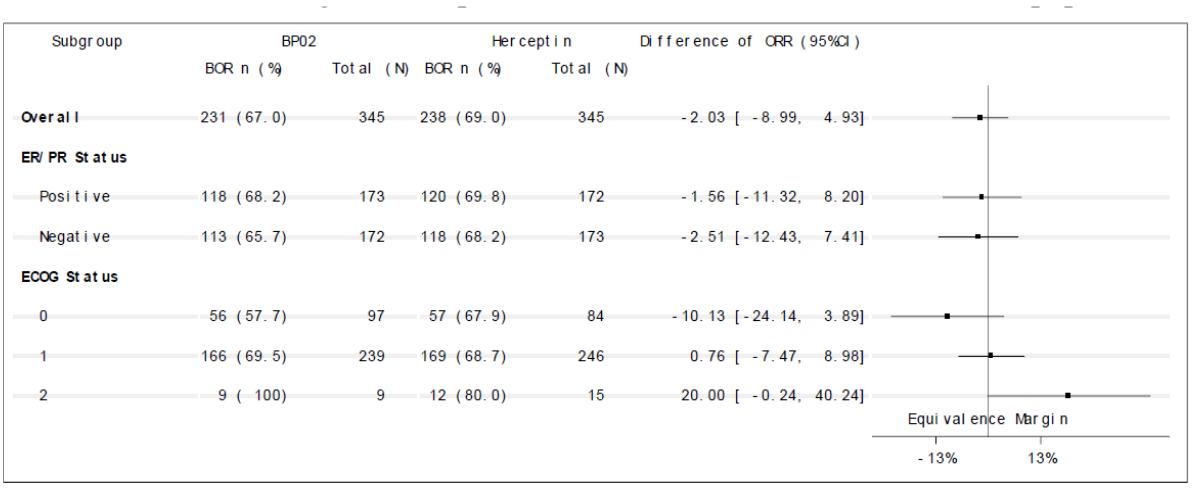
ORR (CR + PR), n (%) (95% CI)			
Risk difference (95% CI)	-2.51 (-12.75, 7.73)		

Due to 43% of patients with a delay of dosing for more than seven days and the opportunity for a reloading dose, a sensitivity analysis of these patients (PP2 population) was performed subsequently. The number of patients without severe delay of dosing was 194 in the BP02- and 202 in the Herceptin arm.

Table 26 - **Objective Response Rate (ORR) at End of Induction -Per Protocol 2 Population – CR201-18**

	BP02 (N=194)	**Herceptin (N=202)**	**Total (N=396)**
EMA Approach			
Proportion of patients achieving ORR (CR + PR), n (%) (95% CI)	142 (73.2) (67.0, 79.4)	142 (70.3) (64.0, 76.6)	284 (71.7) (67.3, 76.2)
Risk difference (95% CIs)	2.90 (-6.24, 12.04)		
FDA Approach			
Proportion of patients achieving ORR (CR + PR), n (%) (90% CI)	142 (73.2) (68.0, 78.4)	142 (70.3) (65.0, 75.6)	284 (71.7) (68.0, 75.4)
Risk ratio (90% CIs)	1.04 (0.94, 1.15)		

Figure 9 - Forest plot for subgroup analyses of risk difference (95% Cis) in objective response rate (ORR) at week 24-ITT population - CR2018-18



Sensitivity analyses provided to estimate the effect of additional loading doses on the primary endpoint ORR and the secondary endpoint PFS.

Table 27 - Objective Response Rate at End of Induction - Risk Difference in Patients Without Reloading Dose (excluding C1D1) during Induction Phase (ITT Population)- CR201-18:

	BP02 (N=215)	Herceptin (N=208)
Proportion of patients achieving ORR (CR + PR), n (%) (95% CIs)	139 (64.7) (58.3, 71.0)	130 (62.5) (55.9, 69.1)
Risk difference (95% CIs)[#]	2.15 (-7.28, 11.58)	

Abbreviations: ITT = Intent to Treat; CI = confidence interval; RECIST = Response Evaluation Criteria in Solid Tumors;
C1D1 = Cycle 1 Day 1.
N: Number of patients in ITT population meeting the criteria in the title. n: Number of patients with best ORR according to RECIST 1.1.

Overall response at each visit is programmatically derived to get best overall response (BOR).
Objective response rate is defined as the proportion of patients with best overall response (BOR) of CR (complete response) or PR (partial response) up to end of induction phase, as per RECIST 1.1 guidance.
Patient with all missing post-baseline tumour assessments is considered as non-responder. 95% CIs of individual proportions are calculated using Wald method.

#: 95% CIs for risk difference (of BP02 - Herceptin) are derived based on Hauck-Anderson method.

Table 28 - Objective Response Rate at End of Induction – Risk Difference in Patients Treated according to the Protocol (Scheduled Visit Day +/- 3 days) During Induction Phase – (ITT Population) - CR201-18

	BP02 (N=120)	Herceptin (N=120)
Proportion of patients achieving ORR (CR + PR), n (%) (95% CIs)	69 (57.5) (48.7, 66.3)	67 (55.8) (46.9, 64.7)
Risk difference (95% CIs)[#]	1.67 (-11.34, 14.67)	

Abbreviations: ITT = Intent to Treat; CI = confidence interval; RECIST = Response Evaluation Criteria in Solid Tumors.
N: Number of patients in ITT population meeting the criteria in the title. n: Number of patients with best ORR according to RECIST 1.1.

Overall response at each visit is programmatically derived to get best overall response (BOR).
Objective response rate is defined as the proportion of patients with best overall response (BOR) of CR (complete response) or PR (partial response) up to end of induction phase, as per RECIST 1.1 guidance.
Patient with all missing post-baseline tumour assessments is considered as non-responder. 95% CIs of individual proportions are calculated using Wald method.

#: 95% CIs for risk difference (of BP02 - Herceptin) are derived based on Hauck-Anderson method.

Table 29 - Progression Free Survival until End of Study - Cox Proportional Hazard Regression Analysis in Patients Treated According to the Protocol (Scheduled Visit day +/- 3 days) - ITT Population - CR201-18

Treatment group	Kaplan-Meier (median) estimate at EOS, % (95% CI)	Hazard ratio* (95% CI)	P-value*	Hazard ratio (95% CI)[#]	P-value[#]
BP02 (N=120)	10.2 (8.6, 14.1)	1.4 (0.9, 2.0)	0.0942	1.3 (0.9, 1.9)	0.1135
Herceptin (N=120)	14.3 (11.7, 17.1)				

Abbreviations: EOS = End of Study; ITT = Intent to Treat; PFS = progression free survival; CI= Confidence Interval.
N: The number of patients in the ITT population meeting the criteria in the title.
Progression free survival defined as the time from date of first dose to the date of documented PD or death due to any cause until end of study.
*From a Cox regression adjusted for the modified ER and PR Status as stratum and treatment as factor. #From a Cox regression adjusted for the treatment as factor.

For the Maintenance Phase CSR analysis, if no death or other censoring (progressive disease) appeared prior to end of study, patients will be administratively censored at last tumour assessment date. If there is no tumour assessment available then patient will be censored at end of study.

Table 30 - PFS Subgroup Analysis for Tumour Assessment Adherence and Deviations - CR201-18

Treatment group	Median PFS in months (95% CI)	Hazard ratio (95% CI)	P-value
Patients with no out of window deviation for tumour assessment			
BP02 (N = 246)	11.2 (9.2, 12.1)	1.1 (0.9, 1.5)	0.3255
Herceptin (N = 230)	11.9 (10.0, 14.5)		
Patients with at least one out of window deviation for tumour assessment			
BP02 (N = 99)	16.3 (12.3, NE)	1.0 (0.6, 1.5)	0.8660
Herceptin (N = 115)	17.3 (13.7, 19.1)		
Patients with at least one (early) out of window deviation for tumour assessment			
BP02 (N = 59)	14.6 (11.8, NE)	1.1 (0.6, 1.7)	0.8434
Herceptin (N = 75)	14.3 (11.7, 18.5)		
Patients with at least one (late) out of window deviation for tumour assessment			
BP02 (N = 48)	NE (12.3, NE)	1.0 (0.5, 2.1)	0.8974
Herceptin (N = 52)	19.8 (17.8, NE)		

NE = not estimable
Patients could have an early and late out of window deviation for tumour assessment

EMA RAW DATA PILOT1 - Sensitivity analyses

A sensitivity analysis on the assumptions underlying the handling of missing data in the primary analysis was conducted within the raw data pilot. There were 41 and 31 patients with incomplete information on the primary outcome in the experimental and the control group, respectively (excluding patients with less than 3 tumour assessments where response was nevertheless observed at one of the non-missed visits, or when had data was missing due to death or progression).

Up until 14 (out of max 31) non-responder with missing data could be switched to responders in the control group while keeping everything as-is in the experimental group before the test was no longer statistically significant. This shows a robust result.

In addition, some checks on the data underlying the main analyses were performed. These found some discrepancies between the values as stored in the ADAM-dataset (and hence used in the analyses) and the values as replicated based on SDTM-data and the definitions provided in SAP.

ORR:

- One patient is indicated to have a new tumour during the induction phase and should be labelled as progressed and non-responder

- Note: While all other variables were used from the SDTM-data, info on 'new tumor' was taken from adrs (variable PARAMCD = NEWCONF), as it could not be found in the SDTM-data

PFS:

- On top of the subject mentioned above (that did progress):

o 4 patients without observed progression and death only after end of induction, should be censored at last tumour assessment

o 1 additional patient has wrong PFS-time:

2 - Subgroup analyses

Additional subgroup analyses for the ORR (primary endpoint) were requested during the assessment, specifically:

• IHC scoring +++ patients vs only IHC scoring ++ patients vs IHC scoring ++ patients with confirmed FISH/ CISH testing

• Within hormone receptor positive patient population, subgroup analysis by prior and/or concomitant use of hormone therapy (with or without hormone therapy)

• Age : <65 years vs 65 years and <60 years vs 60 years

Results of subgroup analysis

ADAM data

In the table below, outcome- and predictor data were based on the available ADAM-datasets (as in the previous replication of the primary analysis). For ORR-definition, 1 patient was mis-labelled (based on what was found in SDTM).

For the definition of patients with and without Hormonal Treatment, patients were labelled as 'Hormonal Treatment TRUE' if they used any prior or concomitant drug from ATC-group L02B. This means these groups are not determined solely on baseline-characteristics, post-randomization information is used as well.

Whether or not the drug use was labelled as prior or concomitant in the data, was ignored. Some drugs were labelled 'Hormonal Treatment' in the dataset, but that was ignored as well (only ATC L02B defined the groups).

For all large subgroups, the lower limit of the confidence intervals for the difference in ORR are above the lower bound of -13%.

Table 31 - Raw data pilot analysis 1

Stratum	value	BP02 + Docetaxel	Herceptin + Docetaxel	Diff
Total	-	231 (67) Ntot = 345	238 (69) Ntot = 345	-2.03 [-8.98 ; 4.94]
AGEGR2	<=60	186 (67.6) Ntot = 275	201 (69.6) Ntot = 289	-1.91 [-9.58 ; 5.74]
AGEGR2	>60	45 (64.3) Ntot = 70	37 (66.1) Ntot = 56	-1.79 [-18.18 ; 15.07]
AGEGR1	<= 65 years	208 (66.9) Ntot = 311	217 (69.8) Ntot = 311	-2.89 [-10.19 ; 4.42]
AGEGR1	> 65 years	23 (67.6) Ntot = 34	21 (61.8) Ntot = 34	5.88 [-16.81 ; 28.03]
IHCSCORE	2	20 (62.5) Ntot = 32	24 (68.6) Ntot = 35	-6.07 [-28.43 ; 16.59]
IHCSCORE	3	211 (67.4) Ntot = 313	214 (69) Ntot = 310	-1.62 [-8.92 ; 5.7]
HormTr_any	FALSE	221 (67.6) Ntot = 327	224 (69.6) Ntot = 322	-1.98 [-9.11 ; 5.17]
HormTr_any	TRUE	10 (55.6) Ntot = 18	14 (60.9) Ntot = 23	-5.31 [-34.58 ; 24.32]

On SDTM transformed data

In trying to replicate the main results it was found that one ORR was mislabelled in the ADAM dataset when compared with the information available in SDTM.

The subgroup-analyses was repeated using our own derivation of the primary outcome (1 responder less in the experimental arm).

This does not significantly impact the results.

Table 32 - Raw data pilot analysis 2

Stratum	value	BP02 + Docetaxel	Herceptin + Docetaxel	Diff
Total	-	230 (66.7) Ntot = 345	238 (69) Ntot = 345	-2.32 [-9.28 ; 4.66]
AGEGR2	<=60	185 (67.3) Ntot = 275	201 (69.6) Ntot = 289	-2.28 [-9.95 ; 5.39]
AGEGR2	>60	45 (64.3) Ntot = 70	37 (66.1) Ntot = 56	-1.79 [-18.18 ; 15.07]
AGEGR1	<= 65 years	207 (66.6) Ntot = 311	217 (69.8) Ntot = 311	-3.22 [-10.52 ; 4.11]
AGEGR1	> 65 years	23 (67.6) Ntot = 34	21 (61.8) Ntot = 34	5.88 [-16.81 ; 28.03]
IHCSCORE	2	20 (62.5) Ntot = 32	24 (68.6) Ntot = 35	-6.07 [-28.43 ; 16.59]
IHCSCORE	3	210 (67.1) Ntot = 313	214 (69) Ntot = 310	-1.94 [-9.25 ; 5.39]
HormTr_any	FALSE	221 (67.6) Ntot = 327	224 (69.6) Ntot = 322	-1.98 [-9.11 ; 5.17]
HormTr_any	TRUE	9 (50) Ntot = 18	14 (60.9) Ntot = 23	-10.87 [-39.58 ; 19.39]

5.1.1.1.1.1. Summary of main efficacy results

Table 33 - Summary of efficacy for the trial of Phase III, Dazublys (trastuzumab) trial - CR201-18

Title: A Multicentre, Double-Blind, Randomized, Parallel-Group, Active-Controlled, Phase III Study to Evaluate the Efficacy, Safety, Immunogenicity, and Pharmacokinetics of BP02 (Trastuzumab) in Comparison with Herceptin-EU in Patients with HER2-Positive Metastatic Breast Cancer (MBC).			
Study identifier	**Protocol Number: CR201-18**		
	CTRI Number: CTRI/2020/04/024456		
Design	Multicentre, Randomized, Double-Blind, Parallel-group, Active-Controlled, Phase III study.		
	Duration of the main phase		8 cycles (6 months)
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase		Not applicable
Hypothesis	Equivalence		
Treatments groups	Group-I (Test): BP02		IV 8 mg/kg (Loading dose) in cycle 1, followed by 6 mg/kg (maintenance dose) for subsequent cycles (Cycle 2-8), N= 345
	Group II (Reference): Herceptin-EU		IV 8 mg/kg (Loading dose) in cycle 1, followed by 6 mg/kg (maintenance dose) for subsequent cycles (Cycle 2-8), N= 345
	Group Descriptor		**Treatment**
Endpoints and definitions	Primary endpoint	Best Objective Response Rate (ORR)	Complete Response (CR) or Partial Response (PR) as assessed by Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 at week 24 without confirmation of response
	Secondary endpoints	PFS and OS	• Progression-free survival (PFS) and Overall Survival (OS) by the end of the induction phase (week 24) and end of the study. • Safety at week 24 and end of the study. • Immunogenicity at week 24 and end of the study. • C_{trough} when administered in combination with Docetaxel in the Induction Phase.
Database	06 June 2023		
Results and Analysis			
Analysis Description	**Primary Analysis (Based on Risk Difference)**		

<table>
<tr><td>Primary Efficacy Endpoint Results</td><td>A two-one-sided test procedure was used to test this hypothesis. This analysis used the ITT (Intend to treat) population. The 95% CI for ORR difference between BP02 (trastuzumab) and Herceptin was estimated and compared to the margin [-13%, +13%], which is deemed to represent a clinically acceptable difference with respect to the ORR. If the 95% CI falls within the interval [-13%, +13%], an equivalence between BP02 (trastuzumab) and Herceptin with respect to ORR, is confirmed (Table 1).</td></tr>
<tr><td>Descriptive statistics and estimate variability</td><td>
Objective response rate (ORR) at week 24 - Risk difference
<table>
<tr><th></th><th>BP02 (N=345)</th><th>Herceptin (N=345)</th><th>Total (N=690)</th></tr>
<tr><td colspan="4">ITT P population</td></tr>
<tr><td>Proportion of patients achieving ORR (CR + PR), n (%)</td><td>231 (67.0)</td><td>238 (69.0)</td><td>469 (68.0)</td></tr>
<tr><td>(95% CIs)</td><td>(62.0, 71.9)</td><td>(64.1, 73.9)</td><td>(64.5, 71.5)</td></tr>
<tr><td>Risk difference (95% CIs) #</td><td colspan="3">-2.03 (-9.15, 5.09)</td></tr>
<tr><td colspan="4">PP Population</td></tr>
<tr><td></td><td>BP02</td><td>Herceptin</td><td>Total</td></tr>
<tr><td></td><td>(N=314)</td><td>(N=323)</td><td>(N=637)</td></tr>
<tr><td>Proportion of patients achieving ORR (CR + PR), n (%)</td><td>229 (72.9)</td><td>238 (73.7)</td><td>467 (73.3)</td></tr>
<tr><td>(95% CIs)</td><td>(68.0, 77.8)</td><td>(68.9, 78.5)</td><td>(69.9, 76.7)</td></tr>
<tr><td>Risk difference (95% CIs) #</td><td colspan="3">-0.75 (-7.80, 6.29)</td></tr>
</table>
Note: #95% CIs for risk difference (of BP02 - Herceptin) are derived based on the Hauck-Anderson method. 95% CIs of individual proportions are calculated using the Wald method.

The primary efficacy results generated using the stratified Mantel-Haenszel method, stratified by the stratification factor of estrogen and progesterone receptor status (positive versus negative95% CIs of individual proportions are calculated using Wald method) for the common risk difference and associated 95% confidence intervals, were provided in the table below. The risk difference of the best ORR (test vs reference) was -2.03 (95% CI, -8.99, 4.92) and was within the predefined equivalence boundaries .
<table>
<tr><th></th><th>BP02 (N=345)</th><th>Herceptin (N=345)</th><th>T Total (N=690)</th></tr>
<tr><td>Proportion of patients achieving ORR (CR + PR), n (%),</td><td>231 (67.0)</td><td>238 (69.0)</td><td>469 (68.0)</td></tr>
<tr><td>(95% CIs)</td><td>(62.0, 71.9)</td><td>(64.1, 73.9)</td><td>(64.5, 71.5)</td></tr>
<tr><td>Risk difference (95% CIs) #</td><td colspan="3">-2.03 (-8.99, 4.92)</td></tr>
</table>
.
</td></tr>
</table>

Secondary Efficacy Analysis	**Progression-free survival (PFS):** PFS defined as the time from the date of first dose to subsequent confirmed progression per RECIST 1.1, derived in months. Patients that do not experience the progression was censored at the date of last tumour assessment. Patients were administratively censored at week 24 if no progression or other censoring appeared prior to week 24. The Kaplan-Meier (KM) method was used to assess the PFS, to estimate the PFS rate, and the confidence intervals of PFS rate. A two-sided log-rank test was used to compare the PFS between the two treatment groups.

Secondary Efficacy Outcomes: Progression-Free Survival

	BP02 (N=345)	Herceptin (N=345)	Total (N=690)	P-value
End of Induction				
Number of patients with PD or death, n (%)	66 (19.1)	60 (17.4)	126 (18.3)	
Number of patients censored n (%)	279 (80.9)	285 (82.6)	564 (81.7)	
Median (95% CI), months	7.2	7.5	7.5	
Min, max	0.2, 7.4	0.2, 8.3	0.2, 8.3	
Log-rank test p-value	0.2984			
Hazard ratio* (95% CI)	1.2 (0.8, 1.7)			0.2924
Hazard ratio# (95% CI)	1.2 (0.8, 1.7)			0.3000
Estimated progression free survival rate at**				
Cycle 3 Day 43 (95% CI)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.96, 0.98)	
Cycle 6 Day 106 (95% CI)	0.95 (0.93, 0.97)	0.95 (0.93, 0.98)	0.95 (0.94, 0.97)	
EOI Day 169 (95% CI)	0.87 (0.83, 0.90)	0.90 (0.87, 0.93)	0.88 (0.86, 0.91)	
End of Study				
	BP02 (N=345)	**Herceptin (N=345)**	**Total (N=690)**	**P-value**
Number of patients with PD or death, n (%)	163 (47.2)	166 (48.1)	329 (47.7)	
Number of patients censored n (%)	182 (52.8)	179 (51.9)	361 (52.3)	
Median	11.9	13.7	12.4	
Min, Max	0.2, 20.6	0.2, 20.3	0.2, 20.6	
Log-rank test p-value	0.3739			
Hazard ratio* (95% CI)	1.1 (0.9, 1.4)			0.3623
Hazard ratio# (95% CI)	1.1 (0.9, 1.4)			0.3738
Estimated progression free survival rate* at				
Cycle 3 Day 43 (95% CI)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.96, 0.98)	
Cycle 6 Day 106 (95% CI)	0.95 (0.93, 0.97)	0.95 (0.93, 0.98)	0.95 (0.94, 0.97)	
EOI Day 169 (95% CI)	0.87 (0.83, 0.90)	0.90 (0.87, 0.93)	0.88 (0.86, 0.91)	
Cycle 13 Day 253 (95% CI)	0.75 (0.70, 0.81)	0.78 (0.73, 0.83)	0.77 (0.73, 0.80)	
Cycle 17 Day 337 (95% CI)	0.56 (0.50, 0.62)	0.61 (0.55, 0.67)	0.59 (0.54, 0.63)	
Cycle 21 Day 421 (95% CI)	0.44 (0.38, 0.51)	0.50 (0.44, 0.56)	0.47 (0.43, 0.52)	
EOS Day 505 (95% CI)	0.39 (0.32, 0.45)	0.41 (0.35, 0.47)	0.40 (0.35, 0.44)	

*From a Cox regression adjusted for the randomization stratum (estrogen and progesterone receptor status (positive versus negative)) as stratum and treatment as factor.
#From a Cox regression adjusted for the treatment as factor.
**Denominator is number of patients with an event till defined time.

Overall survival (OS):
OS is defined as the time from the date of the first dose to subsequent death, derived in months. Patients that do not die during the study were censored at the date of last contact. The KM method was used to assess the OS rate and the confidence intervals of the OS rate. A two-sided log-rank test will be used to compare the OS between the two treatments .

Secondary Efficacy Outcomes: Overall Survival

End of Induction				
	BP02 (N=345)	**Herceptin (N=345)**	**Total (N=690)**	**P-value**
Number of patients with death, n (%)	11 (3.2)	10 (2.9)	21 (3.0)	
Number of patients censored, n (%)	334 (96.8)	335 (97.1)	669 (97.0)	
Median (95% CI), months	NE	NE	NE	
Min, max	0.2, 7.4	0.2, 8.3	0.2, 8.3	
Log-rank test p-value	0.7857			
Hazard ratio* (95% CI)	1.1 (0.5, 2.7)			0.7744
Hazard ratio# (95% CI)	1.1 (0.5, 2.7)			0.7859
Estimated overall survival rate** at				
Cycle 3 Day 43 (95% CI)	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	0.99 (0.98, 0.99)	
Cycle 6 Day 106 (95% CI)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.96, 0.99)	
EOI Day 169 (95% CI)	0.96 (0.94, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.98)	
End of Study				
Number of patients with death, n (%)	12 (3.5)	15 (4.3)	27 (3.9)	
Number of patients censored, n (%)	333 (96.5)	330 (95.7)	663 (96.1)	
Median	NE	NE	NE	
Min, max	0.2, 20.6	0.2, 20.3	0.2, 20.6	
Log-rank test p-value	0.6397			
Hazard ratio* (95% CI)	0.8 (0.4, 1.8)			0.6562
Hazard ratio# (95% CI)	0.81 (0.4, 1.8)			0.6402
Estimated overall survival rate at**				
Cycle 3 Day 43 (95% CI)	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	0.99 (0.98, 0.99)	
Cycle 6 Day 106 (95% CI)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)	0.97 (0.96, 0.99)	
EOI Day 169 (95% CI)	0.96 (0.94, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 0.98)	

Cycle 13 Day 253 (95% CI)	0.96 (0.94, 0.98)	0.95 (0.92, 0.97)	0.95 (0.94, 0.97)	
Cycle 17 Day 337 (95% CI)	0.96 (0.94, 0.98)	0.95 (0.92, 0.97)	0.95 (0.94, 0.97)	
Cycle 21 Day 421 (95% CI)	0.96 (0.94, 0.98)	0.95 (0.92, 0.97)	0.95 (0.94, 0.97)	
EOS Day 505 (95% CI)	0.96 (0.94, 0.98)	0.95 (0.92, 0.97)	0.95 (0.94, 0.97)	

*From a Cox regression adjusted for the randomization stratum (estrogen and progesterone receptor status (positive versus negative)) as stratum and treatment as factor.

#From a Cox regression adjusted for the treatment as factor.

**Denominator is number of patients with an event till defined time.

Conclusion

The risk difference of the overall response rate was found within the predefined margin; based on these results, it can be concluded that BP02 (Trastuzumab) is therapeutically equivalent to the Herceptin- EU.

5.1.1.2. Clinical studies in special populations

Not applicable.

5.1.1.3. In vitro biomarker test for patient selection for efficacy

Female patients with HER2+ MBC by IHC or positive FISH or CISH were enrolled in this study.

Of 690 enrolled patients, for 624 patients HER2 positivity was diagnosed by IHC Score 3+, and the remaining 66 patients had a positive FISH/CISH result.

To determine hormone receptor status in study CR201-18, samples with results: ER+PR+, ER+PR- and ER-PR+ were categorized as hormone positive cases. ER-PR- samples were considered as hormone receptor negative cases. After EMA recommendation, as per ASCO/CAP guideline, the category ER low positive was introduced post hoc, potentially to apply for ER-PR+ tumours.

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

Not applicable.

5.1.1.5. Supportive study(ies)

Not applicable.

5.1.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Two studies were conducted in the clinical trastuzumab biosimilar development programme for BP02 (Dazublys), a Phase I study to demonstrate similarity in clinical pharmacokinetics and pharmacodynamics compared to the reference product, followed by a comparative Phase III study to confirm equivalence in terms of efficacy and safety.

Phase III study CR201-18 is a double-blind, randomized, parallel-group clinical study evaluating the efficacy, safety, PK and immunogenicity of BP02 in combination with docetaxel versus Herceptin in

combination with docetaxel in patients aged 18 years and above with HER2-positive metastatic breast cancer in the first-line treatment setting. Patients were stratified for hormonal receptor status (estrogen /progesterone). BP02 (Dazublys) and Herceptin were both administered in combination with docetaxel for 8 cycles over 24 weeks in the induction period and then continued as monotherapy for up to 16 cycles (about 12 months).

Accrual at 59 sites took from 23 September 2020 to 16 September 2022 (last patient randomised). Monotherapy maintenance phase was completed on 06 April 2024. In the CR201-18 study, BP02 (Dazublys) was administered in line with the approved posology for the reference product Herceptin as indicated during the CHMP Scientific Advice. A combination chemotherapy with docetaxel was administered; the omission of pertuzumab in variation to the current standard of care is endorsed for the purpose of comparability exercise and in line with other trastuzumab biosimilar studies.

The population chosen in the advanced/metastatic breast cancer setting is consistent with the CHMP scientific advice and previous trastuzumab biosimilar procedures (Trazimera, Ogivri, Zercepac) although a study in early breast cancer would have been considered more sensitive to detect differences of the product and less prone to confounding factors. In fact, a separate study part in the neoadjuvant setting was suspended by amendment 01. Eventually, this part was not concluded.

Only patients with measurable disease according to RECIST 1.1 were eligible for randomisation, which is supported for homogeneity reasons. Pre-treatment was allowed in the adjuvant setting with both chemotherapy and trastuzumab with a minimum gap of 12 months for the antibody.

Hormone receptor status was chosen as a stratification factor. Explanation was requested in terms of the definition of hormone–receptor-positivity of tumour samples, following the ASCO/ CAP guideline and estrogen and progesterone receptor (ER/PR) status were re-defined. The risk difference of the best ORR (test vs reference) was -1.73 (95% CI, -11.93, 8.46) in HR positive subgroup according to ASCO/CAP criteria; -2.51 (95% CI, -12.75, 7.73) in the HR negative subgroup and was within the predefined equivalence boundaries. In summary, analysis of patients with hormone receptor positive disease and hormone receptor negative disease did not show meaningful difference in terms of response. In the modified subgroup analyses for HR status (with applied ASCO/CAP definition) risk differences for ORR at week 24 and confidence intervals lie within the prespecified confidence interval.

Site of metastases and disease-free interval after adjuvant therapy were not used for stratification, although recommended in the CHMP Scientific advice. During the assessment, the applicant provided subgroup analyses for the primary endpoint according to site of disease which are endorsed. Point estimates and confidence intervals lay within the prespecified borders for bioequivalence in support of the biosimilarity assumption.

As a novelty in terms of homogeneity in the biosimilar development program, the applicant performed CR201-18 study in a monoethnic population of only Asian Indian women. In the CHMP scientific advice, this was discussed briefly and agreed under the condition to comply with GCP and ICH standards, in particular ICH guidelines on ethnicity (ICH E5(R1)) and multiregional trials (ICH E17). Based on the ICH E5 (R1), all data in the clinical data package, including foreign data, should meet the standards of the new region with respect to study design and conduct and the available data should satisfy the regulatory requirements in the new region." As per ICH E5 (R1), generally, for medicines characterized as insensitive to ethnic factors, no Bridging Study is required if the medicine is ethnically insensitive and extrinsic factors such as medical practice and conduct of clinical trials in the two regions are generally similar or if the medicine is ethnically sensitive but the two regions are ethnically similar and there is sufficient clinical experience with pharmacologically related compounds to provide reassurance that the class behaves similarly in patients in the two regions with respect to efficacy, safety, dosage

and dose regimen. This might be the case for well-established classes of drugs known to be administered similarly but not necessarily identically in the two regions.

Regarding subject selection, the Applicant justified that it was performed while considering potential sources of regional variability and mitigate their impact on trial results. Clear and specific inclusion and exclusion criteria, that are acceptable and could be applied across regions were included in the protocol (ICH E17). Characterization of a medicine as "*ethnically insensitive",* i.e., unlikely to behave differently in different populations, would usually make it easier to extrapolate data from one region to another and need lesser bridging data. The applicant's argumentation for ethnical insensitivity of trastuzumab appears generally reasonable.

The objective of the study is the demonstration of equivalence in terms of best ORR at week 24 between the biosimilar candidate BP02 (Dazublys) and the reference product Herceptin. The definition of ORR (i.e. best overall response) follows the generally accepted regulatory standards. The applicant defined a difference of 13% as equivalence margin and claimed it as clinically acceptable difference. Clinical and statistical justification of this margin were requested during assessment and the equivalence margin and the sample size calculation are justified both from a statistical and clinical perspectives by conducting the meta-analysis of innovator studies performed with inverse variance method (data not shown), supported together with data from other studies conducted with trastuzumab biosimilars.

Although recommended in the CHMP scientific advice, an estimand was not pre-specified and the applicant also did not specify the estimand that was intended to be targeted retrospectively. Therefore, the estimand that was implicitly targeted needed to be reconstructed from the choices that were made for design and analysis. As patients were withdrawn from the study after 'permanent discontinuation of trastuzumab' and no missing data were replaced, this is aligned to a 'while on treatment' strategy. Patients were not withdrawn because of 'temporary discontinuation of trastuzumab' and 'docetaxel delay/ discontinuation', which is aligned to a treatment policy strategy.

Handling the intercurrent events 'temporary discontinuation of trastuzumab' and 'docetaxel delay/ discontinuation' by the treatment policy strategy is acceptable, however, the frequency of these intercurrent events needs to be considered when interpreting the results. The "while on treatment" strategy is in accordance with ICH E9(R1) guideline.
However, the interpretation of the results depends on the time on treatment, consequently, the time to permanent treatment discontinuation was compared between treatments. And the proportion of and time to treatment discontinuation was similar in the treatment groups with a slight trend for more patients discontinuing in the BP02+Docetaxel group after 4 months but the small differences observed do not impact the conclusions.

Additionally, the "while on treatment" strategy for treatment discontinuation may dilute the difference between BP02 and Herceptin, particularly if treatment discontinuation is not related to treatment. Though it is still appropriate to consider response while on treatment for patients discontinuing due to progression or death, alternative strategies for treatment discontinuation due to other reasons could be more sensitive to show differences between treatments (e.g., a hypothetical strategy or a treatment policy strategy) and sensitivity analysis were provided Missing data were not replaced, which is aligned to a "while on treatment strategy" and means that non-response was assumed when a patient missed a visit. Not replacing missing data that do not occur related to progression may generally decrease the sensitivity to show differences between treatments. The following analyses were provided replacing intermediate missing data and missing data after study discontinuation (beside for discontinuation due to a negative outcome such as progression or death): an analysis based on a missing at random assumption; a tipping point analysis (with combination of numbers of responders for test/reference) and a multiple imputation analysis with different combination of response

probabilities in test/reference. The results of these analyses supported the conclusions of the primary analysis.

The Applicant did not explicitly specify an estimand for PFS and OS, however, as patients were not followed after treatment discontinuation and censored at last tumour assessment, the hypothetical effect if no patient had permanently discontinued treatment until week 24 is targeted. This is acceptable in the context of this equivalence study.

For demonstration of equivalence, two different approaches were specified: one using the risk difference , the 95% CI for ORR difference between BP02 (trastuzumab) and Herceptin was estimated and compared to the margin (-13%, +13%) and a second approach using risk ratio, the 90% CI for the ORR ration between BP02 and Herceptin was estimated and compared to the margin (0.80,1.25). This choice was motivated by different EMA and FDA recommendations but none of these approaches was prioritized as primary for the EU in the study protocol or SAP. No multiplicity issue arose as the success criteria were met for both approaches.

Randomisation stratification should be taken into account in the analysis. The Hauck-Anderson method specified for primary analysis does not take stratification factors into account, however, the stratified Mantel-Haenszel method for the confidence interval of the common risk difference was also provided as sensitivity analysis, which is acceptable.

Efficacy data and additional analyses

The phase III efficacy trial CR201-18 for BP02 (Dazublys) reached its primary objective. The primary endpoint best ORR at week 24 was 67.0% (ITT population, 95% CI: 62.0; 71.9) in BP02 and 69.0% (95% CI: 64.1; 73.9) in Herceptin with a risk difference of -2.03 (95% CI:-9.15, 5.09). This effect is reproducible in the submitted per-protocol-population and by a stratified analysis. Based on EMA Raw Data Pilot, a sensitivity analysis was conducted on the assumptions underlying the handling of missing data in the primary analysis, indicating robustness. Due to the change on the definition and number of HR- patients, the subgroup analyses of the best ORR performed by stratification factor (HR+ vs HR-) and other related analyses were re-conducted following ASCO/CAP guideline 2010. As a consequence, the applicant categorised 6 cases with ER-PR+ tumours as a "new" ER low positive subgroup. Further background information was requested on the level of ER and PR expression in these 6 tumour samples and samples with ER expression less than 1% were categorised as HR negative subgroup.

The routine GCP inspection revealed that during study conduct there was a wide variation of study visits up to 21 days and many patients could have received additional loading doses of 8 mg/kg. Dose delays were especially present in cycle 3 and 6 in the induction period due to complication of especially radiological assessment procedures during the COVID pandemic. However, relative dose intensity remained high and equally balanced between the arms (92% in both arms). Furthermore, even in patients with a dose intensity <80% risk difference between the arms remained low (point estimate 0.77). More important, a sensitivity analysis in the attempt to harmonise conditions for the primary endpoint in the 423 patients without any reloading dose was in line with the ITT analysis (Risk difference 2.15; 95% CI: -7.28, 11.58), supporting equivalence in clinical activity. Moreover, a further sensitivity analysis in patients without any dose delays was in line with the result in the ITT with a risk difference of 1.67 (95% CI: -11.34, 14.67). A sensitivity analysis in a population excluding patients with delays of more than seven days reproduced the result of the primary analysis (ORR BP02 73.2% and Herceptin 70.3%, Risk difference 2.9; 95% CI 6.24, 12.04). In conclusion, the shortcomings in study conduct cannot be solved. However, both arms of the phase III trial were equally affected. Regarding the clinical study being one factor contributing to the biosimilarity exercise, the raised issues are considered resolved.

At the end of induction, no statistical difference was observed in the secondary endpoints PFS and OS between the two arms while still being very immature (5.6 months). A stratified analysis regarding HR+/- demonstrated reproducibility of efficiency results, as well as a per-protocol analysis for patients being under treatment and tumour assessments. At the end of the study, median PFS was reached with a non-significant, numerical difference of 1.8 months in favour of the Herceptin arm (11.9 vrs 13.7 months; p= 0.379). In the ITT population, 29.7% had at least one out of window tumour assessment (28.7% vs. 33.3%). However, the impact of delays on results of the secondary endpoint PFS was negligible, the degree and number of deviations was equally distributed between the two arms and all hazard ratios for PFS for subgroups depending on the degree of the deviation range from 1.0 to 1.1.

For OS, at the end of the study no clear trend was obvious (12 (3.5%) in BP02 arm vs 15 (4.3%) events in Herceptin-arm, p=0.64). Reported non–significant differences in terms of exposure to treatment, discontinuation rate and frequency of adverse events (see safety part) each show slight, numerical deviations in favour of the reference product. Eventually, this could be related to chance, differences in product related features or not fully captured baseline imbalances.

5.1.3. Conclusions on the clinical efficacy

The primary efficacy endpoint of study CR201-18 was met, the difference between best ORR of BP02 (Dazublys) and best ORR by BICR of Herceptin was in the a priori defined margin of similarity (13%). Clinical efficacy between BP02 (Dazublys) and Herceptin is considered similar.

5.1.4. Clinical safety

5.1.4.1. Patient exposure

A total of 382 subjects received at least one dose of study drug in the 2 studies (BP02-101 study: 37; BP02-CR201-18 study: 345], US- Herceptin [n=37], and EU- Herceptin [n=382]).

Table 34 - Treatment dose compliance for subjects study BP02-101

S. No	Treatment Compliance (N=111)	
1	Number of subjects completed full infusion	106 (95.5%)
2	Number of subjects did not receive full infusion	5 (4.5%)

SAF TAB 02 provides a summary of treatment compliance of trastuzumab and docetaxel in safety population.

Table 35 - Summary of extent of BP02 and Herceptin exposure of patients-CR201-18 study

	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Induction Phase			
Exposure Duration (days)			
Mean (SD)	157.6 (51.59)	162.3 (48.73)	160.0 (50.20)
Median	177.0	178.0	178.0
Range	21-228	21-239	21-239
Number of Cycles			
Mean (SD)	6.8 (2.18)	7.0 (2.04)	6.9 (2.11)
Median	8.0	8.0	8.0

Range	1-8	1-8	1-8
Number of Patients by Number of Completed Treatment Cycles Received (%)			
Cycle 1 Day 1	345 (100)	345 (100)	690 (100)
Cycle 2 Day 22	328 (95.1)	333 (96.5)	661 (95.8)
Cycle 3 Day 43	309 (89.6)	313 (90.7)	622 (90.1)
Cycle 4 Day 64	300 (87.0)	307 (89.0)	607 (88.0)
Cycle 5 Day 85	295 (85.5)	301 (87.2)	596 (86.4)
Cycle 6 Day 106	266 (77.1)	282 (81.7)	548 (79.4)
Cycle 7 Day 127	254 (73.6)	275 (79.7)	529 (76.7)
Cycle 8 Day 148	243 (70.4)	268 (77.7)	511 (74.1)
Maintenance Phase			
Exposure Duration (days)			
Mean (SD)	409.1 (127.06)	416.0 (125.27)	412.7 (126.02)
Median	374.0	420.5	401.0
Range	198-623	194-618	194-623
Number of Cycles			
Mean (SD)	17.6 (5.44)	17.8 (5.40)	17.7 (5.42)
Median	16.0	17.5	16.0
Range	9-24	9-24	9-24
Number of Patients by Number of Completed Treatment Cycles Received (%)			
Cycle 9 Day 169	197 (57.1)	220 (63.8)	417 (60.4)
Cycle 10 Day 190	192 (55.7)	212 (61.4)	404 (58.6)
Cycle 11 Day 211	185 (53.6)	204 (59.1)	389 (56.4)
Cycle 12 Day 232	177 (51.3)	196 (56.8)	373 (54.1)
Cycle 13 Day 253	130 (37.7)	153 (44.3)	283 (41.0)
Cycle 14 Day 274	126 (36.5)	149 (43.2)	275 (39.9)
Cycle 15 Day 295	121 (35.1)	143 (41.4)	264 (38.3)
Cycle 16 Day 316	118 (34.2)	137 (39.7)	255 (37.0)
Cycle 17 Day 337	93 (27.0)	113 (32.8)	206 (29.9)
Cycle 18 Day 358	88 (25.5)	110 (31.9)	198 (28.7)
Cycle 19 Day 379	88 (25.5)	107 (31.0)	195 (28.3)
Cycle 20 Day 400	86 (24.9)	100 (29.0)	186 (27.0)
Cycle 21 Day 421	71 (20.6)	82 (23.8)	153 (22.2)
Cycle 22 Day 442	71 (20.6)	80 (23.2)	151 (21.9)
Cycle 23 Day 463	71 (20.6)	79 (22.9)	150 (21.7)
Cycle 24 Day 484	69 (20.0)	78 (22.6)	147 (21.3)
N: Number of patients in safety population. SD: Standard Deviation. Exposure duration = Last dose date - First dose date + 21; For number of cycles % = (n/N)*100. Only the actual dose administered and planned dose till the time of discontinuation were considered for compliance calculation for patients who discontinued early in the study.			

Table 36 - Summary of Extent of Docetaxel Exposure of Patients - CR201-18

	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Exposure Duration (days)			
Mean (SD)	152.4 (51.78)	156.4 (50.73)	154.4 (51.26)
Median	175.0	177.0	176.0
Range	21-228	21-239	21-239
Number of Cycles			
Mean (SD)	6.6 (2.18)	6.8 (2.12)	6.7 (2.15)
Median	8.0	8.0	8.0
Range	1-8	1-8	1-8
Number of Patients by Number of Completed Treatment Cycles Received (%)			
Cycle 1 Day 1	344 (99.7)	344 (99.7)	688 (99.7)
Cycle 2 Day 22	325 (94.2)	331 (95.9)	656 (95.1)
Cycle 3 Day 43	309 (89.6)	309 (89.6)	618 (89.6)
Cycle 4 Day 64	299 (86.7)	304 (88.1)	603 (87.4)
Cycle 5 Day 85	290 (84.1)	294 (85.2)	584 (84.6)
Cycle 6 Day 106	257 (74.5)	274 (79.4)	531 (77.0)

Cycle 7 Day 127	220 (63.8)	243 (70.4)	463 (67.1)
Cycle 8 Day 148	210 (60.9)	232 (67.2)	442 (64.1)
N: Number of patients in safety population. SD: Standard Deviation. Exposure duration = Last dose date - First dose date + 21; For number of cycles % = (n/N)*100. Only the actual dose administered and planned dose till the time of discontinuation were considered for compliance calculation for patients who discontinued early in the study.			

Concomitant medications related to prophylaxis in study CR201-18

Table 37 - Summary of Concomitant Medications Related to Prophylaxis (> 10% incidence in either group) (Safety Population) - CR201-18

Indication category/ CM Class/ Preferred term	**BP02 (N=345) n (%)**	**EU-Herceptin (N=345) n (%)**
Induction Phase		
Patients with ≥ 1 concomitant medication related to prophylaxis	340 (98.6)	344 (99.7)
PROPHYLAXIS FOR NEUTROPENIA	326 (94.5)	335 (97.1)
Colony stimulating factors	326 (94.5)	335 (97.1)
PEGFILGRASTIM	326 (94.5)	334 (96.8)
PROPHYLAXIS FOR NAUSEA AND VOMITING	300 (87.0)	312 (90.4)
Serotonin (5HT3) antagonists	227 (65.8)	243 (70.4)
ONDANSETRON	219 (63.5)	229 (66.4)
Propulsives	44 (12.8)	34 (9.9)
DOMPERIDONE	44 (12.8)	34 (9.9)
Corticosteroids, moderately potent (group II)	29 (8.4)	35 (10.1)
DEXAMETHASONE	29 (8.4)	35 (10.1)
PROPHYLAXIS FOR GASTROESOPHAGEAL REFLUX DISEASE	275 (79.7)	291 (84.3)
Proton pump inhibitors	237 (68.7)	255 (73.9)
PANTOPRAZOLE	215 (62.3)	221 (64.1)
H2-receptor antagonists	66 (19.1)	60 (17.4)
RANITIDINE	65 (18.8)	59 (17.1)
PROPHYLAXIS FOR PAIN AND INFLAMMATION	189 (54.8)	188 (54.5)
Anilides	166 (48.1)	169 (49.0)
PARACETAMOL	166 (48.1)	169 (49.0)
Other opioids	124 (35.9)	112 (32.5)
TRAMADOL	98 (28.4)	99 (28.7)
PROPHYLAXIS FOR ALLERGY, PAIN AND INFLAMMATION	107 (31.0)	106 (30.7)
Corticosteroids, moderately potent (group II)	92 (26.7)	92 (26.7)
DEXAMETHASONE	92 (26.7)	92 (26.7)
PROPHYLAXIS FOR CONSTIPATION	81 (23.5)	70 (20.3)
Magnesium compounds	39 (11.3)	44 (12.8)
MAGNESIUM HYDROXIDE	39 (11.3)	44 (12.8)
Softeners, emollients	37 (10.7)	36 (10.4)
PARAFFIN, LIQUID	37 (10.7)	36 (10.4)
Osmotically acting laxatives	35 (10.1)	22 (6.4)
LACTULOSE	35 (10.1)	22 (6.4)

PROPHYLAXIS FOR VITAMIN SUPPLEMENT	64 (18.6)	50 (14.5)
Combinations of vitamins	57 (16.5)	41 (11.9)
ASCORBIC ACID; BIOTIN; CALCIUM PANTOTHENATE; CYANOCOBALAMIN; FOLIC	57 (16.5)	41 (11.9)
PROPHYLAXIS FOR INFLAMMATION	61 (17.7)	49 (14.2)
Corticosteroids, moderately potent (group II)	58 (16.8)	46 (13.3)
DEXAMETHASONE	58 (16.8)	46 (13.3)
PROPHYLAXIS FOR ANEMIA	50 (14.5)	54 (15.7)
PROPHYLAXIS FOR INFECTIONS	62 (18.0)	40 (11.6)
Maintenance Phase		
Patients with at least one concomitant medication related to prophylaxis	128 (37.1)	147 (42.6)
PROPHYLAXIS FOR GASTROESOPHAGEAL REFLUX DISEASE	111 (32.2)	127 (36.8)
Proton pump inhibitors	98 (28.4)	108 (31.3)
PANTOPRAZOLE	89 (25.8)	93 (27.0)
PROPHYLAXIS FOR NAUSEA AND VOMITING	107 (31.0)	113 (32.8)
Serotonin (5HT3) antagonists	73 (21.2)	95 (27.5)
ONDANSETRON	72 (20.9)	94 (27.2)
PROPHYLAXIS FOR PAIN AND INFLAMMATION	62 (18.0)	65 (18.8)
Anilides	56 (16.2)	63 (18.3)
PARACETAMOL	56 (16.2)	63 (18.3)
Other opioids	36 (10.4)	39 (11.3)

n (%) = number and percentage of patients (patients with multiple medications are counted only once per line)

WHO Drug Dictionary Global Version: Induction Phase - B3/C3 format March 1,2023; Maintenance Phase - B3/C3 format March 1, 2024.

5.1.4.2. Adverse events

Phase I study BP02-101

In both study arms of the phase I study, EU- Herceptin and BP02, equally 27 subjects (73%) reported any AEs. The most commonly reported TEAEs by PT with an incidence ≥ 5% in the BP02 group (phase I study) were: headache (27.0%); infusion related reactions (16.2%); upper respiratory tract infection (13.5%); pyrexia, back pain (10.8% each); fatigue, COVID-19, acne (8.1% each); malaise, seasonal allergy, and oropharyngeal pain (5.4% each). The most commonly reported TEAEs by PT with an incidence ≥ 5% in the EU-Herceptin group (phase I study) were: headache (29.7%); upper respiratory tract infection (18.9%); COVID-19 (13.5%); fatigue, pyrexia, infusion related reaction (8.1% each); influenza like illness, infusion site erythema, injection site pain, skin abrasion, and dermatitis contact (5.4% each). The most commonly reported TEAEs by PT with an incidence ≥ 5% in the US-Herceptin group were: headache (37.8%); infusion related reactions (32.4%); upper respiratory tract infection (21.6%); catheter site bruise, pyrexia (10.8%); nausea, non-cardiac chest pain, COVID-19, gastroenteritis, dermatitis contact (8.1% each); diarrhoea, mouth ulceration, fatigue, tonsillitis, viral upper respiratory tract infection, sunburn, myalgia, cough, and rhinorrhoea (5.4% each).

Table 38 - Overall summary of all treatment-emergent adverse events - phase I BP02-101 study

Number of subjects (%)/ [Number of events]

	BP02 (N=37)	EU-Herceptin (N=37)	US-Herceptin (N=37)	All Subjects (N=111)
TEAEs	27 (73.0)/ [80]	27 (73.0)/ [81]	33 (89.2)/ [120]	87 (78.4)/ [281]
Severe TEAEs	0	0	0	0
TEAEs Related to study treatment	18 (48.6)/ [34]	15 (40.5)/ [29]	23 (62.2)/ [43]	56 (50.5)/ [106]
Serious TEAEs	0	1 (2.7)/ [1]	0	1 (0.9)/ [1]
Special Interest TEAEs	8 (21.6)/ [10]	7 (18.9)/ [14]	16 (43.2)/ [26]	31 (27.9)/ [50]
Infusion related reactions	8 (21.6)/ [10]	7 (18.9)/ [13]	16 (43.2)/ [26]	31 (27.9)/ [49]
TEAEs leading to discontinuation from study treatment	1 (2.7)/ [1]	0	4 (10.8)/ [11]	5 (4.5)/ [12]
TEAEs leading to discontinuation from study	1 (2.7)/ [1]	0	3 (8.1)/ [3]	4 (3.6)/ [4]
TEAEs leading to death	0	0	0	0

Abbreviations: n = available data; N = sample size Note: A subject experiencing multiple occurrences of an adverse event in a category was counted, at most, once for that category for each treatment and once for "All Subjects".

Phase III study CR201-18

Table 39 - Summary of Adverse Events during Induction and Maintenance Phase - Safety Analysis Population, p III study, (#= E number of events) - CR201-18

Adverse Event Categories	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patients	**n (%) #E**	**n (%) #E**	**n (%) #E**
Any AE	232 (67.2) 1167	233 (67.5) 992	465 (67.4) 2159
Any AE of Grade 3 or higher	49 (14.2) 107	39 (11.3) 84	88 (12.8) 191
Any TEAE	228 (66.1) 1148	233 (67.5) 972	461 (66.8) 2120
Any TEAE occurring in at least 5% of patients	161 (46.7) 562	176 (51.0) 500	337 (48.8) 1062
Any TEAE of Grade 3 or higher	47 (13.6) 99	39 (11.3) 74	86 (12.5) 173
Any Serious AE (SAE)	34 (9.9) 62	20 (5.8) 31	54 (7.8) 93
Any treatment-emergent SAE (TESAE)	33 (9.6) 59	20 (5.8) 28	53 (7.7) 87
Any TEAE of special interest (AESI)	60 (17.4) 78	44 (12.8) 62	104 (15.1) 140
Any serious adverse drug reactions (SADRs)	0	1 (0.3) 1	1 (0.1) 1
Any suspected unexpected serious adverse reactions (SUSARs)	2 (0.6) 2	0	2 (0.3) 2
Any TEAE related to study drug	61 (17.7) 240	72 (20.9) 201	133 (19.3) 441
Any TESAE related to study drug	2 (0.6) 3	1 (0.3) 1	3 (0.4) 4
Any TEAE related to the study drug occurring in at least 5% of patients	0	0	0
Any AE leading to death	12 (3.5) 33	15 (4.3) 41	27 (3.9) 74
Any TEAE leading to death	11 (3.2) 27	14 (4.1) 31	25 (3.6) 58

Any AE leading to study discontinuation	7 (2.0) 7	6 (1.7) 6	13 (1.9) 13
Any TEAE leading to study discontinuation	7 (2.0) 7	5 (1.4) 5	12 (1.7) 12
Any AE leading to treatment withdrawal	27 (7.8) 54	24 (7.0) 35	51 (7.4) 89
Any TEAE leading to treatment withdrawal	25 (7.2) 45	22 (6.4) 32	47 (6.8) 77
TEAE leading to treatment withdrawal occurring in at least 5% of patients	0	0	0
Any TEAE leading to treatment interruption	19 (5.5) 23	21 (6.1) 35	40 (5.8) 58
TEAE leading to treatment interruption occurring in at least 5% of patients	0	0	0
AE: Adverse event. TEAE: Treatment Emergent Adverse Event. SAE: Serious adverse event. n = Number of patients with at least one AE in each category. #E = Number of events in each category. N = Number of patients in the safety population. % = Percentage of patients with at least one AE in each category relative to the total number of patients in the safety population. All patients are counted only once per treatment in each AE category.			

Table 40 - TEAEs by System Organ Class during Induction and Maintenance Phase - **CR201-18**

System Organ Class	**BP02 (N=345)**	**Herceptin (N=345)**	**Total (N=690)**
Number (%) of Patient's	**n (%) #E**	**n (%) #E**	**n (%) #E**
Number of patients with at least one TEAE	228 (66.1) 1148	233 (67.5) 972	461 (66.8) 2120
General disorders and administration site conditions	118 (34.2) 294	106 (30.7) 207	224 (32.5) 501
Gastrointestinal disorders	85 (24.6) 230	95 (27.5) 195	180 (26.1) 425
Infections and infestations	62 (18.0) 84	59 (17.1) 82	121 (17.5) 166
Musculoskeletal and connective tissue disorders	56 (16.2) 102	61 (17.7) 102	117 (17.0) 204
Nervous system disorders	58 (16.8) 84	42 (12.2) 58	100 (14.5) 142
Skin and subcutaneous tissue disorders	39 (11.3) 58	57 (16.5) 79	96 (13.9) 137
Blood and lymphatic system disorders	46 (13.3) 69	49 (14.2) 74	95 (13.8) 143
Metabolism and nutrition disorders	37 (10.7) 45	28 (8.1) 31	65 (9.4) 76
Respiratory, thoracic and mediastinal disorders	34 (9.9) 58	22 (6.4) 34	56 (8.1) 92
Investigations	28 (8.1) 39	23 (6.7) 36	51 (7.4) 75
Vascular disorders	13 (3.8) 19	14 (4.1) 15	27 (3.9) 34
Cardiac disorders	13 (3.8) 17	7 (2.0) 8	20 (2.9) 25
Immune system disorders	6 (1.7) 7	9 (2.6) 9	15 (2.2) 16
Psychiatric disorders	7 (2.0) 9	5 (1.4) 5	12 (1.7) 14
Reproductive system and breast disorders	7 (2.0) 8	4 (1.2) 6	11 (1.6) 14
Ear and labyrinth disorders	6 (1.7) 7	4 (1.2) 4	10 (1.4) 11
Eye disorders	5 (1.4) 5	5 (1.4) 10	10 (1.4) 15
Hepatobiliary disorders	5 (1.4) 7	2 (0.6) 5	7 (1.0) 12
Renal and urinary disorders	3 (0.9) 3	4 (1.2) 4	7 (1.0) 7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.6) 3	2 (0.6) 3	4 (0.6) 6

Injury, poisoning and procedural complications	0	3 (0.9) 4	3 (0.4) 4
Endocrine disorders	0	1 (0.3) 1	1 (0.1) 1

N = Number of patients in safety population. n = Number of patients with at least one AE in each category. #E = Number of events in each category. % = Percentage of patients with at least one AE in each category relative to the total number of patients in the safety population. All patients are counted only once per treatment in each AE category.

Table 41 - TEAEs by MedDRA System Organ Class with at least ≥ 5% incidence-Induction - CR201-18

System Organ Class Preferred Term [1]	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patients	**n (%) #E**	**n (%) #E**	**n (%) #E**
Number of patients with at least one TEAE	161 (46.7) 562	176 (51.0) 500	337 (48.8) 1062
General disorders and administration site conditions	83 (24.1) 213	77 (22.3) 142	160 (23.2) 355
Pyrexia	51 (14.8)103	40 (11.6) 57	91 (13.2) 160
Pain	35 (10.1) 59	36 (10.4) 50	71 (10.3) 109
Asthenia	34 (9.9) 51	26 (7.5) 35	60 (8.7) 86
Gastrointestinal disorders	68 (19.7) 146	77 (22.3) 131	145 (21.0) 277
Vomiting	42 (12.2) 65	47 (13.6) 59	89 (12.9) 124
Diarrhoea	41 (11.9) 63	39 (11.3) 49	80 (11.6) 112
Constipation	14 (4.1) 18	19 (5.5) 23	33 (4.8) 41
Musculoskeletal and connective tissue disorders	49 (14.2) 85	56 (16.2) 89	105 (15.2) 174
Myalgia	24 (7.0) 42	28 (8.1) 41	52 (7.5) 83
Back pain	15 (4.3) 19	20 (5.8) 28	35 (5.1) 47
Pain in extremity	18 (5.2) 24	15 (4.3) 20	33 (4.8) 44
Infections and infestations	33 (9.6) 35	38 (11.0) 50	71 (10.3) 85
Urinary tract infection	33 (9.6) 35	38 (11.0) 50	71 (10.3) 85
Blood and lymphatic system disorders	28 (8.1) 41	33 (9.6) 36	61 (8.8) 77
Anaemia	28 (8.1) 41	33 (9.6) 36	61 (8.8) 77
Skin and subcutaneous tissue disorders	16 (4.6) 16	31 (9.0) 31	47 (6.8) 47
Alopecia	16 (4.6) 16	31 (9.0) 31	47 (6.8) 47
Nervous system disorders	23 (6.7) 26	21 (6.1) 21	44 (6.4) 47
Headache	23 (6.7) 26	21 (6.1) 21	44 (6.4) 47

N = Number of patients in safety population. n = Number of patients with at least one AE in each category. #E
= Number of events in each category. % = Percentage of patients with at least one AE in each category relative to the total number of patients in the safety population. All patients are counted only once per treatment in each AE category.
[1] Within a System Organ Class, patients may have reported more than one Preferred Term.

5.1.4.3. Serious adverse event/deaths/other significant events

Serious adverse events

Table 42 - Serious TEAE Occurred in at least 5 Patients considering both arms during Induction and Maintenance Phase- Safety Analysis Population - CR201-18

SOC Preferred Term	BP02 N = 345 n (%)	Herceptin N = 345 n (%)	
Gastrointestinal disorders Diarrhoea	5 (1.4)	0	5 (0.7)
General disorders and administration site conditions Death	4 (1.2)	5 (1.4)	9 (1.3)
Respiratory, thoracic and mediastinal disorders Dyspnoea	4 (1.2)	2 (0.6)	6 (0.9)

Treatment emergent adverse events by outcome

Most of the treatment emergent adverse events resolved in both arms. TEAE persisted in 11.3% and 10.1% in the BP-02 and Herceptin arm.

Table 43 - Summary of TEAEs by Outcome during Induction and Maintenance Phase - CR201-18

	Outcome	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
		n (%) #E	n (%) #E	n (%) #E
Number of patients with at least one TEAE		228 (66.1) 1148	233 (67.5) 972	461 (66.8) 2120
	Recovered/Resolved	215 (62.3) 1053	216 (62.6) 890	431 (62.5) 1943
	Recovered/Resolved with Sequelae	6 (1.7) 9	5 (1.4) 7	11 (1.6) 16
	Persisted	39 (11.3) 56	35 (10.1) 41	74 (10.7) 97
	Fatal	11 (3.2) 27	14 (4.1) 31	25 (3.6) 58
N = Number of patients in safety set. n = Number of patients with at least one AE in each category. #E = Number of events in each category. N = Number of patients in the safety population. % = Percentage of patients with at least one AE in each category relative to the total number of patients in the safety population. All patients are counted only once per treatment in each AE category.				

Grade 3- 5 Treatment emergent Adverse Events

Table 44 - TEAEs by MedDRA System Organ Class, Preferred Term and CTCAE Grade during Induction and Maintenance Phase- Safety Analysis Population - CR201-18

System Organ Class	CTCAE Grade	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patient's		n (%) #E	n (%) #E	n (%) #E
Number of patients with at least one TEAE	Grade 5	6 (1.7) 8	9 (2.6) 10	15 (2.2) 18
	≥ Grade 3	47 (13.6) 99	39 (11.3) 74	86 (12.5) 173
General disorders and administration site conditions	Grade 5	4 (1.2) 4	5 (1.4) 5	9 (1.3) 9
	≥ Grade 3	12 (3.5) 13	10 (2.9) 10	22 (3.2) 23
Gastrointestinal disorders	Grade 5	0	0	0
	≥ Grade 3	10 (2.9) 11	4 (1.2) 9	14 (2.0) 20

Infections and infestations	Grade 5	2 (0.6) 2	1 (0.3) 2	3 (0.4) 4
	≥ Grade 3	10 (2.9) 12	4 (1.2) 7	14 (2.0) 19
Musculoskeletal and connective tissue disorders	Grade 5	0	0	0
	≥ Grade 3	3 (0.9) 5	3 (0.9) 6	6 (0.9) 11
Nervous system disorders	Grade 5	0	0	0
	≥ Grade 3	2 (0.6) 4	2 (0.6) 2	4 (0.6) 6
Skin and subcutaneous tissue disorders	Grade 5	0	0	0
	≥ Grade 3	1 (0.3) 1	2 (0.6) 2	3 (0.4) 3
Blood and lymphatic system disorders	Grade 5	0	0	0
	≥ Grade 3	10 (2.9) 14	9 (2.6) 9	19 (2.8) 23
Metabolism and nutrition disorders	Grade 5	0	0	0
	≥ Grade 3	2 (0.6) 2	1 (0.3) 1	3 (0.4) 3
Respiratory, thoracic and mediastinal disorders	Grade 5	1 (0.3) 1	2 (0.6) 2	3 (0.4) 3
	≥ Grade 3	10 (2.9) 16	7 (2.0) 11	17 (2.5) 27
Investigations	Grade 5	0	0	0
	≥ Grade 3	6 (1.7) 8	0	6 (0.9) 8
Vascular disorders	Grade 5	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	5 (1.4) 6	4 (1.2) 4	9 (1.3) 10
Cardiac disorders	Grade 5	0	1 (0.3) 1	1 (0.1) 1
	≥ Grade 3	2 (0.6) 2	2 (0.6) 2	4 (0.6) 4
Immune system disorders	Grade 5	0	0	0
	≥ Grade 3	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Psychiatric disorders	Grade 5	0	0	0
	≥ Grade 3	0	0	0
Reproductive system and breast disorders	Grade 5	0	0	0
	≥ Grade 3	0	1 (0.3) 1	1 (0.1) 1
Ear and labyrinth disorders	Grade 5	0	0	0
	≥ Grade 3	1 (0.3) 1	0	1 (0.1) 1
Eye disorders	Grade 5	0	0	0
	≥ Grade 3	0	1 (0.3) 1	1 (0.1) 1
Hepatobiliary disorders	Grade 5	0	0	0

Adverse events of special interest

Table 45 - Summary of All Treatment emergent Adverse Events of Special Interest by System Organ Class and Preferred Term (Safety Analysis Set - BP02- 101)

System Organ Class/Preferred Term	BP02 (trastuzumab) group (N=37) n (%) E	EU-Herceptin (trastuzumab) group (N=37) n (%) E	US-Herceptin (trastuzumab) group (N=37) n (%) E	Overall (N=111) n (%) E
Number of subjects with TEAEs of Special Interest	8 (21.6)/[10]	7 (18.9)/[14]	16 (43.2)/[26]	31 (27.9)/[50]
GASTROINTESTINAL DISORDERS	0	0	1 (2.7)/[2]	1 (0.9)/[2]
Nausea	0	0	1 (2.7)/[1]	1 (0.9)/[1]
Vomiting	0	0	1 (2.7)/[1]	1 (0.9)/[1]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (5.4)/[2]	4 (10.8)/[6]	4 (10.8)/[5]	10 (9.0)/[13]
Chills	0	1 (2.7)/[1]	1 (2.7)/[1]	2 (1.8)/[2]
Influenza Like Illness	0	1 (2.7)/[1]	0	1 (0.9)/[1]
Infusion Site Erythema	0	1 (2.7)/[1]	0	1 (0.9)/[1]
Malaise	1 (2.7)/[1]	0	0	1 (0.9)/[1]
Pyrexia	1 (2.7)/[1]	3 (8.1)/[3]	4 (10.8)/[4]	8 (7.2)/[8]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6 (16.2)/[8]	3 (8.1)/[4]	12 (32.4)/[12]	21 (18.9)/[24]
Infusion Related Reaction	6 (16.2)/[8]	3 (8.1)/[4]	12 (32.4)/[12]	21 (18.9)/[24]
INVESTIGATIONS	0	1 (2.7)/[1]	0	1 (0.9)/[1]
Ejection Fraction Decreased	0	1 (2.7)/[1]	0	1 (0.9)/[1]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	2 (5.4)/[2]	2 (5.4)/[2]	4 (3.6)/[4]
Muscle Spasms	0	1 (2.7)/[1]	0	1 (0.9)/[1]
Myalgia	0	1 (2.7)/[1]	2 (5.4)/[2]	3 (2.7)/[3]
NERVOUS SYSTEM DISORDERS	0	1 (2.7)/[1]	2 (5.4)/[3]	3 (2.7)/[4]

Adverse Events of Special Interest (AESI) were:

a. Cardiac related: AEs such as decreased LVEF, left ventricular systolic dysfunction, congestive heart failure and overall cardiac safety.

b. Infusion related reactions

c. Neutropenia

d. Pulmonary disorders

e. Allergic-like reactions and hypersensitivity.

Table 46 - Treatment-Emergent Adverse Events of Special Interest (AESI) by System Organ Class, Preferred Term and CTCAE Grade during Induction and Maintenance Phase- Safety Analysis Population - CR201-18

System Organ Class Preferred Term	CTCAE Grade	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patients		**n (%) #E**	**n (%) #E**	**n (%) #E**
Number of patients with at least one TEAESI	Total	60 (17.4) 78	44 (12.8) 62	104 (15.1) 140
	≥ Grade 3	11 (3.2) 12	11 (3.2) 14	22 (3.2) 26
Blood and lymphatic system disorders	Total	14 (4.1) 19	15 (4.3) 24	29 (4.2) 43
	≥ Grade 3	3 (0.9) 3	4 (1.2) 4	7 (1.0) 7
Neutropenia	Total	14 (4.1) 17	12 (3.5) 21	26 (3.8) 38
	≥ Grade 3	3 (0.9) 3	2 (0.6) 2	5 (0.7) 5
Febrile neutropenia	Total	1 (0.3) 2	3 (0.9) 3	4 (0.6) 5
	≥ Grade 3	0	2 (0.6) 2	2 (0.3) 2
Cardiac disorders	Total	13 (3.8) 17	7 (2.0) 8	20 (2.9) 25
	≥ Grade 3	2 (0.6) 2	2 (0.6) 2	4 (0.6) 4
Tachycardia	Total	2 (0.6) 3	2 (0.6) 3	4 (0.6) 6
	≥ Grade 3	1 (0.3) 1	0	1 (0.1) 1
Cardiac dysfunction	Total	1 (0.3) 1	2 (0.6) 2	3 (0.4) 3
	≥ Grade 3	0	1 (0.3) 1	1 (0.1) 1
Left ventricular dysfunction	Total	2 (0.6) 4	1 (0.3) 1	3 (0.4) 5
	≥ Grade 3	0	0	0
Palpitations	Total	2 (0.6) 2	0	2 (0.3) 2
	≥ Grade 3	0	0	0
Acute myocardial infarction	Total	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	1 (0.3) 1	0	1 (0.1) 1
Cardiac arrest	Total	0	1 (0.3) 1	1 (0.1) 1
	≥ Grade 3	0	1 (0.3) 1	1 (0.1) 1
Cardiac failure	Total	0	1 (0.3) 1	1 (0.1) 1
	≥ Grade 3	0	0	0
Cardiomyopathy	Total	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	0	0	0
Diastolic dysfunction	Total	1 (0.3) 2	0	1 (0.1) 2
	≥ Grade 3	0	0	0
Myocardial ischaemia	Total	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	0	0	0
Sinus bradycardia	Total	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	0	0	0
Systolic dysfunction	Total	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	0	0	0
Investigations	Total	12 (3.5) 14	7 (2.0) 8	19 (2.8) 22
	≥ Grade 3	1 (0.3) 1	0	1 (0.1) 1
Ejection fraction decreased	Total	11 (3.2) 12	6 (1.7) 7	17 (2.5) 19
	≥ Grade 3	1 (0.3) 1	0	1 (0.1) 1

Neutrophil count decreased	Total	1 (0.3) 2	1 (0.3) 1	2 (0.3) 3
	≥ Grade 3	0	0	0
Immune system disorders	Total	6 (1.7) 7	9 (2.6) 9	15 (2.2) 16
	≥ Grade 3	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Hypersensitivity	Total	6 (1.7) 7	9 (2.6) 9	15 (2.2) 16
	≥ Grade 3	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Respiratory, thoracic and mediastinal disorders	Total	8 (2.3) 10	4 (1.2) 5	12 (1.7) 15
	≥ Grade 3	3 (0.9) 4	4 (1.2) 5	7 (1.0) 9
Acute respiratory distress syndrome	Total	3 (0.9) 3	1 (0.3) 1	4 (0.6) 4
	≥ Grade 3	2 (0.6) 2	1 (0.3) 1	3 (0.4) 3
Pleural effusion	Total	2 (0.6) 3	1 (0.3) 2	3 (0.4) 5
	≥ Grade 3	0	1 (0.3) 2	1 (0.1) 2
Respiratory distress	Total	2 (0.6) 3	0	2 (0.3) 3
	≥ Grade 3	1 (0.3) 2	0	1 (0.1) 2
Acute respiratory failure	Total	0	1 (0.3) 1	1 (0.1) 1
	≥ Grade 3	0	1 (0.3) 1	1 (0.1) 1
Pneumothorax	Total	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	0	0	0

Respiratory failure	Total	0	1 (0.3) 1	1 (0.1) 1
	≥ Grade 3	0	1 (0.3) 1	1 (0.1) 1
General disorders and administration site conditions	Total	5 (1.4) 5	2 (0.6) 4	7 (1.0) 9
	≥ Grade 3	0	0	0
Infusion site swelling	Total	2 (0.6) 2	1 (0.3) 3	3 (0.4) 5
	≥ Grade 3	0	0	0
Extravasation	Total	2 (0.6) 2	0	2 (0.3) 2
	≥ Grade 3	0	0	0
Infusion site extravasation	Total	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	0	0	0
Injection site inflammation	Total	0	1 (0.3) 1	1 (0.1) 1
	≥ Grade 3	0	0	0
Infections and infestations	Total	4 (1.2) 5	2 (0.6) 3	6 (0.9) 8
	≥ Grade 3	1 (0.3) 1	1 (0.3) 2	2 (0.3) 3
Eye infection	Total	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
	≥ Grade 3	0	0	0
Pneumonia viral	Total	2 (0.6) 2	0	2 (0.3) 2
	≥ Grade 3	1 (0.3) 1	0	1 (0.1) 1
Atypical pneumonia	Total	1 (0.3) 2	0	1 (0.1) 2
	≥ Grade 3	0	0	0
Neutropenic sepsis	Total	0	1 (0.3) 2	1 (0.1) 2
	≥ Grade 3	0	1 (0.3) 2	1 (0.1) 2
Skin and subcutaneous tissue disorders	Total	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
	≥ Grade 3	0	0	0
Erythema	Total	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	0	0	0
Swelling face	Total	0	1 (0.3) 1	1 (0.1) 1
	≥ Grade 3	0	0	0

N = Number of patients in safety set. n = Number of patients with at least one AE in each category. #E = Number of events in each category. % = Percentage of patients with at least one AE in each category relative to the total number of patients in the safety set. All patients are counted only once per treatment in each AE category.

Table 47 - Summary of TEAESI by CTCAE Grade– safety analysis population CR201-18

	CTCAE Grade	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
		n (%) #E	n (%) #E	n (%) #E
Number of patients with at least one TEAESI	Grade 1	11 (3.2) 15	12 (3.5) 17	23 (3.3) 32
	Grade 2	10 (2.9) 14	8 (2.3) 8	18 (2.6) 22
	Grade 3	7 (2.0) 7	2 (0.6) 3	9 (1.3) 10
	Grade 4	1 (0.3) 1	1 (0.3) 2	2 (0.3) 3
	Grade 5	0	3 (0.9) 3	3 (0.4) 3
	Total	29 (8.4) 37	26 (7.5) 33	55 (8.0) 70
	≥ Grade 3	8 (2.3) 8	6 (1.7) 8	14 (2.0) 16

- Cardiac related AEs such as decreased LVEF, left ventricular systolic dysfunction, congestive heart failure and overall cardiac safety.

Table 48 - Cardiac related adverse events (AESI) during Induction and Maintenance CR201-18

MedDRA term (Preferred Term)	BP02 N= 345			Herceptin N= 345		
	Total n (%) E	Resolved	Grade≥3 (n')	Total n (%) E	Resolved	Grade≥3 (n')
Tachycardia	2 (0.6) 3	Resolved	Yes (1) (Grade 3)	2 (0.6) 3	Resolved	No
Cardiac dysfunction	1 (0.3) 1	Resolved	No	2 (0.6) 2	Resolved	Yes (1) (Grade 3)
Left ventricular dysfunction	2 (0.6) 4	Resolved	No	1 (0.3) 1	Resolved	No
Palpitations	2 (0.6) 2	Resolved	No	0	-	-
Acute myocardial infarction	1 (0.3) 1	Resolved	Yes (1) (Grade 3)	0	-	-
Cardiac arrest	0	-	-	1 (0.3) 1	Fatal	Yes (1) (Grade 5)
Cardiac failure	0	-	-	1 (0.3) 1	Resolved with sequelae	No
Cardiomyopathy	1 (0.3) 1	Persisted	No	0	-	-
Diastolic dysfunction	1 (0.3) 1	Resolved	No	0	-	-
Myocardial ischaemia	1 (0.3) 1	Persisted	No	0	-	-
Sinus bradycardia	1 (0.3) 1	Resolved	No	0	-	-
Systolic dysfunction	1 (0.3) 1	Resolved	No	0	-	-
n'= no. of patients with Grade ≥3 AEs						

Signs and symptoms of cardiac toxicity (including MEDRA PT tachycardia, acute myocardial infarction, cardiac arrest, cardiac dysfuncion, cardiac failure, cardiomyopathy, palpitation and sinus bradycardia) was low

Table 49 - Summary of 2D-ECHO/MUGA Test Results - CR201-18

Visit	Test result	BP02 (N=345) n/m (%)	Herceptin (N=345) n/m (%)
Screening (Baseline)	Normal	267/345 (77.4)	252/345 (73.0)
	Abnormal, not clinically significant	78/345 (22.6)	93/345 (27.0)
	Abnormal, clinically significant	0	0
Cycle 3 Day 43	Normal	234/313 (74.8)	235/319 (73.7)
	Abnormal, not clinically significant	77/313 (24.6)	84/319 (26.3)
	Abnormal, clinically significant	2/313 (0.6)	0
	LVEF decrease from baseline of ≥ 10 percentage points and LVEF < 50%	2/313 (0.6)	1/319 (0.3)
Cycle 6 Day 106	Normal	203/277 (73.3)	209/290 (72.1)
	Abnormal, not clinically significant	73/277 (26.4)	81/290 (27.9)
	Abnormal, clinically significant	1/277 (0.4)	0
	LVEF decrease from baseline of ≥ 10 percentage points and LVEF < 50%	1/277 (0.4)	0
End of Induction	Normal	207/272 (76.1)	217/286 (75.9)
	Abnormal, not clinically significant	61/272 (22.4)	68/286 (23.8)
	Abnormal, clinically significant	4/272 (1.5)	1/286 (0.3)
	LVEF decrease from baseline of ≥ 10 percentage points and LVEF < 50%	5/272 (1.8)	1/286 (0.3)

Table 50 - Injection site inflammation (AESI) - CR201-18

Induction Phase

System Organ Class Preferred Term [1]	CTCAE Grade [2]	BP02 (N=345)		Herceptin (N=345)		Total (N=690)	
Number (%) of Patients		n	(%) #E	n	(%) #E	n	(%) #E
Injection site inflammation	Grade 1	0		1	(0.3) 1	1	(0.1) 1
	Grade 2	0		0		0	
	Grade 3	0		0		0	
	Grade 4	0		0		0	
	Grade 5	0		0		0	
	Total	0		1	(0.3) 1	1	(0.1) 1
	≥ Grade 3	0		0		0	

Table 51 - Neutropenia (AESI) - CR201-18

	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Induction Phase			
Neutropenia	11 (3.2) 14	9 (2.6) 9	20 (2.9) 23
Induction and Maintenance Phase			
Neutropenia	14 (4.1) 17	12 (3.5) 21	26 3.8) 38

Table 52 - Pulmonary Toxicities and Infusion reactions (AESI) - CR201-18

MedDRA Term (Preferred Term)	BP02 N = 345 n (%) #E	Herceptin N = 345 n (%) #E
Infusion site extravasation	1 (0.3) 1	0
Infusion site swelling	2 (0.6) 2	1 (0.3) 3
Pulmonary toxicity	0	1 (0.3) 1
Total	**3 (0.9) 3**	**2 (0.6) 4**

Table 53 - Hypersensitivity (AESI) - CR201-18

Induction Phase

System Organ Class Preferred Term [1]	CTCAE Grade [2]	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patients		n (%) #E	n (%) #E	n (%) #E
Hypersensitivity	Grade 1	3 (0.9) 3	7 (2.0) 7	10 (1.4) 10
	Grade 2	2 (0.6) 3	1 (0.3) 1	3 (0.4) 4
	Grade 3	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
	Grade 4	0	0	0
	Grade 5	0	0	0
	Total	6 (1.7) 7	9 (2.6) 9	15 (2.2) 16
	≥ Grade 3	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2

Suspected unexpected serious adverse events

Treatment emergent suspected unexpected serious adverse reactions (TESUSARs) are the unexpected SAEs as per reference safety information and are related to study treatment.

Table 54 - Summary of TESUSARs– safety analysis population - CR201-18

Preferred Term	CTCAE Grade	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patient's		**n (%) #E**	**n (%) #E**	**n (%) #E**
Number of patients with at least one TESUSARs	Total	2 (0.6) 2	0	2 (0.3) 2
	≥ Grade 3	1 (0.3) 1	0	1 (0.1) 1
Diastolic dysfunction	Total	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	0	0	0
Death	Total	1 (0.3) 1	0	1 (0.1) 1
	≥ Grade 3	1 (0.3) 1	0	1 (0.1) 1

Deaths causally related to the medicinal product

Table 55 - Summary of Patient Deaths during Induction and Maintenance phase - CR201-18

Preferred Term [1]	CTCAE Grade [2]	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patient's		**n (%) #E**	**n (%) #E**	**n (%) #E**
Number of patients with at least one TEAE leading to Death	Total	11 (3.2) 27	14 (4.1) 31	25 (3.6) 58
Death	Total	4 (1.2) 4	5 (1.4) 5	9 (1.3) 9
Asthenia	Total	2 (0.6) 2	1 (0.3) 1	3 (0.4) 3
Disease progression	Total	2 (0.6) 2	0	2 (0.3) 2

Pyrexia	Total	0	2 (0.6) 2	2 (0.3) 2
Dyspnoea	Total	1 (0.3) 1	3 (0.9) 3	4 (0.6) 4
Acute respiratory distress syndrome	Total	2 (0.6) 2	1 (0.3) 1	3 (0.4) 3
Hypoxia	Total	1 (0.3) 2	1 (0.3) 1	2 (0.3) 3
Acute respiratory failure	Total	0	1 (0.3) 1	1 (0.1) 1
Interstitial lung disease	Total	0	1 (0.3) 1	1 (0.1) 1
Pleural effusion	Total	0	1 (0.3) 2	1 (0.1) 2
Respiratory distress	Total	1 (0.3) 2	0	1 (0.1) 2
Respiratory failure	Total	0	1 (0.3) 1	1 (0.1) 1
COVID-19 pneumonia	Total	0	1 (0.3) 2	1 (0.1) 2
Dengue fever	Total	1 (0.3) 1	0	1 (0.1) 1
Lower respiratory tract infection	Total	1 (0.3) 1	0	1 (0.1) 1
Neutropenic sepsis	Total	0	1 (0.3) 2	1 (0.1) 2
Pneumonia viral	Total	1 (0.3) 1	0	1 (0.1) 1
Urinary tract infection	Total	0	1 (0.3) 1	1 (0.1) 1
Decreased appetite	Total	1 (0.3) 1	0	1 (0.1) 1
Hypoalbuminaemia	Total	1 (0.3) 1	0	1 (0.1) 1
Hypophagia	Total	0	1 (0.3) 1	1 (0.1) 1
Vomiting	Total	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Abdominal pain	Total	1 (0.3) 1	0	1 (0.1) 1
Diarrhoea	Total	0	1 (0.3) 1	1 (0.1) 1
Acute kidney injury	Total	1 (0.3) 1	0	1 (0.1) 1
Dysuria	Total	0	1 (0.3) 1	1 (0.1) 1
Hypotension	Total	1 (0.3) 2	1 (0.3) 1	2 (0.3) 3
Anaemia	Total	1 (0.3) 1	0	1 (0.1) 1
Cardiac arrest	Total	0	1 (0.3) 1	1 (0.1) 1
Hepatitis acute	Total	1 (0.3) 1	0	1 (0.1) 1
Femoral neck fracture	Total	0	1 (0.3) 2	1 (0.1) 2

Table 56 - Overview of TEAE leading to discontinuation in induction phase - CR201-18

Adverse Event Categories	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patients	**n (%) #E**	**n (%) #E**	**n (%) #E**
Any TEAE leading to study discontinuation	2 (0.6) 2	2 (0.6) 2	4 (0.6) 4
Any AE leading to treatment withdrawal	12 (3.5) 30	12 (3.5) 18	24 (3.5) 48
Any TEAE leading to treatment withdrawal	11 (3.2) 24	10 (2.9) 15	21 (3.0) 39
TEAE leading to treatment withdrawal occurring in at least 5% of patients	0	0	0
Any TEAE leading to treatment interruption	14 (4.1) 18	17 (4.9) 22	31 (4.5) 40
TEAE leading to treatment interruption occurring in at least 5% of patients	0	0	0

5.1.4.4. Laboratory findings

Phase 1: BP02-101 Study No important treatment group differences were noted in the mean change from baseline for any laboratory (hematology, serum chemistry, urinalysis) parameters. No relevant treatment group differences in shift changes were noted for any laboratory (hematology, serum chemistry, urinalysis) parameters.

Phase 3: CR201-18 study Most of the abnormal clinically significant results found in vitals, ECG, physical examination, and laboratory investigations were categorized under TEAEs. A clinically meaningful difference was not observed between both arms with respect to abnormal findings. There is no potential discrepancy between both the test arm and the reference arm to be discussed further

5.1.4.5. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Phase 1: BP02-101 Study

Vital Signs Abnormalities in vital sign results were observed for a number of parameters at one or more assessments; however, none of the vital signs abnormalities were considered CS. No TEAEs related to vital signs abnormalities were recorded. The abnormal values generally occurred in subjects with low or high baseline values that were not notably different from the post-dose results. None of the subjects reported for the clinically significant for vital signs during the entire course of the study for all the treatments BP02, EU Herceptin and US Herceptin

Physical Examination Findings

None of the abnormal physical examination results found to be clinically significant during the course of the study.

Electrocardiogram

The mean values across all time points and all parameters were within the normal range. No relevant differences in mean values and changes from baseline were observed for ECG results over time; no relevant differences were observed between results of subjects who received treatment [BP02 (trastuzumab), EU-Herceptin (trastuzumab) and US-Herceptin (trastuzumab)] groups.

Abnormalities in ECG results were observed for a number of parameters at one or more assessments; however, none of these abnormalities were considered clinically significant by the investigator. No TEAEs related to ECG abnormalities were recorded. The abnormal values generally occurred in subjects with low or high baseline values that were not notably different from the post-dose results.

No subject had corrected QT intervals (QTcB and QTcF) greater than 474 msec, HR (bpm) maximum to 102 bpm, PR (msec) maximum to 252 msec, QRS (msec) maximum to 114 msec and no subject had an increase in QTcB or QTcF interval greater than 464 msec. The abnormal values generally occurred in subjects with low or high baseline values that were not notably different from the post-dose results and none of the values found to be clinically significant.

None of the subjects reported for the clinically significant for ECG assessments shift change from baseline during the entire course of the study for all the treatments BP02, EU Herceptin and US Herceptin.

Echocardiogram

There were no clinically meaningful changes in mean values from baseline to endpoint/during the study of LVEF results within the treatment groups.

Post dose one subject 102-031 demonstrated decrease in left ventricular ejection fraction (LVEF) from pretreatment baseline values and found to be clinically significant as per predefined protocol criteria. For this subject' adverse event was reported as decrease in ejection fraction, moderate in intensity, possibly related to study intervention and the subject received EU Herceptin. The event was resolved with no sequelae. For the other subjects with abnormal Echocardiogram results were found to be non-clinically significant. There were no other adverse events reported for the Echocardiography findings except for the subject 102-031.

Phase 3: CR201-18 study

Vital Signs: Overall, vital signs were within normal parameters at baseline and following Trastuzumab treatment. The observed changes from baseline were not clinically relevant.

Left Ventricular Ejection Fraction: Induction Phase: The LVEF values at baseline in the test arm and in the reference arm did not change appreciably at end of induction phase in test arm and in reference arm.

Maintenance Phase: There was no significant difference between both arms and at end of maintenance phase .ECOG Performance Status:

Table 57 - ECOG Performance Status shift table from baseline to worst post-baseline values- Safety Analysis Population (CR201-18 Study

	Baseline		Worst post-baseline value						
Treatment		n (%)	0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	Missing n (%)
BP02 (N=345)	0	97 (28.1)	62 (63.9)	28 (28.9)	0	0	1 (1.0)	0	6 (6.2)
	1	239 (69.3)	2 (0.8)	214 (89.5)	10 (4.2)	3 (1.3)	0	0	10 (4.2)
	2	9 (2.6)	0	1 (11.1)	8 (88.9)	0	0	0	0
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	345 (100)	64 (18.6)	243 (70.4)	18 (5.2)	3 (0.9)	1 (0.3)	0	16 (4.6)
Herceptin (N=345)	0	84 (24.3)	53 (63.1)	27 (32.1)	2 (2.4)	0	0	0	2 (2.4)
	1	246 (71.3)	9 (3.7)	223 (90.7)	4 (1.6)	1 (0.4)	0	0	9 (3.7)
	2	15 (4.3)	0	3 (20.0)	11 (73.3)	0	0	0	1 (6.7)
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0

Treatment	Baseline		Worst post-baseline value						
		n (%)	0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	Missing n (%)
Total (N=690)	5	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	345 (100)	62 (18.0)	253 (73.3)	17 (4.9)	1 (0.3)	0	0	12 (3.5)
	0	181 (26.2)	115 (63.5)	55 (30.4)	2 (1.1)	0	1 (0.6)	0	8 (4.4)
	1	485 (70.3)	11 (2.3)	437 (90.1)	14 (2.9)	4 (0.8)	0	0	19 (3.9)
	2	24 (3.5)	0	4 (16.7)	19 (79.2)	0	0	0	1 (4.2)
	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	690 (100)	126 (18.3)	496 (71.9)	35 (5.1)	4 (0.6)	1 (0.1)	0	28 (4.1)

Electrocardiogram

Table 58 - Shift Table for ECG- Safety Analysis Population (CR201-18 Study)

			Baseline				
			Normal	Abnormal, CS [1]	Abnormal, NCS [2]	Missing	Total
Visit	Treatment	Post-Baseline	n (%)	n (%)	n (%)	n (%)	n (%)
Induction Phase							
Overall (Worst post baseline)	BP02 (N=345)	Normal	74 (21.4)	0	12 (3.5)	0	86 (24.9)
		Abnormal, CS	2 (0.6)	0	0	0	2 (0.6)
		Abnormal, NCS	109 (31.6)	0	132 (38.3)	0	241 (69.9)
		Missing	6 (1.7)	0	10 (2.9)	0	16 (4.6)
		Total	191 (55.4)	0	154 (44.6)	0	345 (100.0)
	Herceptin (N=345)	Normal	76 (22.0)	0	15 (4.3)	0	91 (26.4)
		Abnormal, CS	0	0	0	0	0
		Abnormal, NCS	111 (32.2)	1 (0.3)	130 (37.7)	0	242 (70.1)
		Missing	2 (0.6)	0	10 (2.9)	0	12 (3.5)
		Total	189 (54.8)	1 (0.3)	155 (44.9)	0	345 (100.0)
Maintenance Phase							
Overall (Worst post baseline)	BP02 (N=197)	Normal	42 (21.3)	0	6 (3.0)	0	48 (24.4)
		Abnormal, CS	0	0	2 (1.0)	0	2 (1.0)
		Abnormal, NCS	77 (39.1)	0	68 (34.5)	0	145 (73.6)
		Missing	0	0	0	2 (1.0)	2 (1.0)
		Total	119 (60.4)	0	76 (38.6)	2 (1.0)	197 (100)
	Herceptin (N=220)	Normal	43 (19.5)	0	11 (5.0)	0	54 (24.5)
		Abnormal, CS	0	0	0	0	0
		Abnormal, NCS	82 (37.3)	1 (0.5)	79 (35.9)	0	162 (73.6)
		Missing	0	0	0	4 (1.8)	4 (1.8)
		Total	125 (56.8)	1 (0.5)	90 (40.9)	4 (1.8)	220 (100)

			Baseline				
			Normal	Abnormal, CS [1]	Abnormal, NCS [2]	Missing	Total
Visit	**Treatment**	**Post-Baseline**	n (%)	n (%)	n (%)	n (%)	n (%)
Induction Phase							
ECG: Electrocardiogram; CS = Clinically Significant; NCS = Not Clinically Significant n: Number of patients with non-missing assessment. % = Percentage of patients with at least one observation in each category relative to the total number of patients in the safety population							

5.1.4.6. In vitro biomarker test for patient selection for safety

Not applicable.

5.1.4.7. Safety in special populations

The Applicant has not conducted specific safety studies in special populations. This is acceptable for this biosimilar application.

5.1.4.8. Immunological events

In phase I study BP02-101, blood samples were collected for analysis of the incidence and titer of anti-trastuzumab antibodies and the incidence of any serum neutralising antibodies (nabs) at the times specified in the schedule of activities (SoA).

In BP02-101, subjects who were confirmed positive for anti-trastuzumab antibodies, including those who discontinued the study after infusion of the study treatment, were followed for up to 12 months. These subjects returned to the clinical centre at 6, 9 and 12 months post-dose for blood samples to confirm their immunoglobulin status or until two consecutive samples were confirmed negative for anti-trastuzumab antibodies, whichever was sooner. SAF TAB 18 summarises the subjects who were positive for anti-drug antibodies (ADA). On day 1, 2 subjects (1.8%) (1 subject each in the EU Herceptin and US Herceptin groups) were positive for ADA. However, these 2 subjects were negative for neutralising antibodies (NAbs). None of the subjects were positive for ADA or NAb at day 50 and day 78.

In the Phase III CR201-18 study, blood samples were collected at baseline (before cycle 1 dosing), before the start of infusion in cycle 4 and at the end of the induction phase during the induction phase. In the maintenance phase, blood samples for antibody testing were to be collected before the start of infusion every 3 cycles starting with cycle 9 (i.e. cycle 12, cycle 15, cycle 18, cycle 21, cycle 24 and end of study/early withdrawal visit). Immunogenicity assessments were to be pooled for the PP population. .

Table 59 - Summary of subjects positive for ADA in phase I study BP02-101

Number (%) of Subjects				
Visit	**BP02 (N=37)**	**EU-Herceptin (N=37)**	**US-Herceptin (N=37)**	**All Subjects (N=111)**
Confirmatory anti-drug antibody				
Day 1	0 (0.0)	1 (2.7)	1 (2.7)	2 (1.8)
Day 50	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 78	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 60 - Summary of Immunogenicity Data based on In-Study Cut Point - CR201-18

Visit	Assay type	Statistic	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Induction phase					
Cycle 1 Day 1	ADA Screening	Reactive	27 (7.9)	21 (6.1)	48 (7.0)
	ADA Confirmatory	Positive	13 (3.8)	9 (2.6)	22 (3.2)
	Neutralizing antibody (NAb) status	Reactive	10 (2.9)	8 (2.3)	18 (2.6)
Cycle 4 Day 64	ADA Screening	Reactive	7 (2.4)	7 (2.3)	14 (2.3)
	ADA Confirmatory	Positive	2 (0.7)	1 (0.3)	3 (0.5)
	Neutralizing antibody (NAb) status	Reactive	2 (0.7)	1 (0.3)	3 (0.5)
End of Induction	ADA Screening	Reactive	8 (3.0)	6 (2.2)	14 (2.6)
	ADA Confirmatory	Positive	1 (0.4)	1 (0.4)	2 (0.4)
	Neutralizing antibody (NAb) status	Reactive	1 (0.4)	1 (0.4)	2 (0.4)
Maintenance phase					
Cycle 12 Day 232	ADA Screening	Reactive	4 (2.3)	2 (1.0)	6 (1.6)
	ADA Confirmatory	Positive	1 (0.6)	0	1 (0.3)
	Neutralizing antibody (NAb) status	Reactive	1 (0.6)	0	1 (0.3)
Cycle 15 Day 295	ADA Screening	Reactive	0	1 (0.7)	1 (0.4)
	ADA Confirmatory	Positive	0	0	0
	Neutralizing antibody (NAb) status	Reactive	0	0	0
Cycle 18 Day 358	ADA Screening	Reactive	0	3 (2.7)	3 (1.5)
	ADA Confirmatory	Positive	0	0	0
	Neutralizing antibody (NAb) status	Reactive	0	0	0
Cycle 21 Day 421	ADA Screening	Reactive	0	1 (1.2)	1 (0.7)
	ADA Confirmatory	Positive	0	0	0
	Neutralizing antibody (NAb) status	Reactive	0	0	0
Cycle 24 Day 484	ADA Screening	Reactive	1 (16.7)	0	1 (8.3)
	ADA Confirmatory	Positive	0	0	0
	Neutralizing antibody (NAb) status	Reactive	0	0	0
End of Maintenance	ADA Screening	Reactive	4 (2.5)	7 (3.7)	11 (3.2)
	ADA Confirmatory	Positive	2 (1.3)	3 (1.6)	5 (1.4)
	Neutralizing antibody (NAb) status	Reactive	1 (0.6)	2 (1.1)	3 (0.9)

5.1.4.9. Safety related to drug-drug interactions and other interactions

Formal studies to assess the potential drug-drug interaction have not been carried out.

5.1.4.10. Discontinuation due to adverse events

Table 61 - Summary of TEAEs leading to Study Discontinuation during Induction and Maintenance Phase- Safety Analysis Population - CR201-18

Preferred Term	BP02 (N=345)	Herceptin (N=345)	Total (N=690)
Number (%) of Patient's	**n (%) #E**	**n (%) #E**	**n (%) #E**
Number of patients with at least one TEAE	7 (2.0) 7	5 (1.4) 5	12 (1.7) 12
Ejection fraction decreased	2 (0.6) 2	2 (0.6) 2	4 (0.6) 4
Cardiac dysfunction	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Myocardial ischaemia	1 (0.3) 1	0	1 (0.1) 1
Neutropenia	0	1 (0.3) 1	1 (0.1) 1
Oedema peripheral	1 (0.3) 1	0	1 (0.1) 1
Hypertransaminasaemia	1 (0.3) 1	0	1 (0.1) 1
COVID-19	0	1 (0.3) 1	1 (0.1) 1
Pneumothorax	1 (0.3) 1	0	1 (0.1) 1

5.1.4.11. Post marketing experience

Not applicable.

5.1.5. Discussion on clinical safety

The safety dataset consists of two studies with overall 382 subjects treated with the medicinal product BP02 (Dazublys). The safety dataset consists of patients enrolled to phase I study BP02-101 (37 patients) and phase III study BP02-CR201-18 (345 patients). These datasets are discussed separately.

Phase I Study BP02-101

Reported TEAEs and AESI are in line with the known safety profile of Herceptin. Most common emergent adverse events were headache (27.0%); infusion related reactions (16.2%); upper respiratory tract infection (13.5%); pyrexia and back pain (10.8% each). In general, numerically more TEAE and AESI appeared in the US Herceptin group, without direct relevance for the similarity exercise of Dazublys, and EU-Herceptin. For BP02 and EU Herceptin, differences in the preferred term infusion-related reactions (6 vs 3/37) were observed without clear interpretability due to the small number of patients. The overall immunogenicity in study BP02-101 was low and comparable between BP02 and Herceptin.

Phase III Study CR201-18

The severity and frequency of the reported adverse reactions were carefully compared between the biosimilar mAb and the reference mAb. Maintenance phase was completed in April 2024 with a median duration of trastuzumab exposure of 374 days for BP02 and 420 days for patients in the Herceptin arm.

At the end of the induction phase, 70% of BP02-/ and 77.7% of Herceptin treated patients were on treatment. The number of patients completing induction therapy was numerically lower in the BP02 arm (difference of 24 patients, 7.3%). Unacceptable toxicity leading to discontinuation was observed only in 2 patients in the BP02 arm (0.6%) and 3 patients in the Herceptin arm (0.9%). Death was the cause of treatment discontinuation in 11 patients (3.2%) in the BP02 arm and 13 patients (3.8%) in the Herceptin arm. The narratives provided underscore the interpretation of heterogeneous disease progression without raising further suspicion in the context of the study / reference drug relationship. There were 27 deaths in the safety population: 25 deaths occurred in the induction phase (11 in BP02 and 12 in Herceptin group), while 2 of them occurred after the last dose of study medication (1 in each group) and were therefore not considered as treatment emergent events. Two additional deaths occurred in the reference arm during the maintenance phase, hence leading to a total of 27 deaths.

The maintenance phase was entered by 57.1% and 63.8% of the initially randomised patients of the BP02 arm and the Herceptin arm, respectively, 20 % and 22.6% completed the 72-week treatment duration. Progressive disease was the main reason for discontinuation in both arms.

The number of patients receiving Trastuzumab or Docetaxel is lower in BP02 group compared to Herceptin group. However, there is no significant difference in the exposure of Trastuzumab and Docetaxel between the groups. A total of 243 (70.4%) and 268 (77.7%) patients in test and reference arms completed 8 cycles of therapy. This is explained by a higher number of discontinuations was reported in the test arm due to progressive disease, voluntary withdrawal by patient, lost to follow-up and missed 2 consecutive cycle dosing. This difference is not statistically significant when compared between the groups. The p value for Trastuzumab exposure calculated by using Student T test at 5% level of significance is 0.221 while that of Docetaxel is 0.306.

The incidence and severity of AESI (cardiac; IRRs; neutropenia, pulmonary disorders, allergy/ hypersensivity) are low and differences between the two arms are difficult to interpret and therefore not conclusive from the clinical point of view. For AESI cardiac AEs, the initially low overall incidence (BP02: 9 cases (2.6%) Herceptin 5 cases (1.4%)) increased over the maintenance period to 13 (3.8%) and 7 (2.0%) cases, with 2 (0.6%) patients with ≥ G3 events in each arm.

Neutropenia was reported rarely with an overall incidence of 28/690 participants (BP02 14/345; Herceptin 12/345). After completing maintenance therapy, overall rates of neutropenia remain low, without imbalance between the two arms (4.1% vs. 3.5% for BP-02 and Herceptin). Coadministration of pegfilgrastim is unlikely to be the single reason for these very low rates. Since WBC- nadirs can be expected 5-10 days after docetaxel application, enough tests to monitor cytopenia in the sensitive interval are essential, timing of blood tests every 3 weeks might be unlikely to detect the majority of neutropenias. The reported rates of more consecutive severe complications "febrile neutropenia" and "neutropenic sepsis" are low as well without an inbalance between the arms. These clinical complications might have been detected without routine blood counts as there are more eminent to the affected patient.

The reported rates for infusion-related reactions, pulmonary disorders, allergic-like reactions and hypersensitivity were very rare without a specific trend for higher rates in one or the other treatment arms.

Numerically there are more individual TEAEs in the BP02 arm (+18%, 1167 events compared to 992 events) than in the Herceptin arm.With inclusion of the events of the maintenance phase, absolute number of events and patients affected by TEAE increased. The relative difference of reported events approximated to 17.6% (1167 vrs 233 events) from 23% before at soft lock in favour of the Herceptin arm. The amount of patients affected by TEAE of any severity equalised to 66.1% and 67.5% with a decent tendency in favour of BP02. The proportion of patients experiencing treatment-emergent adverse events was with no clear overall trend towards one drug or the other.

During induction phase patients with an ADA positive status, experience more treatment emergent adverse events (TEAEs) > grade 3, compared to the ADA negative patients. For BP02, 26.7% of the ADA+ patients (n=15) compared to 10.6% of the ADA- patients (n=329) experience such an TEAE. For the Herceptin, similar difference seems apparent with 50% of the ADA+ patients (n=10) and 8.7% in the ADA- patients (n=335). Also for treatment emergent serious adverse events, this trend can be observed. 20% vs 7.6% in the BP02 group and 40% vs 4.5% in the Herceptin group. Important side note is that these are very small subgroups (10 vs 329 and 15 vs 335 for BP02 and Herceptin respectively). Possible similar trends can be observed in TEAEs leading to treatment interruption and withdrawal but numbers are too low to be interpreted. A similar observation can be made for the longer observation period (induction phase combined with the maintenance phase). Excluding the patients with ADA positivity at baseline lead to 332 patients in the BP02 arm and 336 patients in the Herceptin arm. The safety profile is comparable between the two groups (BP02 vs Herceptin), both for the overall number of adverse events observed during the induction phase as for the adverse events ordered per system organ class and preferred term.

The presence of ADA positivity seems correlated with a lower C_{trough} indicating rather a patient related effect than a drug effect.

The Applicant has provided further analysis on the impact of ADAs on the C_{trough} data collected during study CR201-18. A similar trend to lower C_{trough} is usually observed for both the biosimilar and the reference products across cycles but the limited number of patients with ADA positive status prevent to draw a definitive conclusion. However, overall, very low and comparable immunogenicity potential was reported both for the biosimilar and the reference product following administration, as expected for trastuzumab products.

5.1.6. Conclusions on the clinical safety

Clinical safety data is qualitatively comparable between BP02 (Dazublys) and Herceptin and in line with the Herceptin Product Information.

5.2. Risk Management Plan

5.2.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	Cardiac dysfunction Oligohydramnios Administration-related reactions (ARR's)
Important potential risks	Medication error (subcutaneous administration)
Missing information	None

5.2.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

5.2.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Cardiac dysfunction	Routine risk minimisation measures: SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects Monitoring to identify patients who develop cardiac dysfunction and clinical recommendation algorithm to deal with LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.4 of SmPC Pack size: Each carton contains one vial Legal Status: Dazublys is a prescription only medicine	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Oligohydramnios	Routine risk minimisation measures: SmPC Section 4.6 Fertility, pregnancy and lactation If a pregnant woman is treated with trastuzumab or if a patient becomes pregnant while receiving trastuzumab or within 7 months following last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable. This has been captured in Section 4.6 of SmPC. Pack size: Each carton contains one vial Legal Status: Dazublys is a prescription only medicine	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction
Administration-Related Reactions (ARRs)	Routine risk minimisation measures: SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Warnings and Precautions for Use SmPC Section 4.8 Undesirable effects	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

	Guidance on observation period after administration has been adequately captured in Section 4.2 of SmPC. Pack size: Each carton contains one vial Legal Status: Dazublys is a prescription only medicine	
Important Potential Risks		
Medication error (subcutaneous administration)	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration Legal Status: Dazublys is a prescription only medicine	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up form for medication error

5.2.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

5.3. Pharmacovigilance

5.3.1. 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.

5.3.2. 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.

5.4. Product information

5.4.1. 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.*

5.4.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Dazublys (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.

6. Biosimilarity assessment

6.1. Comparability exercise and indications claimed

The applicant claims early breast cancer, metastatic breast cancer and metastatic gastric cancer (only intravenous application intended) as indications for BP02 (Dazublys). The objective of the development programme was to demonstrate biosimilarity to the reference product Herceptin in terms of quality, PK, efficacy and safety.

Breast cancer

Metastatic breast cancer

Dazublys 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

Dazublys 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) (seesection 5.1).
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide in combination withpaclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Dazublys therapy for locally advanced (including inflammatory) disease or tumors> 2 cm in diameter (see sections4.4 and 5.1).

Dazublys should only be used in patients with metastatic or early breast cancer whose tumors haveeither HER2 overexpression or HER2 gene amplification as determined by an accurate and validatedassay (see sections 4.4 and 5.1).

Metastatic gastric cancer

Dazublys 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.

Dazublys should only be used in patients with metastatic gastric cancer (MGC) whose tumors 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).

6.2. Results supporting biosimilarity

Quality

BP02 FP batches generated at the proposed commercial scale were used for analytical similarity assessment. The analytical methods used to study the structural, physicochemical, and functional attributes of trastuzumab for the assessment of analytical similarity seem adequate. It is noted that the panel of functional assays used for the similarity exercise is much larger that the panel used for characterisation of BP02. Their validation/qualification status is acceptable and indicate that the methods are suitable for generation of data for similarity assessment.

The protein concentration of BP02 was compared to the quality ranges of EU-approved Herceptin and is considered similar. Intact mass analysis was performed using electrospray ionization coupled liquid chromatography mass spectrometry (ESI LC-MS). Reduced Tryptic peptide mapping analysis by LC–MS/MS confirmed the complete amino acid sequence of BP02 and is found to be identical to that of EU-approved Herceptin. The sequence coverage for BP02, EU-approved Herceptin was 100%. The N-terminal and C-terminal sequence data of heavy chain and light chain confirms the identity of N-terminal and C-terminal peptide sequences of BP02 batches with EU-approved Herceptin batches. Amino acid composition analysis was performed by hydrolysis followed by derivatization and analysis by RP-HPLC with fluorescence detection. The relative molar ratios show that the BP02 batches are comparable to EU-approved Herceptin batches.

Purity determination by reduced CE-SDS revealed lower NGHC content in BP02 compared to EU-approved Herceptin. Considering the overall low NGHC content no impact of this small difference is expected and the CE-SDS profiles under reducing conditions can be considered comparable. Charge distribution is very conserved for EU-Herceptin resulting in a narrow quality range. In the absence of CpB treatment the % acidic peak, % main peak and % basic peak area of BP02 display differences compared to the quality ranges of EU-approved Herceptin. It is noted that the differences are almost diminished following CpB digestion, suggesting that the basic species is due to the presence of C-terminal lysine. A difference in this C-terminal modification does not preclude biosimilarity. The oligosaccharide profiles demonstrated that the % afucosylation, % fucosylation and % mannose of BP02 are highly similar and comparable to the quality ranges of EU-approved Herceptin. For sialylated oligosaccharides in human oligosaccharides with N-acetylneuraminic acid (NANA) are more common whereas N-glycolylneuraminic acid (NGNA) are found in other species such as rhesus, and mouse IgGs. Analysis of sialic acid content show that NANA is the major sialic acid present with minor levels of NGNA in both BP02 and EU-Herceptin. Lower levels of lower levels of NGNG content was observed in BP02 compared to EU-approved Herceptin and thus an impact on immunogenicity is not expected.

Other post-translational modifications are determined by the RP-UPLC tryptic peptide mapping method for deamidation and oxidation. The deamidation modifications at different amino acid positions for heavy chain and light chain are comparable between BP02 and EU-approved Herceptin. Also, oxidation, pyroglutamate and C-terminal lysine modifications are confirmed and overall considered comparable. The higher order structure of BP02 is typical for a mAb and similarity to EU-Herceptin is proven by multiple methods including Near and FAR-UC CD, FTIR, DSC, SEC-MALS. Free thiols and formation of disulphide bridges were confirmed by Ellman's Assay and ESI LC-MS/MS respectively.

The selection of batches for functional analytical similarity is provided. Equivalence testing was performed for relative potency data of BT474 proliferation inhibition assay for EU-approved Herceptin) US-licensed Herceptin and BP02 samples. The equivalence margin was set for the data from EU-approved Herceptin (n=18) and subjected to an equivalence testing taking the standard deviation of the data points generated from EU-approved Herceptin and compared for their lower and upper threshold for equivalence to that of the BP02 batches. On performing pairwise comparison, the observed difference in means along with the upper and lower 95% confidence intervals using TOST analysis were well within the defined equivalence acceptance criteria. Trastuzumab binds to extracellular domain IV of the HER2 receptor. This was demonstrated by cell-based ELISA. Surface plasmon resonance (SPR) technology was used to determine the binding affinity of trastuzumab to FcRn. Slightly higher binding of BP02 to the FcRn was observed. It is argued that no significant effect was observed in the half-life during clinical pharmacokinetic study compared to EU-approved Herceptin.

BP02 binding affinity to FcγRIIIA (V176) and (F176) receptors can be considered similar to EU-approved Herceptin. BP02 binding affinity to FcγRIIIB receptor can be considered similar to EU-approved Herceptin.

BP02 binding affinity to C1q can be considered similar to EU-approved Herceptin. Absence of CDC activity of trastuzumab was demonstrated using rituximab as positive control.

ADCC-V and F activity of BP02 can be considered similar to EU-approved Herceptin. Results obtained in comparative thermal stress stability, comparative accelerated stability and force degradation studies revealed that BP02 FP, US Herceptin and EU Herceptin showed a similar degradation profile and there are no significant differences in their trends over time.

BP02 FP, US-licensed Herceptin and EU-approved Herceptin were investigated in a head-to-head study to compare the degradation pathways and degradant product profiles when exposed to thermal stress, photo stress, pH stress (high pH), and white light stress. Linear regression plots demonstrate comparative degradation profiles between the three products.

With the assessment, the Applicant provided further evidence that clinical and PPQ batches are comparable and that PPQ batch data indicate that the BP02 manufacturing process is under control and will perform consistently.

Based on the consistency of data presented for the BP02 PPQ and post-PPQ batches, the additional biosimilarity analyses for BP02 showed comparable results with EU-Herceptin for all physicochemical parameters, except for some minor differences: higher %acidic peaks, lower %main peaks, slightly lower high mannose, slightly higher total fucosylation. However, these minor differences did not translate into significant differences with respect to the functionality parameters. Only minor differences in FcRn binding (higher), FcγRIa binding (higher) and ADCP activity (slightly lower) were found, which were also observed in the initial biosimilarity exercise. The Applicant justified the differences by stating that these are minor and not clinically meaningful, since all endpoints in the Phase I (PK) and Phase III clinical studies have been met.

Additional biosimilarity analyses have not been conducted for size heterogeneity by SV-AUC and SEC-MALS, PTMs by LC-MS/MS (deamidation, oxidation, N-terminal pyroglutamate, C-terminal lysine), sialylation by RP-HPLC, monosaccharide composition by GC-MS, CDC activity and immunogenicity assays as initially performed, but this can be considered acceptable based on the current available data. Furthermore, an additional comparative forced degradation study between PPQ FP batches, EU-Herceptin and US-Herceptin batches was performed which did not reveal significant differences between BP02 and EU/US-Herceptin under the conditions tested (i.e. thermal stress, high pH and photo stress).

In conclusion, the overall available data are sufficient to conclude that the commercial FP can be considered biosimilar to EU-Herceptin.

Non-clinical

Non-clinical pharmacology studies comprised in vitro studies to evaluate potency and functionality evaluated under the quality part.

Clinical

Two studies were performed: Phase 1 study in healthy male volunteers (BP02-101) and one Phase 3 study (induction part completed, maintenance part completed during the MA procedure) in patients with Human epidermal growth factor receptor-2 (HER2)-positive breast cancer (CR201-18).

In the phase I study BP02-101, PK equivalence was reported for BP02 and Herceptin since the ratios (90% CI) of geometric means for primary PK endpoints $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} are within the acceptance range of 80-125%. In addition, the mean secondary PK endpoints have shown to be similar for the Dazublys and Herceptin treatment groups.

In the randomised controlled phase 3 study the primary efficacy endpoint of best ORR at week 24 of treatment was met, with the 95% confidence interval within the predefined margins, supporting biosimilarity. In addition, a per-protocol analysis including all patients in the CR201-18 study who received trastuzumab and were assessed, supports these findings. In terms of safety, the safety profile is comparable between the two treatment arms.

In the Phase I study, overall immunogenicity was low and comparable.

6.3. Uncertainties and limitations about biosimilarity

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

6.4. Discussion on biosimilarity

Quality

Overall, the proposed biosimilarity approach follows the general principles as outlined in in the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance. Based on the provided data it is agreed that similarity is demonstrated and Dazublys can be considered as a biosimilar to EU-Herceptin.

Clinical

In the phase I study BP02-101, design and methodology used are deemed appropriate. PK equivalence was demonstrated between BP02 and Herceptin and the mean secondary PK endpoints have shown to be similar for the Dazublys and Herceptin treatment groups.

Analyses in the special populations are not relevant in the Dazublys MAA as the biosimilarity relies on the information already known for the reference product. No formal drug-drug interaction studies are considered needed.

From a clinical pharmacology point of view biosimilarity can be concluded and the application is approvable based on the current data. In the randomised controlled phase 3 study the primary efficacy endpoint of best ORR at week 24 of treatment was met, supporting biosimilarity. In addition, a per-protocol analysis including all patients in the CR201-18 study who received trastuzumab and were assessed, supports these findings. In terms of safety, the safety profile is comparable between the two treatment arms.

6.5. Extrapolation of safety and efficacy

The applicant applies for the same indications as approved for the reference Product EU-Herceptin, - early breast cancer, metastatic breast cancer and metastatic gastric cancer (only intravenous application intended).

CR201-18 was a Phase III Study to evaluate the Efficacy, Safety, Immunogenicity and Pharmacokinetics of BP02 (Trastuzumab) in comparison with Herceptin-EU was performed in Patients with HER2- Positive Metastatic Breast Cancer (MBC). The study was performed in the metastatic breast cancer setting with the goal to support biosimilarity.

The Applicant has provided a sufficient rationale as to why the data from the CR201-18 trial could support the indication in metastatic gastric cancer and early breast cancer which is recommended in the "Guideline on similar biological medicinal products" (CHMP/437/04 Rev 1): as "If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification."

6.6. Additional considerations

None.

6.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Dazublys is considered biosimilar to EU-Herceptin. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

7. Recommendations

Outcome

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

Breast cancer

Metastatic breast cancer

Dazublys 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

Dazublys 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) (seesection 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 Dazublys therapy for locally advanced (including inflammatory) disease or tumors> 2 cm in diameter (see sections4.4 and 5.1).

Dazublys should only be used in patients with metastatic or early breast cancer whose tumors haveeither HER2 overexpression or HER2 gene amplification as determined by an accurate and validatedassay (see sections 4.4 and 5.1).

Metastatic gastric cancer

Dazublys 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.

Dazublys should only be used in patients with metastatic gastric cancer (MGC) whose tumors 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 marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and

any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

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

Not applicable.