14 September 2017
EMA/CHMP/9855/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ontruzant

International non-proprietary name: trastuzumab

Procedure No. EMEA/H/C/004323/0000

Note

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

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List of abbreviations

ADA	Anti-drug Antibody
ADCC	Antibody-dependent Cell-mediated Cytotoxicity
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALND	Axillary Lymph Node Dissection
ALP	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
ANSM	The National Agency for the Safety of Medicines and Health Products
AS	Active Substance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-time Curve
AUC_{inf}	Area Under the Concentration-time Curve from Time Zero to Infinity
$\%AUC_{extrap}$	Area Under the Concentration-time Curve from Time t to Infinity as a Percentage of Total AUC
AUC_{last}	Area Under the Concentration-time Curve from Time Zero to the Last Quantifiable Concentration
BC	Breast Cancer
BL	Baseline
BMI	Body Mass Index
bpCR	Breast Pathological Complete Response
BSA	Body Surface Area
BT	Biotinylated
C1q	Complement Component 1, q Subcomponent, A Chain
cCR	Clinical Complete Response
CD	Cluster Dichroism
CDC	Complement-dependent Cytotoxicity
CDR	Complementarity Determining Region
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CIPC	Critical in Process Control
CISH	Chromogenic in situ Hybridisation
CL	Clearance
C_{max}	Maximum Observed Concentration at T_{max}
C_{min}	Minimum Observed Concentration at T_{max}
cPD	Clinical Progressive disease
CPP	Critical process parameter
cPR	Clinical Partial Response
CQA	Critical quality attributes
CR	Complete Response
CS	Clinically Significant
cSD	Clinical Stable Disease
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Serum Concentration at baseline and prior to dosing
CV	Coefficient of Variation
DLS	Dynamic Light Scattering
DNA	Deoxyribonucleic Acid
DP	Drug Product
DSC	Differential Scanning Calorimetry
EBC	Early Breast Cancer
ECD	Extracellular Domain
ECOG	Eastern Cooperative Oncology Group
EEPCB	Extended End-of-Production Cell Banks

EFS	Event-free Survival
EMA	European Medicines Agency
ENR	Enrolled Set
EOS	End of Study
EPAR	European Public Assessment Report
ER	Estrogen Receptor
EU	European Union
FAS	Full Analysis Set
Fc	Fragment Crystallisable Region
FcR	Fc Receptor
FcγRIIa	Fc gamma receptor IIa
FDA	US Food and Drug Administration
FEC	5 Fluorouracil, Epirubicin, Cyclophosphamide
FISH	Fluorescence in situ Hybridization
FLR	Fluorescence
FP	Finished product
FTIR	Fourier Transform Infrared Spectroscopy
GCP	Good Clinical Practice
GeoLSMean	Geometric Least Squares Mean
GMP	Good Manufacturing Practice
H/DX	Hydrogen/Deuterium exchange
HC	Heavy Chain
HCP	Host cell protein
HER2	Human Epidermal growth factor Receptor 2 protein
HM	High Mannose
HMW	High Molecular Weight
HPC	High Positive Control
HPLC	High Performance Liquid Chromatography
HQC	High Quality Control
HR	Hazard Ratio
IV	Intravenous
ICF	Informed Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IgG1	Immunoglobulin Gamma Subclass 1
IHC	Immunohistochemistry
INN	International Non-proprietary Name
IP	Investigational Product
IPC	In Process Control
IPT	In Process Tests
IRR	Infusion-Related Reaction
KCP	key control parameters
LABC	Locally Advanced Breast Cancer
λz	Terminal Rate Constant
LC	Light Chain
LD	Longest Diameter
LSMean	Least Squares Mean
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MAA	Marketing Authorisation Application
mAb	Monoclonal Antibody
MAPK	Mitogen-Activated Protein Kinase
Max	Maximum
MBC	Metastatic Breast Cancer
MFI	Micro-Flow Imaging
MCB	Master Cell Bank
MGC	Metastatic Gastric Cancer
Min	Minimum
MoA	Mechanism of Action
MS	Mass Spectrometry
mTOR	Mammalian Target of Rapamycin
MUGA scan	Multigated Acquisition Scan

MW	Molecular Weight
NAb	Neutralising Antibody
NC	Negative Control
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not Clinically Significant
NK	Natural Killer
N-KCP	Non-Key Control Parameters
NYHA	New York Heart Association
OPD	O-Phenylenediamine
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
PC	Positive Control
pCR	Pathologic Complete Response
PD	Pharmacodynamics
PD	Progressive Disease
PEI	Paul Ehrlich Institute
Ph.Eur.	European Pharmacopoeia
PI3K	Phosphatidylinositol 3-kinase
PIND	Pre-Investigational New Drug application
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PL	Parametric Logistic
PPS	Per-Protocol Set
PR	Partial Response
PR	Progesterone Receptor
PrV	Pseudorabies Virus
PSPC	Plate Specific Cut Point
PT	Preferred Term
PTEN	Phosphatase Tensin Homolog
PVR	Process Validation Run
QC	Quality Control
RAN	Randomised Set
RDI	Relative Dose Intensity
Reo-3	Reovirus
RMP	Risk Management Plan
RRS	Research Reference Standard
RU	Ruthenylated
SA	Scientific Advice
SA	Streptavidin
SAE	Serious Adverse Event
SAF	Safety Set
SAWP	Scientific Advice Working Party
SD	Standard Deviation
SD	Stable Disease
SE-HPLC/MALLS	Size Exclusion High Performance Liquid Chromatography Coupled with Multiangle Laser Light Scattering
SISH	Silver in situ Hybridization
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SV-AUC	Sedimentation Velocity Analytical Ultracentrifugation
$t_{½}$	Terminal Half Life
TEAE	Treatment-Emergent Adverse Event
TGI	Tumour Growth Inhibition
TK	Toxicokinetic
T_{max}	Time to Reach Maximum (Peak) Plasma Concentration (C_{max})
TMB	Tetramethylbenzidine
TNM	Tumour, Nodes, Metastasis
tpCR	Total Pathological Complete Response
TSE	Transmissible Spongiform Encephalopathy
TTP	Time to Progression
Vz	Volume of Distribution During the Terminal Phase
WBC	White Blood Cell

WCB	Working Cell Bank
WFI	Water for Injection
X-MuLV	Xenotropic Murine Leukaemia Virus-Related Virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Samsung Bioepis UK Limited (SBUK) submitted on 30 August 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Ontruzant, 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

Ontruzant 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

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

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

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

Metastatic gastric cancer

Ontruzant 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-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

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

The legal basis for this application refers to:

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

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

The chosen reference product is:

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

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

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

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

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

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

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

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Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 23 July 2015. The Scientific Advice pertained to quality and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Koenraad Norga Co-Rapporteur: Greg Markey

- The application was received by the EMA on 30 August 2016.
- The procedure started on 29 September 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 December 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 December 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 3 January 2017.
- During the meeting on 26 January 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 May 2017.
- The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at 3 sites (Sponsor, CRO and one clinical investigator site) in Republic of Korea, United States and Poland between February and March 2017. The outcome of the inspection carried out was issued on 5 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 June 2017.
- During the PRAC meeting on 6 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 20 July 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 11 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 August 2017.
- During the meeting on 11-14 September 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ontruzant on 14 September 2017.

2. Scientific discussion

2.1. Problem statement

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

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

Trastuzumab (Herceptin) was first authorised in the EU on 28 August 2000 (see Herceptin EPAR). It is currently approved for the treatment of HER2 positive early and metastatic breast cancer and HER2 positive metastatic gastric cancer.

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

About the product

Ontruzant (trastuzumab) is a humanised IgG1 monoclonal antibody produced by mammalian Chinese hamster ovary (CHO) cell suspension culture and purified by several chromatography steps including specific viral inactivation and removal procedures.

The Applicant claimed the same therapeutic indications and posology for the proposed biosimilar Ontruzant as granted for Herceptin in the European Union (EU):

Breast cancer

Metastatic breast cancer

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

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

- 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.

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

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

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

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

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

- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see SmPC sections 4.4 and 5.1).

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

Metastatic gastric cancer

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

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

Ontruzant is available as 150 mg powder for concentrate for solution for intravenous infusion.

HER2 testing is mandatory prior to initiation of therapy (see SmPC sections 4.4 and 5.1). Ontruzant treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see SmPC section 4.4), and should be administered by a healthcare professional only.

Ontruzant intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only.

In order to prevent medication errors it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Ontruzant (trastuzumab) and not trastuzumab emtansine.

Type of Application and aspects on development

This application concerns a centralised procedure for marketing authorisation of Ontruzant (also referred to as “SB3”), as a biosimilar product to the European reference product Herceptin (trastuzumab). This application concerns only IV administration. Ontruzant will be available as 150 mg powder for concentrate for solution for infusion.

A comparability exercise has been performed in a stepwise approach to assess the similarity between Ontruzant and the reference product. All studies were conducted against the EU-approved Herceptin as reference product. In some (non)clinical studies, the applicant also compared Ontruzant to the US-approved Herceptin. Ontruzant has been developed in accordance with applicable EU guidelines, in particular:

- "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – quality issues, Revision 1" (EMA/CHMP/BWP/247713/2012);
- "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1)
- "Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010);
- "Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins" (CHMP/EWP/89249/2004);
- "Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins" (EMEA/CHMP/BMWP/14327/2006 Rev. 1)

For the development of Ontruzant, the Applicant sought Scientific Advice (SA) from the EMA Scientific Advice Working Party (SAWP) to discuss the physicochemical, pharmaceutical and biological, and clinical development of Ontruzant (EMA/CHMP/SAWP/466180/2015).

2.2. Quality aspects

2.2.1. Introduction

Ontruzant (also referred to as SB3) finished product (FP) is presented as a sterile, lyophilised powder for concentrate for solution for infusion containing 150 mg trastuzumab as active substance (AS). Other ingredients are L-histidine hydrochloride monohydrate; L-histidine; α,α-trehalose dihydrate and polysorbate 20. The product is supplied in a clear glass type I (Ph. Eur.) vial with butyl rubber stopper as described in section 6.5 of the SmPC. Ontruzant is produced by mammalian CHO cell suspension culture.

All materials used in the manufacture of Ontruzant active substance (AS) and finished product (FP) are of non-animal origin.

2.2.2. Active Substance

General information

Ontruzant (trastuzumab) is a recombinant DNA-derived, humanised monoclonal antibody (IgG1 kappa) that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2. Ontruzant consists of 1,328 amino acids and has a molecular weight of approximately 148 kDa. Trastuzumab is comprised of two identical HCs and two identical LCs. One N-linked glycosylation site is located at Asparagine-300 on each heavy chain. There are no O-linked glycosylation sites.

The mechanism of action of trastuzumab is known to be its selective binding to the extracellular domain of HER2 receptor. This prevents dimerisation of HER2 receptor, which increases endocytotic destruction of

the receptor, inhibits shedding of its extracellular domain, and activates immune response. This results in a decrease in cell signalling through the RAS-MAPK pathway, which leads to inhibition of tumour cell proliferation.

Manufacture, characterisation and process controls

Ontruzant active substance (AS) is manufactured at the Biogen large-scale manufacturing facility in Hillerød, Denmark.

Description of manufacturing process and process controls

After thawing of the WCB vial, the culture is serially expanded in cell mass and volume for inoculation into the production bioreactor. The cell culture fluid is subsequently purified through a series of chromatographic steps, virus inactivation and filtration steps.

Control of materials

Details of the various solutions and media used in the manufacturing process are described. All materials used in the manufacture of Ontruzant AS are of non-animal origin. Both compendial and non-compendial raw materials are used during production of Ontruzant AS, although non-compendial raw materials were not used in the purification process. The water for injection (WFI) meets Ph. Eur. requirements. Information and testing for raw materials has been provided.

The host cell line used in Ontruzant manufacturing is the CHO cell line.

Gene and vector construction, development of the production cell line are suitably detailed. Materials of animal origin were used only during early cell line development and a TSE risk assessment has been provided.

Cell bank testing was performed according to ICH Q5A(R1), ICH Q5B and ICH Q5D.

Control of critical steps and intermediates

For the control of the Ontruzant AS manufacturing process, critical (CCP), key (KCP) and non-key (N-KCP) control parameters have been defined for each step in the process. The criticality is associated with the impact on the defined critical quality attribute (CQA) of the Ontruzant AS. Performance parameters are designated in-process controls (IPC), critical in-process controls (CIPCs), or in-process tests (IPT) and critical in-process tests (CIPTs). These have been defined in the dossier and are based on development experience and risk assessments, which are detailed in the submission. Critical Quality Attributes were described in detail. Appropriate actions, taken if limits are exceeded, have been specified.

Process validation

Ontruzant active substance manufacturing process validation included process consistency studies, shipping qualification, impurity clearance studies, viral clearance studies, intermediate hold studies and column lifetime studies. Scale-down models used in the validation studies were suitably qualified.

Validation of the purification confirms that each step shows consistent product yield and reduces the impurity content to an acceptable level. Impurities include cell-derived impurities (DNA and HCP), process-related impurities and product-related impurities. Suitable process controls have been applied at all stages of the manufacturing process.

The maximum hold times of process intermediates was evaluated.

Following the completion of process validation studies, process controlled parameters were re-evaluated.

Shipping qualification data have been provided for the active substance.

Overall, results from the process validation studies show that the manufacturing process consistently produces AS of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

The manufacturing process was initially developed at pilot scale. The process was scaled up as well as moved to a new facility. For the process validation (and commercial) batches some further (minor) modifications and optimisations were introduced. Comparability studies were performed for pilot scale lots, clinical lots and process validation run (PVR)/commercial lots. Based on the results to date, it is concluded that the clinical and PVR batches of Ontruzant as well as pilot and clinical batches, are comparable.

Characterisation

The characterisation of Ontruzant included a comprehensive battery of physicochemical and biological tests using sensitive and orthogonal state-of-the-art qualified analytical methods in order to elucidate the primary, secondary and higher-order structure, post-translational modifications, glycosylation, charge variants, purity/impurities, quantity and biological properties.
As for the process-related impurities (including HCP and host cell DNA), clearance validation studies have been performed to demonstrate that the Ontruzant manufacturing process provides adequate clearance of such impurities.

Biological potency was determined by anti-proliferation assays and antibody dependent cell-mediated Cytotoxicity (ADCC). The Anti-proliferation assays with Ontruzant were performed using a HER2 overexpressing human breast cancer cell line. The ADCC assay was performed using a human breast cancer cell line overexpressing HER2 as target cells, and NK-CD16 cell line, a human natural killer cell line expressing CD16 as effector cells.

Specification

The proposed specification for Ontruzant has been provided with information on the analytical methods used for control of Ontruzant active substance. This includes general tests, biological activity, identity tests, quantitation, tests for purity and impurity, and safety tests. Stated impurities have been present in material used in clinical trials.

Analytical methods

The analytical procedures have been described. Validation reports from the QC testing site were given. Compendial methods were verified.

Batch analysis

Batch analysis data show that the results are consistent and all within the acceptance criteria in place at the time of testing.

Reference materials

The reference standards used in the release and stability testing of Ontruzant active substance are the same as those used for the release and stability testing of Ontruzant finished product. The applicant has provided detailed information on Reference Standards used to date. Each lot of Reference Standard was extensively qualified according to release tests as well as additional characterisation tests. The applicant

also provided the testing program that will be used for qualification of future Working Reference Standards. This test panel is deemed sufficient.

Stability

The proposed shelf-life of the active substance is based on the long-term stability results.

Real time, real condition stability data have been presented for active substance (stored in containers representative of the proposed container for AS storage). Studies were conducted in accordance with ICH guidelines and analytical methods were stability-indicating. Since the pilot and clinical batch are comparable to and representative of the commercial AS batches, these data can be used to support the shelf-life of the AS. Supportive accelerated stability data are also presented. In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The stability results indicate that the AS is sufficiently stable and justifies the proposed shelf life in the proposed container.

Comparability exercise for Active Substance

See manufacturing process development section above.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Ontruzant finished product (FP) is a sterile, white to pale yellow, lyophilised powder for concentrate for solution for infusion. Lyophilised Ontruzant FP is reconstituted with 7.2 mL of sterile water for injection (WFI) to yield a single dose formulation of approximately 21 mg/mL trastuzumab at pH 6.0, and is further diluted in 0.9% sodium chloride solution. The finished product is intended to be stored at 2°C to 8°C.

One single-use vial contains 150 mg trastuzumab as the active substance and the excipients α,α-trehalose dihydrate, polysorbate 20, L-histidine, L-histidine hydrochloride monohydrate, which are all of Ph.Eur. compendial grade. There are no novel excipients used in the finished product formulation.

The composition of Ontruzant finished product is presented in Table 2 below.

Table 1: Complete composition of Ontruzant finished product

Ingredient	Reference	Function
Trastuzumab	In-house	Active substance
L-histidine HCl monohydrate	Ph Eur/JP	Buffering agent
L-histidine	Ph Eur/USP/JP	Buffering agent
Trehalose dihydrate	Ph Eur/USP/NF	Bulking agent
Polysorbate 20	Ph Eur/NF/JP	Surfactant
Water for injection*	Ph Eur/USP	Solvent

*WFI evaporates during FP manufacturing process

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

Pharmaceutical development

The formulation composition proposed is identical to that of Herceptin. Formulation studies were performed to ensure the robustness of Ontruzant formulation, as well as the effects of pH, protein concentration and excipients on the stability of Ontruzant FP. Accelerated, stress and ongoing stability studies confirm the compatibility of Ontruzant AS with the excipients.

The changes of the manufacturing process between clinical and PVR batches were suitably described, and the potential impact of these changes was evaluated. PVR batches were manufactured based on the findings from process characterisation studies and engineering runs. After the completion of process validation, performance parameters were reviewed and modified, taking the knowledge gained from the PVR campaign, manufacturing experience, additional process characterisation results, risk assessments, and overall process capabilities into account.

Acceptable comparability between clinical lots and PVR lots was demonstrated and the modifications introduced subsequently are minor and acceptably justified.

The primary packaging material for Ontruzant FP (150 mg powder for concentrate for solution for infusion in a vial) consists of a depyrogenated and sterilised 15 mL Type I borosilicate glass vial, stoppered with a sterilised bromobutyl rubber stopper and sealed with an aluminium crimping cap. The finished product vials are packaged in a carton to protect from light. Compatibility of the container closure system with Ontruzant FP comprised a toxicological assessment of detected extractables and leachables studies. Integrity of the container closure system was confirmed.

Manufacture of the product and process controls

The FP manufacturing process involves thawing of active substance, pooling/mixing of the active substance, followed by sterile filtration and vial filling/stoppering, lyophilisation and crimping. The vials are subjected to visual inspection before packaging.

The controlled parameters, in-process tests and controls have been given for all relevant manufacturing steps, with associated in-process specifications and/or action limits where applicable. The definitions and terminology for the classification of the controlled parameters were also given.

The process controls and hold times have been validated through engineering and process validation runs. PVR studies included manufacturing process validation, media fill validation, sterile filter validation, cleaning validation and shipping validation. Based on the results obtained from the validation study, it was confirmed that the commercial manufacturing process for Ontruzant FP was validated.

Product specification

The proposed commercial Ontruzant finished product release and shelf-life specifications have been provided. Many test methods of the commercial Ontruzant finished product release and shelf-life specifications are identical to those of the active substance; specifications for quantity, identity, biological activity, purity and impurities, and safety are included. Other general tests are also included in the specification for the finished product.

Analytical methods

Most of the analytical procedures specific for finished product are compendial methods which have been verified to be suitable for intended use; the non-compendial method has been validated.

Batch analysis

Batch data has been provided, which showed consistent results for all the batches manufactured at commercial scale.

Reference materials

See AS section.

Stability of the product

The proposed shelf life for the Ontruzant FP is 36 months when stored at 5 ± 3°C in the commercial container closure system.

Stability data, in accordance with ICH guidelines, have been provided for Ontruzant finished product under long-term (5 ± 3°C), accelerated and stressed conditions in the container closure system intended for the commercial product, to support the proposed shelf life. Analytical methods are stability indicating.

Ontruzant FP was stable even within immediate packaging under extreme light. An infusion study showed that Ontruzant FP reconstituted solution for injection is stable for 48 hours at 5°C and is suitable for administration into patients intravenously through infusion bags/systems of PVC or PP or PE or Glass materials at 30°C for a period of 24 hours. In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The proposed shelf life for FP of 36 months when stored at 5 ± 3°C in the commercial container closure system is acceptable. After reconstitution with sterile water for injection the reconstituted solution is physically and chemically stable for 48 hours at 2°C - 8°C.

Comparability exercise for finished medicinal drug product

The comparability assessments were performed to ensure that the batches used at each stage of Ontruzant development are representative of subsequent development stages.

Biosimilar comparability exercise for Ontruzant and Herceptin

A comprehensive similarity study has been performed to assess the biosimilar comparability of Ontruzant with Herceptin, including characterisation of structural, physicochemical and biological properties of Ontruzant clinical material and PVR batches, in side-by-side assays with EU Herceptin (Reference Product).

Ontruzant active substance and finished product batches used in the biosimilar comparability exercise were all manufactured at commercial scale at the proposed manufacturing sites. Several EU Herceptin lots were used for the biosimilar comparability assessment. The Applicant employed statistical analysis involving tolerance intervals. Since the use of tolerance interval based ranges may result in broad similarity ranges, the results have been re-evaluated based on the actual range of data (minimum and maximum values) obtained from these EU batches, in additional to the data from side-by-side assays. Supportive data was also provided from US Herceptin and Korean Herceptin, although these were not considered in the main evaluation. Results from primary structural analysis showed that the molecular weights, N-terminal and C-terminal sequences, peptide maps, disulphide bonds, levels of free thiol group and the N-linked glycosylation site were similar for Ontruzant and EU Herceptin. Slightly lower levels of N-terminal pyroglutamate were detected in Ontruzant batches. During C-terminal sequencing, Ontruzant was found to have a higher C-terminal lysine content and higher C-terminal α-amidated Pro content

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

compared to the EU Herceptin. Heterogeneity of C-terminal residues is characteristic of therapeutic monoclonal antibodies and since C-terminal lysine is cleaved by the carboxypeptidase enzyme when it enters the blood, it is not expected to impact the PK profile. Levels of proline α-amidation are low and the small difference is not expected to influence the effector function and antigen binding affinity of these antibodies.

Structure-activity relationship studies performed in Ontruzant and EU Herceptin showed that there was no difference in the biological activities between the basic isoforms. Minor differences were found in methionine oxidation and deamidation profiles of Ontruzant compared to EU Herceptin. However, Ontruzant and EU Herceptin showed similar FcRn binding activities, which indicates that the difference in Met oxidation was not significant and antigen binding was not affected.

The analysis of the N-glycan profiles included a detailed quantitative and qualitative measurement of all major glycoforms. Ontruzant has a single N-linked glycosylation site at Asn300, occupied predominantly by fucosylated biantennary structures containing 0, 1, or 2 terminal galactose residues and afucosylated biantennary structures with no terminal galactose. Low levels of high mannose (HM) structures were also identified, with total levels of afucosylated species (%afucose + %HM) evaluated. Data from Ontruzant and EU Herceptin appeared highly similar.

The results showed that the purity of Ontruzant and EU Herceptin was similar. On the other hand, the results showed that the %Main peak of Ontruzant was slightly lower than that of EU Herceptin. However, the results showed that Ontruzant PVR batches were within the similarity range, whereas Ontruzant clinical FP batches had a slightly higher HMW impurity level compared to EU Herceptin. Overall, the level of HMW was low in all batches of Ontruzant. Orthogonal analyses results followed a similar trend with comparable levels of HMW species. There was no difference between Ontruzant and EU Herceptin.

Charge variants analysis of Ontruzant and EU Herceptin was performed. Results showed that the relative content of acidic and basic variants for Ontruzant was higher than those of EU Herceptin, with a consequent lower %main peak for Ontruzant compared to Herceptin. However, further studies performed using isolated charge variants showed that all variants had comparable biological activities for Ontruzant and EU Herceptin.

The secondary structure was elucidated by far-UV CD and FTIR; the tertiary structure by near-UV CD, hydrogen/deuterium exchange (H/DX) and differential scanning calorimetry (DSC); the size distribution by SE-HPLC/MALLS and SV-AUC; the sub-visible particles by dynamic light scattering (DLS) and micro-flow imaging (MFI). Qualitative analyses of the results suggest that the Ontruzant PVR batches are similar to Herceptin in the higher-order structures. The protein contents were determined in terms of concentration (A_{280}), although the results showed that the protein content of Ontruzant was at the lower end of the range determined for EU Herceptin.

In order to assess biological activity of Ontruzant, various cell-based and binding assays were performed. Results from cell-based assays, including the anti-proliferation assay showed that Ontruzant activity was similar to EU Herceptin in terms of biological properties (cellular potency). Results from the ADCC assay for Ontruzant and EU Herceptin were also comparable. Results from binding assays including HER2 binding, Fc receptors (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb and FcRn) binding and C1q binding assay showed similar immunochemical properties between Ontruzant and EU Herceptin. Results from additional biological assays demonstrated similarity between Ontruzant and EU Herceptin in terms of potential MoA of trastuzumab.

In addition to comprehensive and state-of-the-art characterisation study, the comparative stability study was performed for Ontruzant FP and Herceptin in several stress conditions. The results demonstrated that the stability profile of Ontruzant FP was similar to that of Herceptin.

In summary, according to the overall characterisation results performed for Ontruzant and EU Herceptin, it is concluded that Ontruzant is similar to EU Herceptin in terms of physicochemical and biological attributes.

Analytical Result Summary of Additional Batches of Herceptin and Ontruzant Clinical FP

After similarity assessment between Ontruzant and EU Herceptin was completed, additional Herceptin lots were analysed by the applicant for monitoring purposes. During this analysis, it was noted that for many of the more recent batches of EU Herceptin (starting from the lots with expiry dates of Oct 2018) and US Herceptin (lots with expiry dates from Aug 2018), apparent shifts were found in terms of ADCC activity.

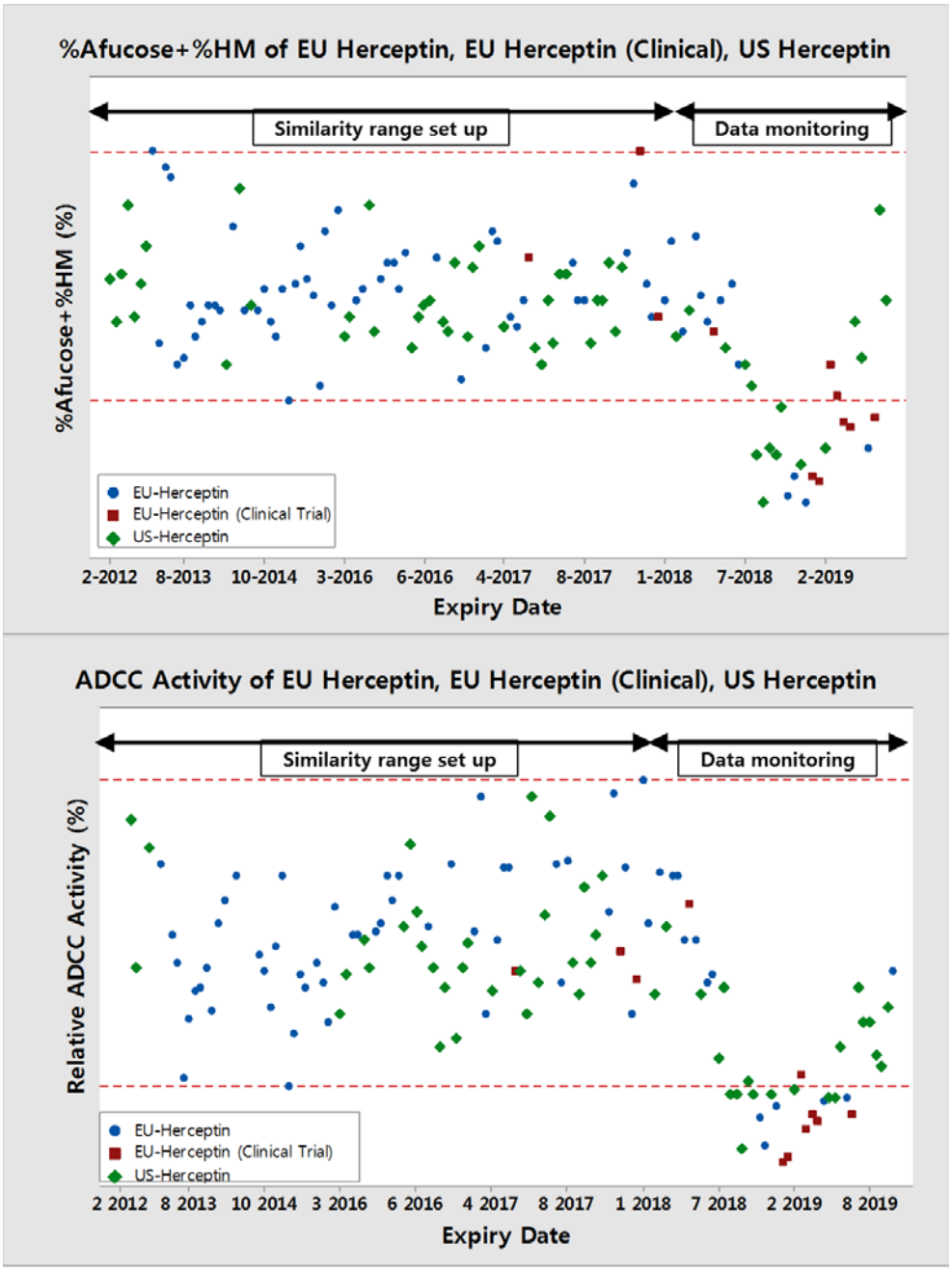


Figure 1: Trend analysis of %Afucose +%HM, or ADCC for Herceptin

Quality trends over time in %Afucose+%HM and ADCC activity were analysed (Figure 3) and individual lots of EU Herceptin (blue dots) and US Herceptin (green dots) from historical data were plotted by expiry date (EU lots that were used in the Phase III clinical study are indicated as red dots). Since ADCC is one of main MoA of trastuzumab, the quality shift may be considered as a factor that may impact on the clinical efficacy. Further detailed discussion is provided in the clinical section.

Adventitious agents

The manufacturing process of Ontruzant active substance and finished product does not contain any material of human or animal origin and therefore the risk from adventitious agents is low. The risk of microbial and mycoplasma contamination is adequately addressed. Animal-derived raw materials were used to establish the Ontruzant cell line and certificates of suitability and/or certificates of origin have been provided for these raw materials. Mycoplasma and sterility testing was performed on the cell banks in accordance with ICH Q5D. Low bioburden is specified for active substance bulk and the finished product must be sterile.

Due to the expression system with CHO cells, virus validation studies are performed as required in the EMEA/CHMP/BWP/398498/2005, ICH Q5A(R1) and ICH Q5D guidelines. The choice of model viruses is considered appropriate. The MCB, WCB and EEPCB were analysed and confirmed to be free of adventitious viruses.

The virus clearance capacity of the Ontruzant AS purification process has been validated in accordance with ICH Q5A (R1). All purification process steps, which comprise dedicated viral removal steps and virus inactivation have been validated. The potential number of retrovirus-like particles present in the maximum dose has been calculated, and the safety margin to viral clearance capacity is acceptable.

In conclusion, the viral and TSE safety of this product have been suitably addressed.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance and finished product manufacturing process and process controls for Ontruzant are, in general, described in sufficient detail. Raw materials have been sufficiently described and controlled on the whole. A two-tier cell bank system was established, with testing and qualification of the MCB and WCB according to ICH Q5A, Q5B and Q5D. Critical process parameters were identified for the manufacturing process and the process was appropriately validated for AS and FP. Viral clearance studies have confirmed sufficient viral inactivation/removal over several steps in the purification process.

Analytical methods were suitable and adequately validated. The proposed specifications and acceptance limits are deemed acceptable to control the quality of the active substance and finished product. However, although specifications for two FP tests are acceptable for authorisation, CHMP has recommended that the limits be reviewed in the light of manufacturing experience. Tests for HCP, microbial contamination, adventitious viruses (*in vitro* testing), mycoplasma and MMV are performed as critical in-process controls on the unprocessed bulk harvest, which is acceptable. Container closure systems of AS and FP were qualified. The claimed 36 month shelf life for Ontruzant FP stored at 5 ± 3°C is supported by stability data. A comprehensive similarity study has been performed to assess the biosimilar comparability of Ontruzant with EU Herceptin, including characterisation of structural, physicochemical and biological properties in side-by-side assays. Results from primary structural analysis showed that these were comparable, apart from slightly lower levels of N-terminal pyroglutamate, slightly higher C-terminal lysine and C-terminal α-amidated Pro content in Ontruzant batches. However, these differences were small and unlikely to have any impact on safety and/or efficacy. Minor differences in methionine oxidation and deamidation profiles of Ontruzant compared to EU Herceptin did not appear to affect biological activities (HER2 binding, ADCC

and anti-proliferation assay). The major N-glycan structures were similar, although minor differences in the relative content of N-glycans (G0F, G1F and G2F) were found between Ontruzant and EU Herceptin, including a slightly higher content of %Afucose +%HM in Ontruzant. Charge variant analysis revealed slightly higher levels of acidic and basic variants in Ontruzant. Importantly, the biological function parameters (HER2 binding, anti-proliferation, ADCC, C1q binding and Fc receptor binding) of Ontruzant were all similar to those of EU Herceptin, particularly when data from several EU Herceptin batches was considered in addition to the side-by-side assays. Results from additional biological assays demonstrated similarity between Ontruzant and EU Herceptin in terms of potential MoA of trastuzumab. The stability profiles of Ontruzant and EU Herceptin were also comparable. Therefore, it can be concluded that from a quality point of view, Ontruzant can be considered as biosimilar to EU Herceptin. It is noted that the more recent batches of EU Herceptin showed shifted %Afucose + %HM and ADCC levels; this is discussed further in the clinical section.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The applicant is requested to take into account two quality recommendations.

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.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP has recommended two points for investigation as stated in the report.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical programme consisted in a series of *in vitro* PD studies conducted to assess the biological activity of Ontruzant (also referred as SB3) compared to EU or US Herceptin using various cell-based and binding assays. An *in vivo* study assessing the therapeutic efficacy of Ontruzant compared to EU Herceptin and US Herceptin in the orthotopic BT-474 human breast cancer cell xenograft mouse model was also submitted.

Results of a 4 week repeat dose toxicity study of SB3/BIIB604 by intravenous in cynomolgus monkeys (including toxicokinetics on day 1 and 22) were also provided as supportive information (data not shown).

2.3.2. Pharmacology

In vitro assays included anti-proliferation assay, ADCC and ADCP assays. In addition, the binding properties were compared in terms of HER2 binding, Fc receptors (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb and FcRn) binding and C1q binding.

Additional biological assays including surface HER2 expression level measurement, HER2 ECD shedding, inhibition of AKT phosphorylation, *in vitro* angiogenesis and combination treatment with chemotherapy completed the in vitro similarity assessment.

Primary pharmacodynamic studies

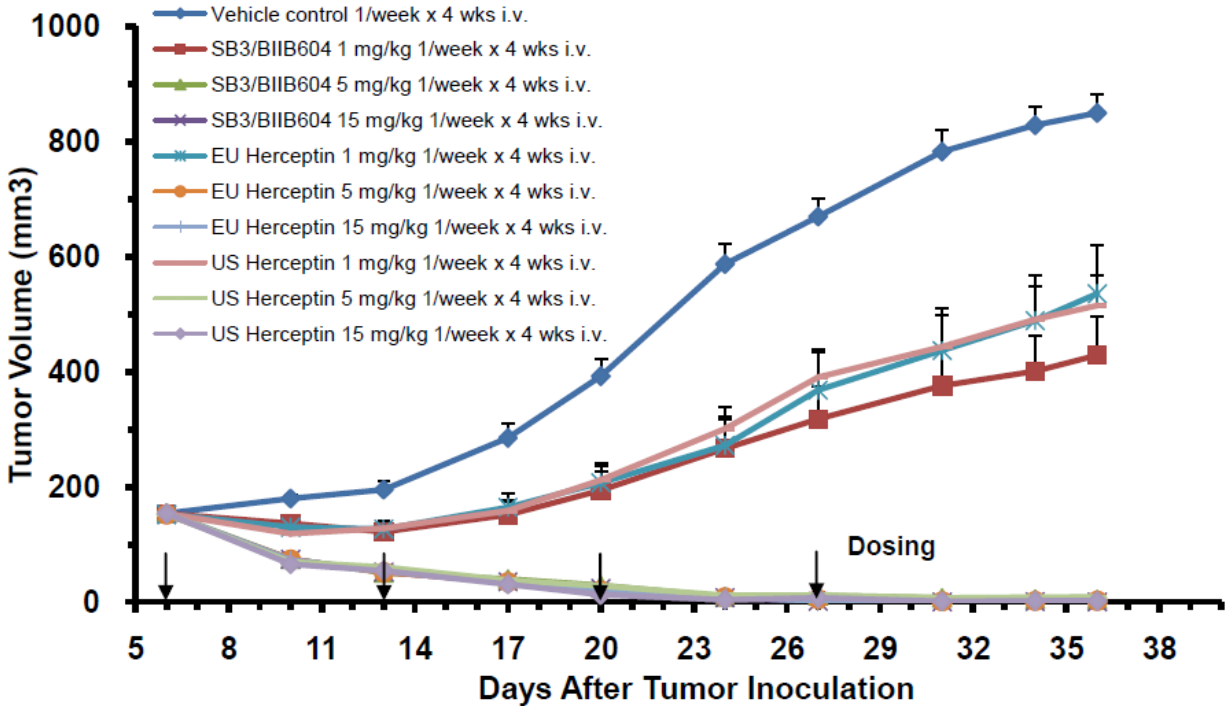
Based on the *in vitro* data provided, results of the assay showed that the anti-proliferation potency of Ontruzant was within the similarity range. The data also support the similar binding and functional characteristics in terms of HER2 binding, ADCC activity, ADCP, Fc-related functions, and C1q binding. Additional studies performed supported the similar functionality of Ontruzant and EU Herceptin.

Evaluation of the efficacy of Ontruzant and Herceptin in the treatment of orthotopic BT-474 human breast tumour xenograft model

To evaluate the anti-tumour efficacy of Ontruzant in the orthotopic BT-474 human breast cancer cell xenograft model, 10 groups of BT-474 xenograft mice, each consisting of 12 females (9 weeks of age) received intravenously Ontruzant formulation buffer (hereinafter, vehicle), Ontruzant, or EU or US Herceptin at dose levels of 1, 5, and 15 mg/kg weekly for 4 weeks.

The results (Figure 4) showed that Ontruzant exerted similar effects in terms of tumour growth inhibition on Day 36 compared to Herceptin at each same dose level of 1, 5, and 15 mg/kg. Tumour growth inhibition was measured by the difference in tumour volume for treated versus vehicle tumour on the last day of therapy or harvest day.

Figure 4 Tumour Weight of the Mice between SB3 and Herceptin Treated Groups on Day 36



Secondary pharmacodynamic studies

See discussion on non-clinical aspects.

Safety pharmacology programme

See discussion on non-clinical aspects.

Pharmacodynamic drug interactions

See discussion on non-clinical aspects.

2.3.3. Pharmacokinetics

See discussion on non-clinical aspects.

2.3.4. Toxicology

Single dose toxicity

See discussion on non-clinical aspects.

Repeat dose toxicity

The applicant provided as supportive information the results of a repeat dose toxicity study of SB3/BIIB604 given weekly for 4 times by the intravenous route in Cynomolgus Monkeys (data not shown, see discussion on non-clinical aspects).

Genotoxicity

See discussion on non-clinical aspects.

Carcinogenicity

See discussion on non-clinical aspects.

Reproduction Toxicity

See discussion on non-clinical aspects.

Toxicokinetic data

See discussion on non-clinical aspects.

Local Tolerance

See discussion on non-clinical aspects.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant provided a justification for not providing an environmental risk assessment. Trastuzumab is already marketed and no significant increase in environmental exposure is anticipated with Ontruzant. Furthermore, the *"Guideline on the Environmental Risk* Assessment of Medicinal Products for Human Use" (EMENCHMP/SWP/4447/00 corr. 2*) makes specific reference for certain types of products such as

proteins, that due to their nature they are unlikely to result in a significant risk to the environment. Therefore, considering that Ontruzant is a protein and there is no expected increased environmental exposure, the absence of formal environmental risk assessment studies for Ontruzant is considered justified.

2.3.6. Discussion on non-clinical aspects

The pharmacology programme focused on primary pharmacodynamics. A set of *in vitro* and *in vivo* studies was performed to assess any potential differences in biological activity between Ontruzant and Herceptin. Given that Ontruzant is developed as a biosimilar and in line with the EMA guideline (EMEA/CHMP/BMWP/42832/2005 Rev1), secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interaction studies were not deemed necessary.

The biological and functional similarity of Ontruzant was compared with EU- and US-approved Herceptin using multiple assays to measure both the Fab and Fc functionality. These included measurement of primary mechanism of action involving Fab, i.e., binding to Her-2 receptor and inhibition of proliferation of cells that overexpress Her-2 and mediation of the effector functions of immune cells through the constant region (Fc) of the antibody (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb and FcRn) and C1q binding.

The *in vitro* results presented support the biosimilarity of Ontruzant and EU Herceptin. Only FcγRIIa and FcγRIIb results appeared slightly lower for Ontruzant compared to Herceptin. The applicant provided a comparison of Ontruzant and Herceptin showing similar potential to elicit ADCP. The ADCP assay has been described in details and the qualification summary provided is adequate.

FcγRIIA and FcγIIIA receptors are subject to polymorphism: 2 forms exist for FcγRIIA: 131H and H131R depending on histidine or arginine at position 131 and 2 forms for FcγRIIIA: 158V and 158 F depending on valine or a phenylalanine at amino-acid position 158. The applicant provided additional comparative binding data for isoforms 131H / 131R of receptor FcyRIIa and 158V / 158F for the FcyRIIIA, showing that both Ontruzant and EU Herceptin bind the two isoforms with similar affinity by the SPR method.

Additional biological assays including surface HER2 expression level measurement, HER2 ECD shedding, inhibition of AKT phosphorylation, *in vitro* angiogenesis and combination treatment with chemotherapy, were also performed and showed similarity between Ontruzant and the reference product.

An in vivo pharmacodynamic (PD) study and an *in vivo* toxicity study for comparison of Ontruzant with EU Herceptin were not required if the quality comparability exercise and the non-clinical *in vitro* studies were considered satisfactory and no critical issues were identified, which is the case for this application. *In vivo* studies including an efficacy study in orthotopic BT-474 human breast cancer cell xenograft mice. The therapeutic efficacy of Ontruzant was compared to EU Herceptin and US Herceptin in the BT-474 human breast carcinoma which is characterised by the overexpression of HER2 and oestrogen receptors. Therefore, the selected animal model is deemed appropriate. The anti-tumour activities were found similar between Ontruzant and Herceptin in terms of tumour growth inhibition (TGI) rate (data not shown), tumour volume and weight compared to vehicle treated group. A repeat-dose toxicity study using cynomolgus monkeys was also performed (data not shown) and the data are considered supportive of the main pharmacological results.

There was no information provided on the distribution, elimination, excretion or pharmacokinetic drug interactions which is considered acceptable for a biosimilar application.

No local tolerance study and single dose, genotoxicity, carcinogenicity or reproductive and developmental toxicity studies were conducted for Ontruzant , as such studies are not essential for a similar biological product medicinal product (EMA 2006 Guidance [EMEA/CHMP/BMWP/42832/2005]).

2.3.7. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2: Summary of clinical studies

Study	Objectives	Design	Population	Primary Endpoints
SB3-G11-NHV Phase I (Germany) Healthy Male Subjects	Comparative PK, safety, tolerability, immunogenicity For EMA: To investigate and compare the pharmacokinetic (PK) profiles between SB3 and European Union (EU) sourced Herceptin in healthy male subjects. For FDA: To investigate and compare the PK profiles between SB3 and EU sourced Herceptin, between SB3 and United State of America (US) sourced Herceptin and between EU sourced Herceptin and US sourced Herceptin in healthy male subjects.	Randomised, double-blind, three-arm, parallel group, single-dose study in healthy male subjects. In each arm, all subjects received a single dose of either SB3, EU sourced Herceptin, or US sourced Herceptin by intravenous (IV) infusion for 90 minutes.	Healthy male subjects N=108 (SB3 36; US Herceptin 36; EU Herceptin 36)	For EMA: AUC_{inf} For FDA: AUC_{inf}, AUC_{last}, C_{max}
SB3-G31-BC	The *primary objective* is to	Randomised, double-blind, parallel	Patients with newly diagnosed primary	Efficacy Pathological

Phase III (Bulgaria, Poland, Czech Republic, Romania, France, Russia, Ukraine, Mexico, Korea, India, Malaysia, Philippines, Bosnia and Herzegovina, and Vietnam) Women with Newly Diagnosed HER2 Positive Early or Locally Advanced Breast Cancer	demonstrate comparable clinical efficacy of SB3 and Herceptin, in terms of pathologic complete response (pCR) rate of the primary breast tumour in women with HER2 positive early or locally advanced breast cancer (LABC) in neoadjuvant setting. *Secondary objectives* included total pCR; overall clinical response rate; event free survival; overall survival; safety and tolerability; PK; immunogenicity	group, multicentre study in women with HER2 positive EBC or LABC in neoadjuvant setting. Patients were randomised in a 1:1 ratio to either receive SB3 or Herceptin in neoadjuvant setting for 8 cycles concurrently with 8 cycles of chemotherapy (4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/ cyclophosphamide). Subjects will then undergo surgery. After surgery, patients will receive further 10 cycles of adjuvant SB3 or Herceptin as per randomisation to complete one year of therapy.	HER2 positive early or locally advanced breast cancer N= 875 (SB3 437; EU Herceptin 438) PK population = 313 (SB3 161; EU Herceptin 152)	complete response rate of the primary breast tumour PK sub-study C_{trough} at pre-dose of cycle 1, 3, 5, 7 and 8

2.4.2. Pharmacokinetics

Pharmacokinetics comparability data were provided from one single dose PK study SB3-G11-NHV conducted in healthy volunteers and one phase III study in patients with Her2+ advanced breast cancer.

Study SB3-G11-NHV

The study was a randomised, double-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics, safety, tolerability, and immunogenicity of the three formulations of Trastuzumab (Ontruzant), EU Sourced Herceptin and US Sourced Herceptin) in healthy male subjects.

The primary objective of this study was to investigate and compare the pharmacokinetic (PK) profiles between Ontruzant and European Union (EU) sourced Herceptin in healthy male subjects. The secondary objectives were to investigate and compare the safety, tolerability, and immunogenicity between Ontruzant and EU sourced Herceptin in healthy male subjects.

This study was initiated in January 2014 (first subject signed informed consent) and completed in April 2014 (last subject last visit). The study was performed at one centre in Germany.

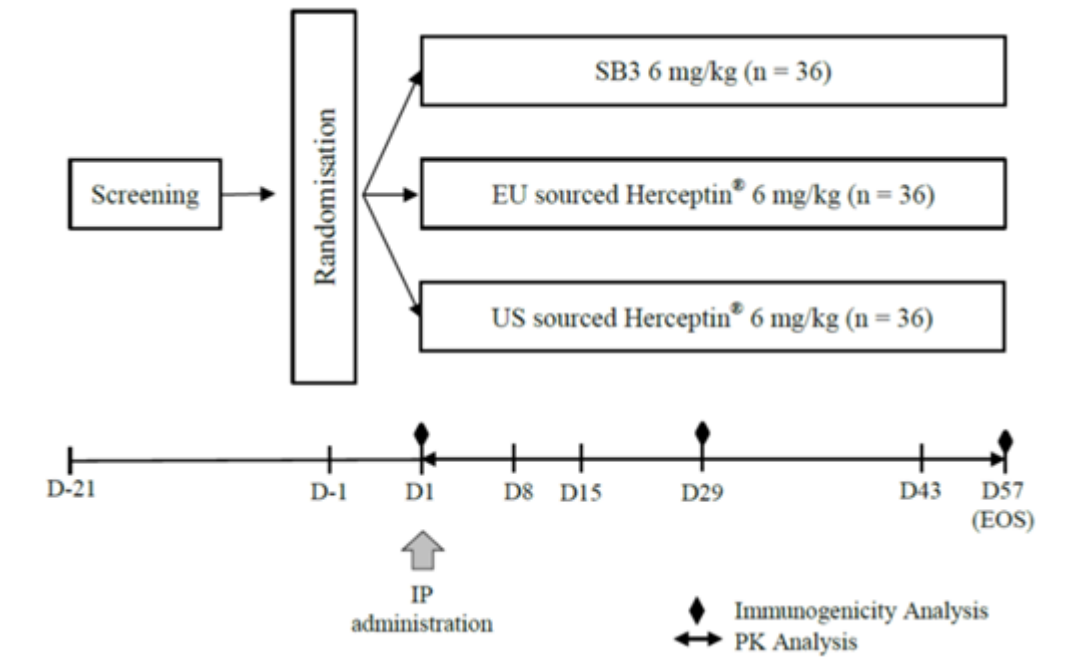


Figure 5: Schematic diagram representing each arm of the study

Table 3: Investigational products (IP)

Active pharmaceutical ingredient: trastuzumab			
	SB3	EU sourced Herceptin®	US sourced Herceptin®
Formulation	150 mg lyophilised sterile powder for concentrate for solution for infusion	150 mg lyophilised sterile powder for concentrate for solution for infusion	440 mg lyophilised sterile powder for concentrate for solution for infusion

The single dose of 6 mg/kg (IV infusion for 90 minutes) was followed by a maximum of 8 weeks during which the PK, safety, and immunogenicity measurements were made. Mode of administration: IV infusion for 90 minutes.

A total of 36 subjects were enrolled in each of the SB3 and US sourced Herceptin treatment groups, and 37 subjects were enrolled in the EU sourced Herceptin treatment group. One subject in the EU sourced Herceptin treatment group withdrew consent before administration of the IP, and was not included in the Safety set. Therefore, there were 36 subjects in each treatment group included in the Safety set. All subjects included in the Safety set were also included in the PK population.

Healthy female subjects were excluded to avoid any risk with formation of anti-trastuzumab antibodies in individuals who are more likely to require trastuzumab for the treatment of breast cancer compared to healthy male subjects.

A sample size of 33 completing subjects from each arm of the clinical study will provide 90% power to detect a 20% difference in pharmacokinetics between the test product and reference product. This is based on an assumption of 5% difference in true geometric mean between test and reference product and an inter-subject coefficient of variation (CV) of 24%. This is a two one-sided t-test with 5% significance level. A 8% dropout rate is anticipated so approximately 36 subjects in each arm were enrolled.

Blood samples for PK analysis were collected prior to start of infusion and at 0.75, 1.5 (end of infusion), 3, 6, 12, 24, 48, 72, 96, 168, 336, 672, 1008 and 1344 hours after start of infusion.

A total of 22.0% of the subjects (30.6% of subjects who received Ontruzant, 13.5% of subjects who received EU sourced Herceptin, and 22.2% of subjects who received US sourced Herceptin) had minor protocol deviations reported. No subjects had major protocol deviations reported.

Pharmacokinetics results

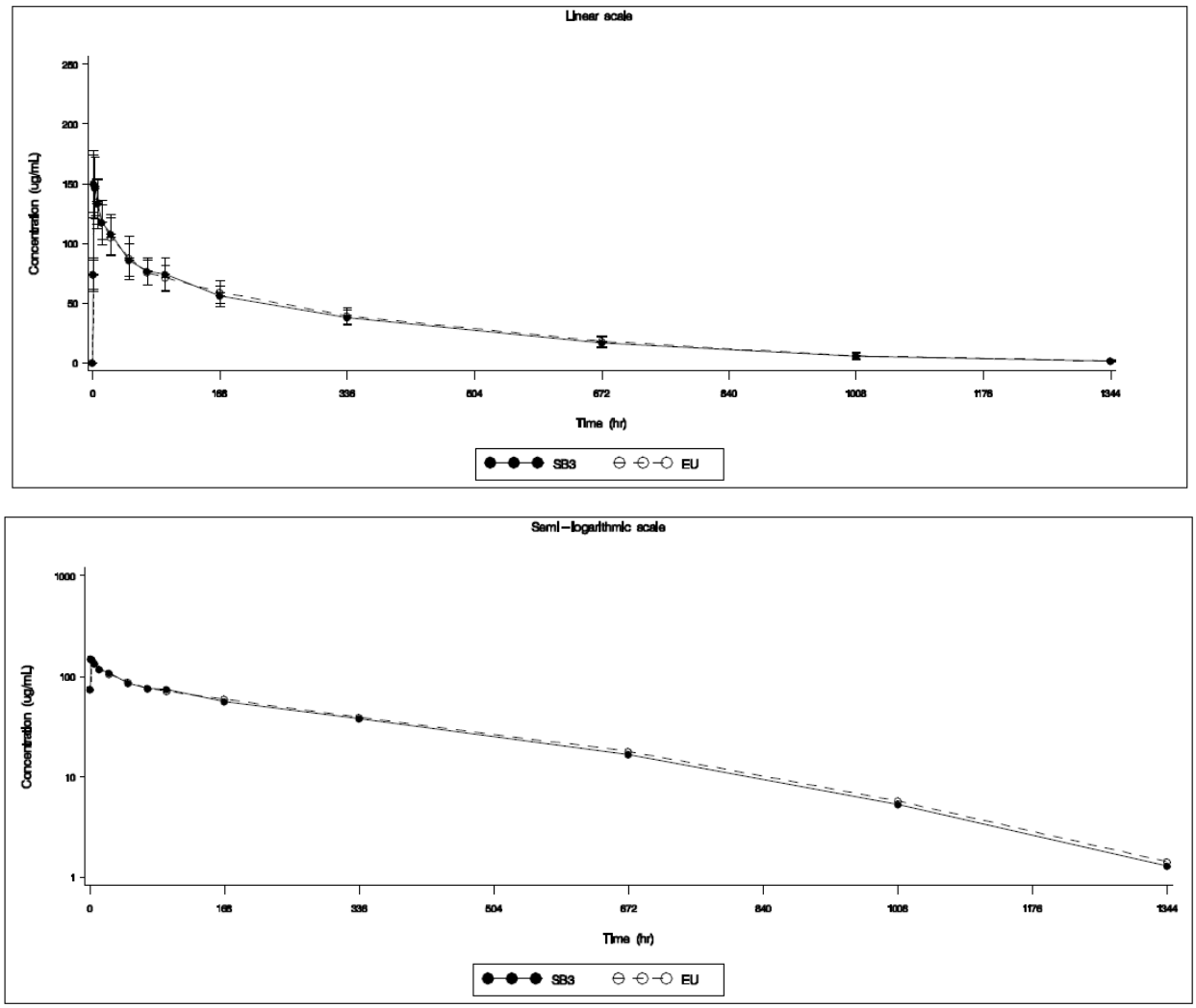


Figure 6: Mean serum concentrations versus nominal times on linear (top graph) and semi-logarithmic scale (bottom graph) of EU sourced Herceptin.

Table 4: Statistical comparison of primary PK parameters between SB3 and EU sourced Herceptin (PK population)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (µg·h/mL)	SB3	36	36	34331.4	0.969	0.908;1.034
	EU sourced Herceptin®	36	36	35426.8		
AUC_{last} (µg·h/mL)	SB3	36	36	33902.9	0.971	0.911;1.034
	EU sourced Herceptin®	36	36	34932.8		
C_{max} (µg/mL)	SB3	36	36	151.747	1.001	0.935;1.072
	EU sourced Herceptin®	36	36	151.520		

A: SB3, B: EU sourced Herceptin®.

LSMean = least squares mean; CI = confidence interval; N = number of subjects in PK population; n = number of subjects who contributed to analysis.

Source: Table 14.2-2.1

Table 5: Statistical comparison of primary PK parameters between SB3 and US sourced Herceptin (PK population)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (µg·h/mL)	SB3	36	36	34331.4	0.930	0.872;0.991
	US sourced Herceptin®	36	36	36924.1		
AUC_{last} (µg·h/mL)	SB3	36	36	33902.9	0.934	0.878;0.994
	US sourced Herceptin®	36	36	36279.3		
C_{max} (µg/mL)	SB3	36	36	151.747	0.988	0.924;1.057
	US sourced Herceptin®	36	36	153.564		

A: SB3, B: US sourced Herceptin®.

LSMean = least squares mean; CI = confidence interval; N = number of subjects in PK population; n = number of subjects who contributed to analysis.

Source: Table 14.2-2.1

Table 6: Statistical comparison of primary PK parameters between EU and US sourced Herceptin (PK population)

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio A/B	90% CI of Ratio
AUC_{inf} (µg·h/mL)	EU sourced Herceptin®	36	36	35426.8	0.959	0.900;1.023
	US sourced Herceptin®	36	36	36924.1		
AUC_{last} (µg·h/mL)	EU sourced Herceptin®	36	36	34932.8	0.963	0.905;1.025
	US sourced Herceptin®	36	36	36279.3		
C_{max} (µg/mL)	EU sourced Herceptin®	36	36	151.520	0.987	0.926;1.051
	US sourced Herceptin®	36	36	153.564		

A: EU sourced Herceptin®, B: US sourced Herceptin®.

LSMean = least squares mean; CI = confidence interval; N = number of subjects in PK population; n = number of subjects who contributed to analysis.

Source: Table 14.2-2.1

Table 7: Descriptive statistics of secondary PK parameters T1/2, clearance, T_{max} and Vz

Pharmacokinetic Parameter	Statistics	Treatment: SB3 6mg/kg N=36	Treatment: EU sourced Herceptin 6mg/kg N=36	Treatment: US sourced Herceptin 6mg/kg N=36
$t_{1/2}$(h)	n	36	36	36
	Mean	195.91	198.03	214.89
	SD	45.189	41.923	52.972
	CV%	23.067	21.170	24.650
	SEM	7.532	6.987	8.829
	Geo. mean	191.16	193.82	208.26
	Geo. SD	1.248	1.234	1.295
	Geo. CV%	22.467	21.243	26.325
	90% CI of Geo. mean	179.580; 203.486	182.690; 205.637	193.618; 224.005
	Median	181.4	190.8	207.0
	Min	137.0	130.2	127.6
	Max	296.9	291.1	322.8
CL (mL/h)	n	36	36	36
	Mean	13.832	13.519	12.816
	SD	2.0990	2.4301	2.2370
	CV%	15.1748	17.9757	17.4555
	SEM	0.3498	0.4050	0.3728
	Geo. mean	13.678	13.318	12.632
	Geo. SD	1.1642	1.1893	1.1874
	Geo. CV%	15.2944	17.4717	17.3080
	90% CI of Geo. mean	13.1048; 14.2765	12.6837; 13.9849	12.0353; 13.2580
	Median	13.53	13.33	12.54
	Min	9.68	9.71	9.16
	Max	17.77	19.65	19.25
T_{max}(h)	n	36	36	36
	Mean	4.691	3.529	2.799
	SD	15.6597	7.6948	3.7569
	CV%	333.8359	218.0684	134.2283
	SEM	2.6099	1.2825	0.6262
	Geo. mean	2.204	2.291	2.189
	Geo. SD	2.0540	1.8871	1.7211
	Geo. CV%	82.3909	70.4764	58.5570
	90% CI of Geo. mean	1.7993; 2.6987	1.9162; 2.7400	1.8786; 2.5506
	Median	1.58	1.61	1.57
	Min	1.52	1.53	1.53
	Max	95.95	48.07	24.03
Vz (mL)	n	36	36	36
	Mean	3831.5	3792.1	3876.7
	SD	710.20	714.29	795.09
	CV%	18.54	18.84	20.51
	SEM	118.37	119.05	132.51
	Geo. mean	3772.2	3724.2	3795.1
	Geo. SD	1.19	1.22	1.24
	Geo. CV%	17.87	19.74	21.43
	90% CI of Geo. mean	3588.52; 3965.35	3524.70; 3935.05	3575.28; 4028.52
	Median	3802	3815	3889
	Min	2517	2479	2288
	Max	6442	5371	5527

Table 8: Statistical Comparison of Secondary Pharmacokinetic Parameters

				Ratio of SB3/Reference Herceptin® or HL estimates	
PK Parameter	Treatment	N	Geo-LSMean or Median	Estimate	90% CI
T_{max} (h)	SB3	36	1.58		
	EU Herceptin®	36	1.61	0.000	−0.030 ; 0.020
	US Herceptin®	36	1.57	0.000	−0.020 ; 0.020
V_z (mL)	SB3	36	3772.2		
	EU Herceptin®	36	3724.2	1.013	0.941 ; 1.090
	US Herceptin®	36	3795.1	0.994	0.921 ; 1.073
λ_z (1/h)	SB3	36	0.00361		
	EU Herceptin®	36	0.00358	1.010	0.927 ; 1.100
	US Herceptin®	36	0.00332	1.086	0.987 ; 1.196
$t_{1/2}$ (h)	SB3	36	181.4		
	EU Herceptin®	36	190.8	−5.300	−21.600 ; 12.300
	US Herceptin®	36	207.0	−22.900	−40.400 ; 0.300
CL (mL/h)	SB3	36	13.678		
	EU Herceptin®	36	13.318	1.027	0.963 ; 1.095
	US Herceptin®	36	12.632	1.083	1.016 ; 1.154
$\%AUC_{extrap}$ (%)	SB3	36	0.939		
	EU Herceptin®	36	1.074	0.874	0.649 ; 1.175
	US Herceptin®	36	1.235	0.760	0.544 ; 1.061

Study SB3-G31-BC

Study SB3-G31-BC is a phase III randomised, Double-Blind, parallel Group, multicentre study to compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between Ontruzant (proposed trastuzumab biosimilar) and Herceptin in Women with Newly Diagnosed HER2 Positive Early or Locally Advanced Breast Cancer in Neoadjuvant Setting. One of the secondary parameters of this study was to evaluate pharmacokinetics (PK) of Ontruzant compared to Herceptin.

The PK analyses were performed on the PK Population consisting of 313 subjects (161 subjects in the Ontruzant and 152 subjects in the Herceptin treatment groups). Blood samples were collected at pre-dose of Cycle 1, 3, 5, 7 and 8. All samples collected during the study are listed but the samples which were collected post-dose or not collected on the exact scheduled day (a visit window was not allowed for the PK analysis) were excluded from the summary statistics and statistical analyses.

Eleven subjects had quantifiable concentrations at pre-dose of Cycle 1. Those subjects were investigated to see whether there was any event that could make quantifiable concentrations at pre-dose of Cycle 1. However, none of the subjects had experiences of trastuzumab prior to participation of this study and the PK samples of those subjects were collected before start of infusion. Thus, those serum concentrations were included in the summary statistics.

The statistical analysis of the log-transformed C_{trough} at pre-dose of Cycle 8 was performed using the analysis of variance model (ANOVA).

Protocol deviations

Protocol deviations related to PK evaluation were defined before database lock as follows; 1) PK blood sampling time on or after start of IP infusion time, 2) PK sampling was done but not at the exact scheduled date (i.e., 21 days after previous administration of IP), and 3) PK sampling was not done at Cycle 1, 3, 5, 7, and 8. The data points which meet the protocol deviation definitions were excluded from the descriptive statistics and equivalence test but listed. Among 313 subjects who were participating PK evaluation, 166 subjects (84 subjects in the Ontruzant treatment group and 82 subjects in the EU Herceptin treatment group) had at least one protocol deviation related to PK. The most frequent protocol deviation was that PK sampling was done but not at the exact scheduled date (158 subjects; 80 subjects in the Ontruzant treatment group and 78 subjects in the EU Herceptin treatment group).

Table 9: Summary of Protocol Deviation Related to PK Evaluation (PK Population)

Number of subjects	SB3 N=161 n (%)	EU Herceptin® N=152 n (%)	Total N=313 n (%)
With at least one PK related protocol deviation	84 (52.2%)	82 (53.9%)	166 (53.0%)
(1) PK blood sampling time on or after start of IP infusion time	1 (0.6%)	3 (2.0%)	4 (1.3%)
(2) PK sampling was done but not at the exact scheduled date (i.e., 21 days after previous administration of IP)	80 (49.7%)	78 (51.3%)	158 (50.5%)
(3) PK sampling was not done at Cycle 1, 3, 5, 7, and 8	9 (5.6%)	7 (4.6%)	16 (5.1%)

N: number of subjects in the PK Population, n: number of subjects with protocol deviation
Source: Section 5.3.5.1 Main CSR Amendment, SB3-G31-BC, Listing 16.2.2-1.1

From the above results, the number, type and distribution of protocol deviations in the PK subset were balanced across the treatment groups.

Missing data

In clinical Phase III study of Ontruzant (SB3-G31-BC), PK population consisted of 313 patients (161 patients in the Ontruzant and 152 patients in the EU Herceptin treatment groups). Nonetheless, 27 to 42 patients per treatment group were excluded from the analysis of C_{trough} by each cycle due to various reasons.

Table 10: Summary of Patients with Missing C_{trough} Data at Cycles 3 to 8 (PK Population)

Timepoint	SB3 N=161							EU Herceptin® N=152						
	n	n1	n2	n3	n4	n5	n6	n	n1	n2	n3	n4	n5	n6
Cycle 3	129	32	0	30	1	1	0	125	27	0	23	2	2	0
Cycle 5	119	42	0	36	2	3	1	119	33	1	27	1	3	1
Cycle 7	126	35	0	24	6	4	1	118	34	0	27	2	4	1
Cycle 8	128	33	0	24	1	6	2	113	39	0	29	2	4	4

N: number of patients in the PK Population; n: number of patients at each timepoint.
Source: Section 5.3.5.1 Main CSR Amendment, SB3-G31-BC, Table 11-19, Listing 16.2.5-2.1

Patients missing C_{trough} data (n1) include those who had protocol deviation of PK blood sampling (n2, n3, and n4), those who discontinued from the study (n5), and those whose samples were taken but not analysed (n6) for other reasons.

Pharmacokinetics results

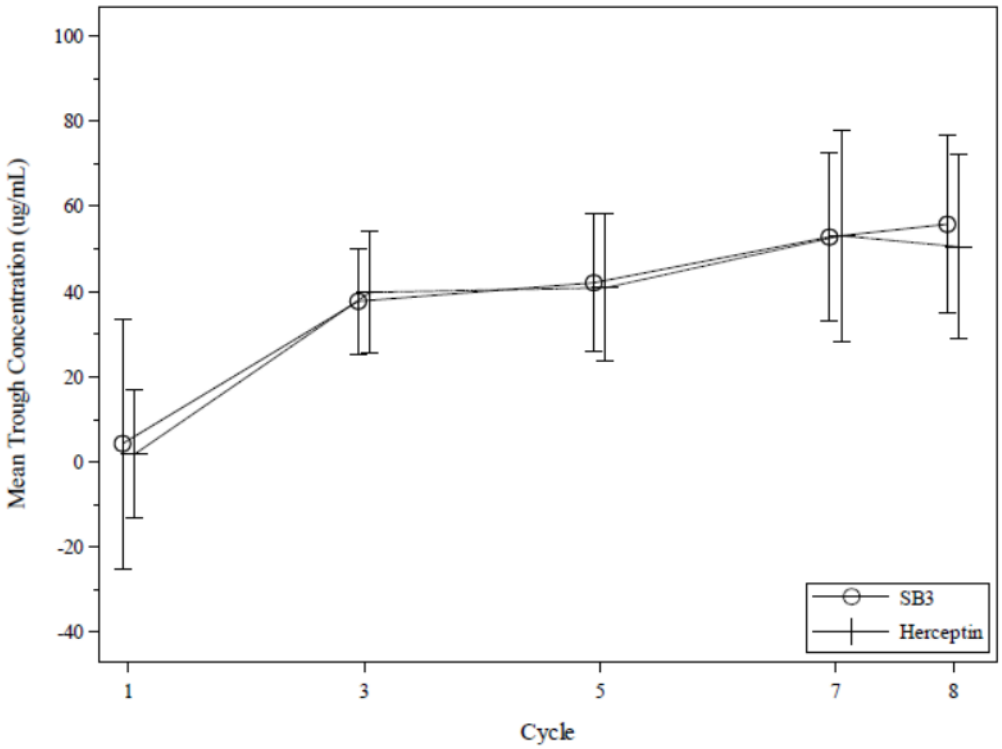


Figure 7: Mean Serum Trough (Pre-dose) Concentration-time Profiles from Cycle 1 to Cycle 8

Table 11: Summary of Serum Trough (C_{trough}) Concentration (µg/mL) (PK Population)

Timepoint	Statistics	SB3 N=161	Herceptin® N=152
Cycle 1 (baseline)	n	156	149
	Mean (SD)	4.309 (29.3273)	1.798 (15.0560)
	CV%	680.5795	837.4774
	Min, Max	0.00, 230.39	0.00, 147.61
Cycle 3	n	129	125
	Mean (SD)	37.714 (12.3797)	39.829 (14.3223)
	CV%	32.8253	35.9599
	Min, Max	0.00, 83.09	15.98, 97.88
Cycle 5	n	119	119
	Mean (SD)	42.062 (16.2136)	40.896 (17.2324)
	CV%	38.5467	42.1371
	Min, Max	14.71, 102.79	0.00, 136.44
Cycle 7	n	126	118
	Mean (SD)	52.807 (19.7430)	53.134 (24.8162)
	CV%	37.3872	46.7051
	Min, Max	22.98, 175.02	0.42, 169.97
Cycle 8	n	128	113
	Mean (SD)	55.799 (20.9167)	50.502 (21.5428)
	CV%	37.4857	42.6573
	Min, Max	19.00, 189.70	0.00, 172.68

CV% = coefficient variation; N = number of subjects in the PK Population; Max = maximum;
Min = minimum; n = number of subjects in a cycle; PK = pharmacokinetic; SD = standard deviation.
Source: Table 14.2-7.1

Table 12: Statistical Comparison for the C_{trough} at Pre-dose of Cycle 8 (PK Population)

	SB3 N=161	Herceptin® N=152
n	128	111
GeoLSMean (ug/mL)	52.535	47.816
GeoLSMean ratio (%)	109.869	
90% CI of GeoLSMean ratio (%)	[101.543, 118.878]	

CI = confidence interval; GeoLSMean = geometric least squares mean; N = number of subjects in the PK Population; n = number of subjects in a cycle; PK = pharmacokinetic.
Source: Table 14.2-7.5

Serum HER2 level

Blood samples for serum HER2 levels were taken pre-dose on Day 1 of Cycle 1 and Cycle 8. The serum HER2 level between the two treatment groups were comparable at the time-point of Cycle 1 (Baseline) and Cycle 8.

Table 13: Summary of Serum HER2 Level in Pharmacokinetic Population

Timepoint Statistic	SB3 N=161	EU Herceptin® N=152	Total N=313
Cycle 1 (BL)			
n	158	149	307
Mean	26.872	21.735	24.379
SD	41.8616	26.8694	35.4246
Median	14.765	13.860	14.290
Min, Max	4.77, 432.38	5.49, 218.08	4.77, 432.38
Cycle 8			
n	152	142	294
Mean	11.621	10.774	11.212
SD	5.2300	3.8163	4.6136
Median	10.505	9.830	10.045
Min, Max	5.69, 51.63	4.90, 30.65	4.90, 51.63

Sensitivity analysis of the PK data

Excluding patients with non-verifiable data

A sensitivity analysis excluding the 11 patients excluded from the per protocol set (PPS) in the main study population due to it being impossible to verify any source data. Excluding 11 patients having non-verifiable data, the proportion of patients with C_{trough} exceeding 20 µg/mL was also similar between the two treatment groups at each cycle. A total of 99.2% of patients in the Ontruzant treatment group and 97.2% of patients in the EU Herceptin treatment group had C_{trough} values at pre-dose of Cycle 8 greater than 20 µg/mL. The geometric least squares mean (GeoLSMean) ratio of C_{trough} between the two treatment groups at Cycle 8 was 110.343%. The 90% CI was [101.791%, 119.615%] which was contained within the pre-defined equivalence margin of [80%, 125%].

Excluding patients with quantifiable concentration at pre-dose of Cycle 1

Eleven patients had quantifiable concentration at pre-dose of Cycle 1. The majority of these subjects had significant levels of IP detected in the serum, including 5 patients with levels over 100 µg/mL. Per the Agency's request, the Applicant provided a sensitivity analysis of the PK data excluding these eleven patients. Those subjects were investigated to see whether there was any event that could make quantifiable concentrations at pre-dose of Cycle 1. However, none of the patients had experiences of trastuzumab prior to participation of this study and the PK samples of those patients were collected before start of infusion. Excluding eleven subjects having quantifiable pre-dose concentration, mean C_{trough} collected after IP administration was similar between the Ontruzant and Herceptin treatment groups from Cycles 3 to 8. Variability in trough concentrations was also similar in C_{trough} collected from Cycle 3 to Cycle 8. The proportion of subjects with C_{trough} exceeding 20 µg/mL was similar between the treatment groups at each cycle. A total of 99.2% of subjects in the Ontruzant treatment group and 97.2% of subjects in the Herceptin treatment group had C_{trough} values at pre-dose of Cycle 8 greater than 20 µg/mL. The geometric least squares mean ratio of C_{trough} between the two treatment groups at Cycle 8 was 108.158%. The 90% CI was [99.828%, 117.184%], which was contained within the predefined equivalence margin of [80%, 125%]. From the above results of sensitivity analysis, PK parameters were comparable between the two treatment groups even when 11 patients with quantifiable concentrations of IP at pre-dose of Cycle 1 were excluded.

Excluding patients with irregular/non-verifiable data

The applicant provided a sensitivity analysis of the PK data in study SB3-G31-BC, excluding all 22 patients with irregular/non-verifiable data (i.e. the 11 patients with quantifiable baseline pre-dose concentrations of IP and the additional 11 patients excluded from the PPS).

The proportion of patients with C_{trough} exceeding 20 µg/mL was similar between the two treatment groups at each cycle. A total of 99.2% of patients in the Ontruzant treatment group and 97.1% of patients in the EU Herceptin treatment group had C_{trough} values at pre-dose of Cycle 8 greater than 20 µg/mL

The geometric least squares mean (GeoLSMean) ratio of C_{trough} between the two treatment groups at Cycle 8 was 108.586%. The 90% CI was [100.023%, 117.881%] which was contained within the pre-defined equivalence margin of [80%, 125%].

From the above results of sensitivity analysis, PK parameters were comparable between the two treatment groups even when all 22 patients with irregular/non-verifiable data were excluded.

Impact of Anti-drug antibodies (ADA) on PK parameters

In the study SB3-G11-NHV, there was no indication of immunogenicity in the population of healthy volunteers after administration of Ontruzant or Herceptin as no detectable ADA was seen. This absence of ADA was expected following a single dose being administered in healthy subjects.

In the study SB3-G31-BC, within the PK population, one subject in the Ontruzant treatment group and no subject in the Herceptin treatment group were reported to have an ADA positive result up to Cycle 9. One subject had a positive result of ADA at Cycle 5 pre-dose and negative results at other time points. The serum trough concentration at Cycle 5 was relatively low at 15.46 µg/mL but within the range of 14.71 to 102.79 µg/mL of the cycle. The trough concentrations (46.35 and 56.08 µg/mL for Cycle 7 and Cycle 8, respectively) in the later cycles were similar to other subjects (ranging from 22.98 to 175.02 µg/mL and from 19.00 to 189.70 µg/mL for Cycle 7 and Cycle 8, respectively). Due to the low incidence of positive ADA results, the impact of the presence of ADA up to Cycle 9 on the PK cannot be compared.

Two subjects in the Ontruzant treatment group and one subject in the Herceptin treatment group were reported to have pre-existing positive ADA results. The serum trough concentrations of subjects with pre-existing ADA were similar to the trough concentrations in the corresponding treatment groups and cycles.

2.4.3. Pharmacodynamics

Mechanism of action

See discussion on clinical pharmacology.

Primary and Secondary pharmacology

See discussion on clinical pharmacology.

2.4.4. Discussion on clinical pharmacology

With respect to the clinical pharmacokinetics, the development program to assess the similarity between Ontruzant and Herceptin is in general adequate and was performed according to the guidance on similar biological products and the recommendations given in the national and CHMP Scientific Advice. The comparability exercise was performed between EU/US sourced reference products and the formulation of Ontruzant intended to be marketed in the European Union.

The Ontruzant PK program consists of one pivotal phase I study carried out in healthy subjects (Clinical Study SB3-G11-NHV) and the PK data collected in the pivotal phase III study SB3-G31-BC in patients with HER2-positive early breast cancer (EBC) or locally advanced breast cancer (LABC) in neoadjuvant setting.

The single dose PK study SB3-G11-NHV is judged appropriate and the clinical site is judged GCP compliant. In the case of a monoclonal antibody with per definition a long half-life and a potential of immunogenicity, a parallel design for the single dose study SB3-G11-NHV is accepted. The subject population including male volunteers has been selected with the aim of minimizing variability and permitting detection of differences between pharmaceutical products. This is considered a sensitive population for comparative investigation of PK. A single dose is considered 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. The single dose of 6 mg/kg in intravenous infusion (over 90 minutes) is judged adequate based on the posology of the reference product as this corresponds to a widely used treatment schedule in patients who receive an initial 8 mg/kg loading dose followed by a maintenance dose of 6 mg/kg every 3rd week.

The sample size is adequate and has been selected to account for potential dropouts and provided 90% power overall, a true geometric mean ratio between 95 and 105% and a 8% dropout rate. The power calculation is for a 90% CI around the GMR to be in the 80-125% range with an alpha=0.05. Inter-subject CV% was similar across the three treatment groups. When sample size was calculated, inter-subject CV% was expected to be 24%. The actual inter-subject CV% derived from this study was smaller than the expected value.

A sufficient number of samples to adequately characterise the whole profile were collected, with sufficient sampling around predicted Tmax to provide reliable estimate of peak exposure. Even if the length of the study is relatively short in view of the half-life of trastuzumab (approx. 22 days in volunteers), a blood sampling carried out over a period of 8 weeks is accepted for characterisation of the elimination phase as

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-∞).

In the phase I PK study SB3-G11-NHV, the pharmacokinetics for Ontruzant (SB3) and Herceptin showed comparability between the two products as the ratios (90% CI) of geometric means for primary PK endpoints $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} were 0.971, 0.969 and 1.001, respectively and hence were all within the acceptance range of 80-125%.

Per request, the secondary PK parameters (Vz, λz, CL, $\%AUC_{extrap}$, T_{max}, and $t_{1/2}$) were compared using a pre-defined equivalence margin of 0.8 to 1.25. Secondary PK parameters support biosimilarity in terms of pharmacokinetics between Ontruzant and EU Herceptin. It is noted that the mean T_{max} value for Ontruzant was slightly longer compared to EU- and US-sourced Herceptin (4.69 hours versus 3.53 and 2.80 hours respectively), probably due to 3 patients with outlying very high recorded T_{max} results. When these 3 outliers are excluded from the analysis, the median T_{max} values and ranges were similar between groups and the geometric LSMean ratios in AUC_{inf}, AUC_{last} and C_{max} remained within the pre-defined equivalence margin of 0.8 to 1.25 (data not shown). No explanation is available to substantiate the unusual second peaks observed after the completion of the intravenous infusion in some subjects. This observation has been described for Herceptin in the past but to a lesser extent (T_{max}=24 hours) (Wynee et al., 2013) while an unusual high T_{max}= 96 hours was observed for Ontruzant in study SB3-G11-NHV. Nevertheless, this issue does not compromise the final conclusions of PK similarity between Ontruzant and Herceptin, T_{max} being a secondary parameter less clinically relevant when Ontruzant is used in the current indications.

In the phase III study SB3-G31-BC, a statistical analysis of the log-transformed C_{trough} at pre-dose of Cycle 8 was performed using ANOVA. Mean pre-dose serum trough concentration (C_{trough}) profiles up to Cycle 8 suggest the two treatments show similar C_{trough} profiles over time in patients. The minimum target concentration of 20 µg/ml established for trastuzumab was reached at cycle 3 for both products. Steady state appeared to be reached at Cycle 7.

Several sensitivity analyses of the PK data were provided excluding the 11 patients having non-verifiable data; 11 patients with quantifiable concentration at pre-dose of Cycle 1; all 22 patients with irregular/non-verifiable data. Overall, PK parameters were comparable between the two treatments in all sensitivity analyses.

The conduct of study SB3-G31-BC for the PK subset was considered acceptable. The number, type and distribution of protocol deviations were balanced across the treatment groups. The reasons for the number of patients with missing C_{trough} data at cycles 3 to 8 was adequately investigated. Numbers of patients with missing C_{trough} data at each time point were generally comparable between the two treatment groups. The corresponding reasons for missing C_{trough} data were also comparable at each timepoint. Within each treatment group, there were some fluctuations on numeric numbers. However, no trend of data exclusion could be observed throughout the timepoints in study SB3-G31-BC. Therefore, the results from the PK comparability are found to be reliable.

To evaluate shed antigen's potential impact on PK profile of Ontruzant, relationship between log transformed C_{trough} and log transformed baseline HER2 level (generally higher than Cycle 8 serum HER2 level) in PK population with Ontruzant were investigated at each cycle. The serum HER2 levels between the two treatment groups were comparable at the time-point of Cycle 1 (Baseline) and Cycle 8. There appeared to be a weak correlation at Cycle 3, but no correlation at other cycles. Therefore, shed antigen did not have a significant impact on the PK profile of Ontruzant (data not shown).

No analyses were provided in the special populations which is acceptable considering the biosimilar relies on the information already known of the reference product. No formal drug-drug interaction studies are judged needed.

To date no validated PD biomarkers exist for trastuzumab efficacy and consequently no clinical comparability PD studies have been performed with Ontruzant. Studies on the mechanism of action were not provided which is acceptable for a biosimilar.

With regards to immunogenicity data, the applicant has provided further justification for the very low ADA incident rates seen in both treatment arms of the SB3-G31-BC clinical study. Namely the additional HER2 depletion step used which can lower the false positive rate in ADA determination from HER2 level in the serum, and lower incidence rates seen in another recent clinical trial. In addition, the applicant has appropriately addressed the concerns raised regarding the capability of the immunogenicity assays used to detect all antibody positive samples. Therefore, the assay is considered reliable to detect antibodies to Ontruzant and to EU Herceptin with equivalent extent.

2.4.5. Conclusions on clinical pharmacology

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

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Dose response studies were not submitted (see discussion on clinical efficacy).

2.5.2. Main study

Study SB3-G31-BC

SB3-G31-BC is a Phase III double-blind, parallel group, multicentre study intended to evaluate the efficacy, safety, PK and immunogenicity of Ontruzant compared to Herceptin in women suffering from HER2-positive early breast cancer (EBC) or locally advanced breast cancer (LABC).

Methods

Study Participants

This study was conducted in 97 study centres: 5 centres in Korea, 3 centres in Malaysia, 1 centre in Mexico, 6 centres in the Philippines, 4 centres in Vietnam, 2 centres in Bosnia and Herzegovina, 15 centres in Ukraine, 3 centres in Bulgaria, 2 centres in the Czech Republic, 2 centres in France, 9 centres in Romania, 10 centres in Poland, 16 centres in India and 19 centres in the Russian Federation.

Inclusion criteria

1. Female aged 18-65 years
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
3. Non-metastatic, unilateral newly diagnosed primary breast cancer of clinical stage II to III including inflammatory breast cancer with:

- tumour size ≥ 2 cm
- histologically confirmed primary invasive adenocarcinoma of the breast
- HER2-positivity confirmed by a central laboratory or an accredited local laboratory and defined as immunohistochemistry 3+ or fluorescence in situ hybridisation (FISH) +

4. Known hormone receptor (oestrogen receptor [ER] and progesterone receptor [PR]) status
5. Baseline left ventricular ejection fraction (LVEF) ≥ 55% measured by echocardiography or multiple gated acquisition (MUGA) scan
6. Subjects had to be able to provide informed consent, which had to be obtained prior to any study-related procedures.

Exclusion criteria

1. Metastatic (stage IV) or bilateral breast cancer or clinically detectable two separate breast cancer masses by physical examination (palpation)
2. History of any prior invasive breast carcinoma, except for subjects with a past history of ductal carcinoma in situ and/or lobular carcinoma in situ treated with surgery only
3. Past or current history of malignant neoplasms within 5 years prior to Randomisation, except for curatively treated carcinoma in situ of uterine cervix, basal cell carcinoma of the skin or squamous cell carcinoma of the skin (malignant neoplasm occurring more than 5 years prior to Randomisation were permitted if curatively treated with surgery only)
4. Previous history of radiation therapy, immunotherapy, chemotherapy or biotherapy (including prior HER2 directed therapy)
5. Major surgery within 4 weeks prior to Randomisation and minor surgery within 2 weeks prior to Randomisation (major surgery was defined as surgery which required general anaesthesia; the diagnostic procedures such as open and/or core-needle biopsies were not regarded as surgeries mentioned above; sentinel lymph node biopsy before initiation of neoadjuvant therapy was exempted from this criterion)
6. Serious cardiac illness that would preclude the use of trastuzumab such as:
    a. history of documented congestive heart failure (CHF; New York Heart Association [NYHA] class II or greater heart disease)
    a. LVEF < 55% by echocardiography or MUGA scan
    b. angina pectoris requiring anti-anginal medication
    c. evidence of transmural infarction on electrocardiogram (ECG)
    d. uncontrolled hypertension (systolic > 180 mmHg and/or diastolic > 100 mmHg)
    e. clinically significant valvular heart disease
    f. high risk uncontrolled arrhythmias
7. Serious pulmonary illness enough to cause dyspnoea at rest or requiring supplementary oxygen therapy
8. Known history of hepatitis B virus (excluding immunized or fully recovered from the past infection), hepatitis C virus or human immunodeficiency virus infection

9. Other concurrent serious illnesses that could interfere with planned treatment including severe cardiovascular, pulmonary, metabolic or infectious conditions
10. Known hypersensitivity to the IPs, non-IPs or any ingredients or excipients of the IPs or non-IPs
11. Known hypersensitivity to murine proteins
12. Known history of dihydropyrimidine dehydrogenase deficiency
13. Pre-existing peripheral sensory or motor neuropathy ≥ grade 2, defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0
14. Any of the following abnormal laboratory tests:
    a. serum total bilirubin > 1.5 × upper limit of normal (ULN); in cases of known Gilberts syndrome, level of total bilirubin within 3 × ULN was permitted
    g. aspartate transaminase (AST) and/or alanine transaminase (ALT) > 1.5 × ULN
    h. alkaline phosphatase (ALP) > 2.5 × ULN
    i. serum creatinine > 1.5 × ULN
    j. haemoglobin < 9 g/dL
    k. absolute neutrophil count (ANC) < 1500/mm3 (< 1.5 × 109/L)
    l. platelets count < 100000/mm3 (< 100 × 109/L)
15. Pregnant or lactating women. A pregnancy test result was required for all women of childbearing potential including women who had menopause onset within 2 years prior to Randomisation. Women of childbearing potential had to agree to use non-hormonal contraceptive methods during the study and 7 months after the last dose IP
16. Concurrent hormonal therapy including birth control pills, ovarian hormone replacement for menopause, selective oestrogen receptor modulator (SERM) either for osteoporosis or breast cancer prevention
17. Subjects unwilling to follow the study requirements

Treatments

Investigative and comparison treatments

Ontruzant and Herceptin administered every 3 weeks for a total of 18 cycles (8 cycles of neoadjuvant therapy and 10 cycles of adjuvant therapy) unless Investigator-assessed clinical disease progression or recurrence of disease, or intolerable toxicity occurred. Ontruzant or Herceptin was administered intravenously at a loading dose of 8 mg/kg and at a maintenance dose of 6 mg/kg for the subsequent cycles.

Neo-adjuvant chemo-therapy

All patients received 75 mg/m^2 docetaxel given every 3 weeks for 4 cycles followed by 4 cycles of FEC (5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2) given every 3 weeks.

After completing the cycles, patients underwent surgery and subsequently received an additional 10 cycles of intravenous trastuzumab as per randomisation to complete 1 year of treatment.

After completion of the adjuvant therapy, patients were followed up for additional 30 days after the last dose of IP to the end of study (EOS) visit. Radiotherapy was administered as per local practice. Hormone receptor-positive patients could receive adjuvant hormonal therapy as per local practice.

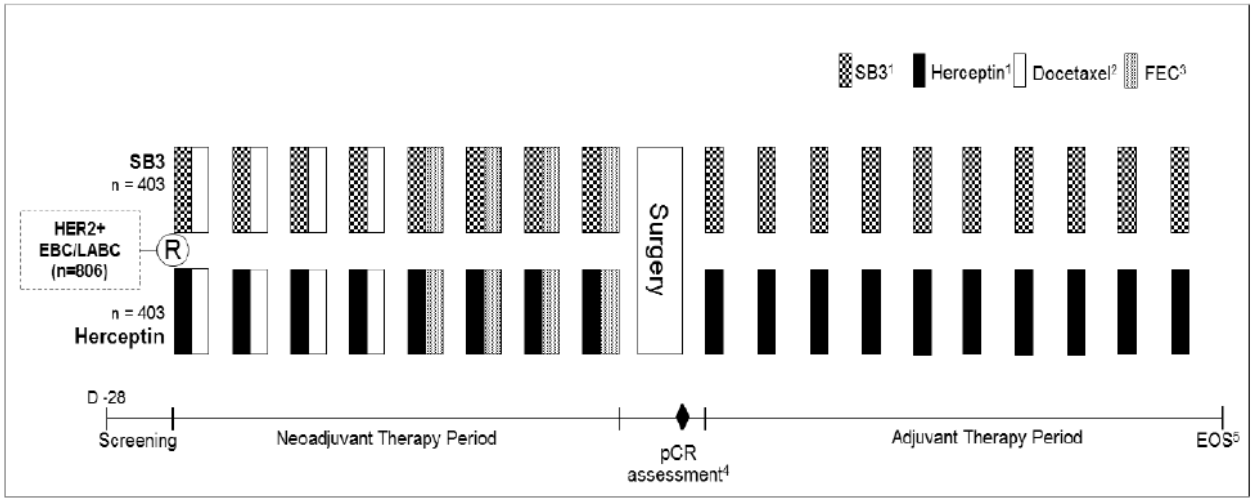


Figure 8: Schematic representation of the SB3-G31-BC trial setup

Objectives

Primary

To demonstrate comparable clinical efficacy between Ontruzant and EU Herceptin, by means of pathologic complete response (pCR) rate of the primary breast tumour in women with HER2 positive EBC or LABC in the neoadjuvant setting.

Secondary

To evaluate the efficacy of Ontruzant compared to EU Herceptin by total pathological complete response (tpCR) rate, overall clinical response rate, event-free survival and overall survival.

To evaluate comparable safety / tolerability, PK and immunogenicity between Ontruzant and EU Herceptin.

Outcomes/endpoints

Primary endpoint

The primary endpoint was pathological complete response rate of the primary breast tumour. pCR was defined as no histological evidence of residual invasive tumour cells in the breast specimen removed at surgery [bpCR]. Non-invasive breast residuals were allowed and the pathological examination of axillary lymph nodes was not to be considered; ypT0/is, ypN0/+.

The difference in bpCR rate was analysed for the primary analysis. Equivalence was declared when the 95% CI of the difference in the bpCR rate between treatments was entirely contained within the equivalence margin of [−13%, 13%]. The 95% CIs for the difference were estimated in the Per-protocol Set (PPS).

Secondary endpoints

- Total pathological complete response. tpCR was defined as the absence of invasive residual tumour cells in both breast and lymph nodes.
- Overall clinical response rate during neoadjuvant therapy (by RECIST criteria). The overall clinical response rate was defined as the percentage of subjects achieving cCR or cPR for the best overall response during the neoadjuvant therapy period.
- Event-free survival, defined as the time from the date of randomisation to the date where an event occurred. An event was disease recurrence or progression (local, regional, distant or contralateral) or death due to any cause.
- Overall survival, defined as the time from the date of randomisation to the date of death, regardless of the cause of death. Subjects who were alive at the time of analysis were censored at the date of the last follow-up assessment.

Breast and total pCR (tpCR)

Pathological complete response was assessed by the local pathologist. For pCR quality control, pCR results of selected samples were reviewed by the study Pathologist Board. The role of the pathologist board review was to check data accuracy and consistency and to check overall quality of pCR assessment procedure by reviewing both local pathology report (LPR) used in the investigator site and pathology report worksheet (PRW) provided for this study. The sponsor's clinical research physician and medical advisor monitored periodically the pCR data (pCR form of Post-Surgery sheet) extracted from eCRF (all entered till cut-off) to search out pCR cases entered by Investigator sites. Missing responses were treated as failures.

Clinical tumour response

Clinical tumour response was assessed using the criteria for clinical response evaluation modified from Response Evaluation Criteria in Solid Tumors (RECIST), the latter which was modified to the neoadjuvant setting in as much as clinical tumour response was measured using assessment by ultrasound or caliper in order to achieve consistency in tumour assessments across sites. In subjects with inflammatory breast cancer, the measurement of breast tumour size was not available and thus they were not included in the analysis population for clinical response evaluation.

If there was suspicion of disease progression based on clinical findings before the scheduled tumour assessment, an unscheduled assessment was performed. If a lesion showed clear signs of progression, the subject was removed from study and provided with the local standard of care.

Safety

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of symptomatic cardiac events and asymptomatic left ventricular dysfunction
- Incidence of infusion-related reactions
- Laboratory value abnormalities

Pharmacokinetics

- Trough serum concentration (C_{trough}) at pre-dose of Cycle 1, 3, 5, 7, and 8

Immunogenicity

- Incidence of anti-drug antibodies (ADAs) and neutralising antibodies (NAbs) at pre-dose of Cycle 1, 5, 9, 14 and 30 days after the last dose of IP.

Sample size

To calculate the equivalence margin, neoadjuvant studies randomised to receive Herceptin in combination with taxane- and/or anthracycline-containing chemotherapies or only chemotherapies without Herceptin were searched. There were only 3 studies found from the literature that randomised to include a non-Herceptin control arm with bpCR reported in subjects treated with these regimens.

The Buzdar and Chang studies included only operable EBC subjects with stage II to III with resulting bpCR rates of 65% (26% for non-Herceptin group) and 31% (9% for non-Herceptin group), respectively, and the NOAH study included only LABC patients in reporting a bpCR rate of 43% (22% for non-Herceptin group).

Two analyses were implemented to compare the primary endpoint, one on the ratio of bpCR rates and one on the difference of bpCR rates between the biosimilar and reference product in the per protocol set.

Table 14: Breast pCR rates from reference studies, SB3-G31-BC

Study	Herceptin® Event/Total	No Herceptin® Event/Total	Difference	Ratio
Buzdar (2005)	15/23 (65%)	5/19 (26%)	39%	2.5
Gianni (2010) NOAH trial	50/117 (43%)	26/118 (22%)	21%	2.0
Chang (2008)	4/13 (31%)	1/11 (9%)	22%	3.4
Meta-analysis			23.3% [16.6;29.9]†	2.07 [1.546, 2.795]‡

† 80% confidence interval, ‡ 90% confidence interval

The ratio of bpCR rates was calculated at 2.07 with the 90% CI of [1.546, 2.795] from meta-analysis using the above three references. The asymmetric equivalence margin for the ratio of bpCR rates was calculated as [0.785, 1.546] where the lower limit was preserved at least 50% of Herceptin treatment effect over the placebo, i.e., 0.785 = 1/(1+0.5×(1.546-1)). The upper equivalence limit of 1.546 was taken from the lower limit of 90% CI of the ratio between treatments.

With the expected bpCR rate of 37.5%, 358 subjects per arm should be evaluable in terms of bpCR to meet 80% power to detect the equivalence within the margin of [0.785, 1.546] under the assumption of no difference between two treatments in terms of bpCR rate.

The difference of bpCR rates between treatments was calculated as 23.3% with the 80% CI of [16.6%, 29.9%] from meta-analysis using the three reference studies. The equivalence margin for the difference was derived as 13% (= 16.6%×0.8).

Given that 236 subjects were to be randomised in each group to achieve the 80% power with 13% margin and 37.5% expected bpCR rate for the difference-based approach, the sample size of 358 per group derived from the ratio-based approach would satisfy both primary analyses for the ratio and difference of bpCR rates.

Considering the non-evaluable cases for pCR (e.g., inoperable cases), 403 subjects per treatment group (overall 806 subjects) were to be randomised into the study and, incorporating an 11% drop-out rate, would mean 358 subjects per treatment group would have assessable tumour cells to meet the 80% power to detect the equivalence within the margin of [0.785, 1.546].

Randomisation

Randomisation to either Ontruzant or Herceptin in a 1:1 ratio. Randomisation was stratified by hormone receptor status and disease stage.

Blinding (masking)

This study was double- blinded. Ontruzant or Herceptin presented as a white to pale yellow lyophilised powder. Ontruzant or Herceptin was provided as a single vial of 150 mg. These were pre-packaged and labelled in a double-blinded form.

Statistical methods

Analysis sets

Enrolled Set (ENR)*:* The ENR consisted of all subjects who provided informed consent for this study.

Randomised Set (RAN): The RAN consisted of all subjects who received a randomisation number at the Randomisation Visit. For analyses and displays based on the RAN, subjects were classified according to the treatment they were assigned at randomisation.

Full Analysis Set (FAS)*:* The FAS consisted of all subjects who were randomised at the Randomisation Visit. Following the intent-to-treat principle, subjects were analysed according to the treatment they were assigned at randomisation. However, subjects who did not qualify for randomisation and were inadvertently randomised into the study were excluded from the FAS, provided these subjects did not receive IP during that study phase.

Per-protocol Set (PPS)*:* The PPS consisted of all FAS subjects who completed the 8 cycles of neoadjuvant therapy and surgery. The PPS was the primary analysis set. Major protocol deviations that led to exclusion from this set were pre-specified prior to unblinding the treatment codes for analyses. Subjects who did not have a pathological response assessment were excluded from the PPS.

Safety Set (SAF)*:* The SAF consisted of all subjects who received at least one dose of double-blind study drug during the study phase. Subjects were analysed according to the treatment received.

Primary variable analysis

The primary efficacy analysis aimed to demonstrate equivalence in the bpCR rate between Ontruzant and Herceptin treatment groups. The null hypothesis tested for the primary efficacy analysis was that either (1) Ontruzant is inferior to Herceptin or (2) Ontruzant is superior to Herceptin based on a pre-specified equivalence margin.

To demonstrate equivalence in the bpCR rate between the two treatment groups in accordance with both FDA and EMA recommendations, the ratio and the difference in bpCR rate were analysed for the primary analysis. Equivalence was declared if the 90% confidence interval (CI; instead of 95% CI as specified in the protocol) of the ratio in the bpCR rate between the two treatment groups was entirely contained within the pre-defined equivalence margin of [0.785, 1.546] or equivalence was declared if the 95% CI of the difference in the bpCR rate between treatments was entirely contained within the pre-defined equivalence margin of ± 13%.

The adjusted difference in bpCR rate (Ontruzant -Herceptin) between the two treatment groups was calculated using a stratified Cochran-Mantel-Haenszel (CMH) test and 95% Wald CIs were presented; the adjusted ratio in bpCR rate (Ontruzant /Herceptin) and its 90% CIs were also calculated using a stratified

CMH test. The stratification factors for CMH tests were hormone receptor status, breast cancer type and region.

Primary analyses were conducted using the PPS.

The following sensitivity analyses were performed to explore the robustness of the primary efficacy result:

1. Stratified CMH test used for the primary efficacy analysis was repeated for the FAS where subjects with missing bpCR assessment were regarded as non-responders.

2. The stratum-adjusted difference in bpCR rate between the two treatment groups and its 95% CIs was calculated using an identity-linked binomial model, and the stratum-adjusted ratio in bpCR rate between the two treatment groups and its 90% CIs was calculated using log-linked binomial model, including stratification factors of hormone receptor status, breast cancer type and region for the PPS.

3. The crude difference in bpCR rate between the two treatment groups and its 95% CIs, and crude ratio in bpCR rate between the two treatment groups and its 90% CIs were calculated using Chi-square test for the PPS.

In addition, the adjusted ratio in bpCR rate (Ontruzant /Herceptin) and its 95% CIs were calculated using a stratified CMH test as an additional analysis to support the primary efficacy result. The 95% CIs were compared to the pre-defined equivalence margin of [0.785, 1.546].

Secondary variable analysis

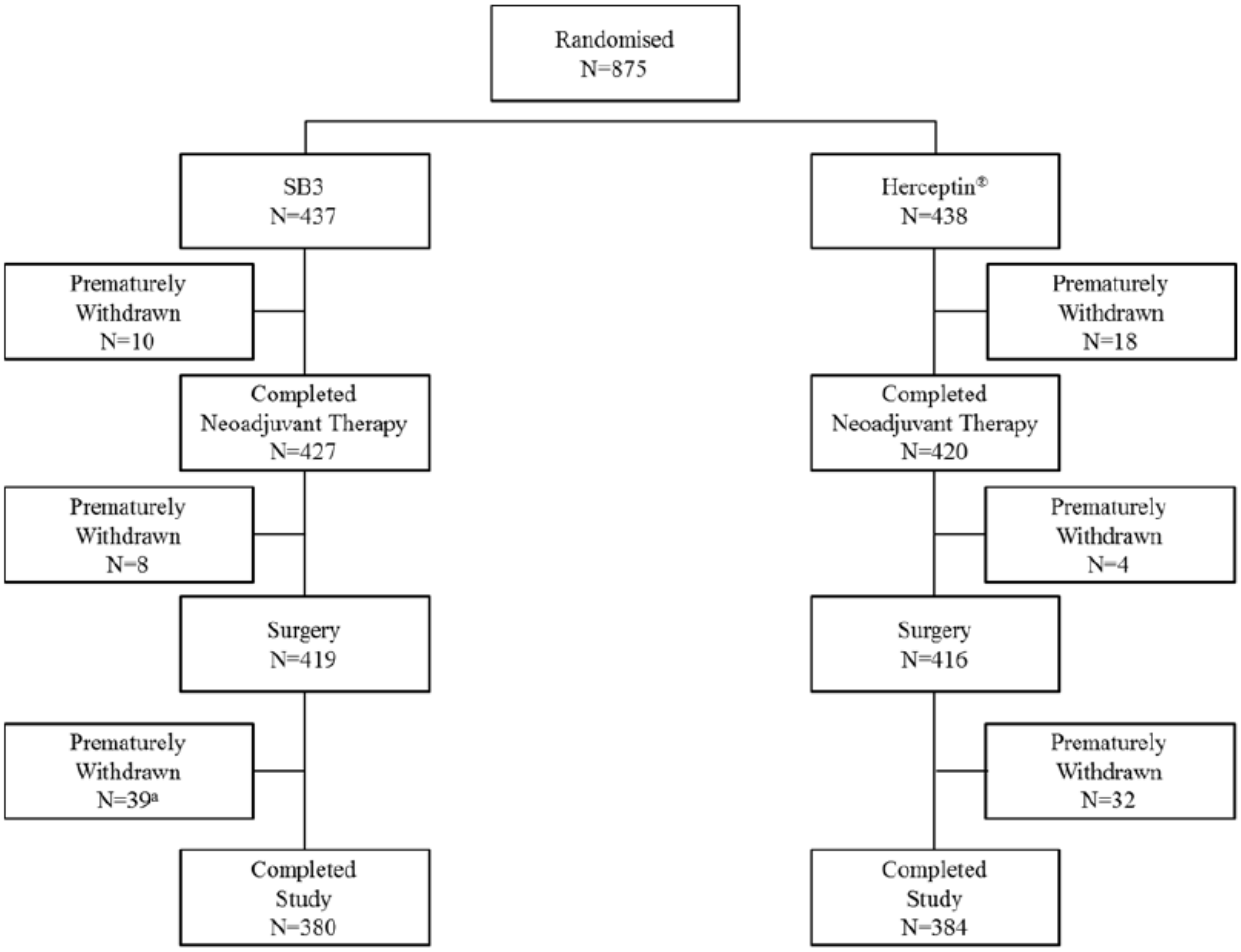
The secondary variables of tpCR and overall response rate were analysed similarly to the primary variable. For time to event variables, Kaplan-Meier curves were calculated and displayed. Median survival times and the corresponding 95% CI and p-value were provided. The estimated hazard ratio with 95% CI and p-value was obtained from a Cox regression model.

All efficacy variables were summarised descriptively by treatment group for PPS and FAS. Efficacy data were also listed by subject.

Results

Participant flow

Table 15*: Disposition of subjects (enrolled set)*, SB3-G31-BC *(final CSR)*



N = number of subjects
[a] One subject in the SB3 treatment group was lost to follow-up after completion of adjuvant therapy.
Source: Table 14.1-1.1

Table 16*: Summary of subjects withdrawn by treatment group (randomised set),* **SB3-G31-BC** *(final CSR)*

	SB3		Herceptin®		Total	
	N=437		N=438		N=875	
	n (%)		n (%)		n (%)	
Withdrew before surgery	18	(4.1)	22	(5.0)	40	(4.6)
Reason for withdrawal						
Progressive disease/disease recurrence	6	(1.4)	4	(0.9)	10	(1.1)
Adverse events	2	(0.5)	7	(1.6)	9	(1.0)
Withdrawal of consent	5	(1.1)	6	(1.4)	11	(1.3)
Lost to follow-up	1	(0.2)	1	(0.2)	2	(0.2)
Death	1	(0.2)	3	(0.7)	4	(0.5)
Administrative or other reasons	3	(0.7)	1	(0.2)	4	(0.5)
Withdrew during adjuvant therapy	38	(8.7)	32	(7.3)	70	(8.0)
Reason for withdrawal						
Progressive disease/disease recurrence	17	(3.9)	18	(4.1)	35	(4.0)
Adverse events	11	(2.5)	5	(1.1)	16	(1.8)
Protocol violation	1	(0.2)	0	(0.0)	1	(0.1)
Withdrawal of consent	5	(1.1)	3	(0.7)	8	(0.9)
Lost to follow-up	3	(0.7)	3	(0.7)	6	(0.7)
Death	0	(0.0)	2	(0.5)	2	(0.2)
Administrative or other reasons	1	(0.2)	1	(0.2)	2	(0.2)
Withdrew after adjuvant therapy	1	(0.2)	0	(0.0)	1	(0.1)
Reason for withdrawal						
Lost to follow-up	1	(0.2)	0	(0.0)	1	(0.1)

N = number of subjects in the Randomised Set; n = number of subjects
Percentages were based on the number of subjects in the Randomised Set.
Source: Table 14.1-1.1

Recruitment

Study initiation date: Apr 14, 2014 (first subject signed informed consent)

Study completion date: Feb 14, 2017 (last subject/last visit)

Data cut-off dates: 08 March 2016; 15 November 2016; 14 February 2017

Final date of study report: 09 June 2017 (version 1.0)

Conduct of the study

Protocol amendments

Five global amendments and 4 country-specific amendments were made to the original protocol (dated Nov 08, 2013). The Amendment 5 is dated Apr 23, 2015.

Under Amendment 4.1 (Dec 17, 2014), determination of sample size and its rationale was updated as a result of newly found literature and references added to the bibliography. The expected bpCR rate was changed from 40% to 37.5%, the number of evaluable subjects to meet an 80% power changed from 220 to 358 subjects per arm and the equivalence margin changed from within 15% to 0.785 to 1.546. The number of subjects to be randomised was therefore changed from 249 to 403 per arm and the expected dropout rate changed from 12% to 11%.

The number of subjects to be randomised was increased from 498 to 806 and the expected recruitment period increased from 12 to 15 months.

The criteria for declaring equivalence between the two treatments (primary efficacy endpoint) was modified from "Equivalence between the two treatment groups will be declared if the two-sided 95% (CI) of the difference in the pCR rate between treatments is entirely contained within the equivalence margin of [-15%, 15%]. The two-sided 95% CI of the difference will be estimated for the PPS" to:

"To demonstrate equivalence in the pCR rate between the two treatment groups in accordance with both FDA and EMA recommendation, the ratio and the difference in pCR rate will be analysed for the primary analysis. Equivalence will be declared if the two-sided 95% (CI) of the ratio in the pCR rate between treatments is entirely contained within the equivalence margin of [0.785, 1.546] or, if the 95% CI of the difference in the pCR rate between treatments is entirely contained within the equivalence margin of [-13%, 13%]. The 95% CIs of the difference will be estimated for the PPS. The difference of pCR will be used for EMA submission and the relative ratio of pCR will be used for FDA submission".

The PK Population definition was revised from the one specified in the protocol to take into consideration any subjects whose samples were collected but not analysed for any reason (including regional issues in Eastern Ukraine), resulting in no serum trough concentration data. These subjects were not to be included in the PK Population.

Protocol deviations

Table 17*: Summary of Major Protocol Deviations by Treatment Group,* **SB3-G31-BC** *(Randomised Set)*

	SB3		Herceptin®		Total	
Subjects with protocol deviation	**N=437 n (%)**		**N=438 n (%)**		**N=875 n (%)**	
With at least one major protocol deviation	224	(51.3)	219	(50.0)	443	(50.6)
Subjects excluded from PPS as a result of major protocol deviation	17	(3.9)	20	(4.6)	37	(4.2)
Efficacy criteria	10	(2.3)	9	(2.1)	19	(2.2)
Study procedures criteria	6	(1.4)	5	(1.1)	11	(1.3)
Eligibility and entry criteria	1	(0.2)	4	(0.9)	5	(0.6)
IP and non-IP compliance	1	(0.2)	3	(0.7)	4	(0.5)
Withdrawal criteria	0	(0.0)	1	(0.2)	1	(0.1)
Subjects with other major protocol deviations	219	(50.1)	213	(48.6)	432	(49.4)
Study procedures criteria	154	(35.2)	143	(32.6)	297	(33.9)
Randomisation criteria	36	(8.2)	37	(8.4)	73	(8.3)
IP and non-IP compliance	31	(7.1)	36	(8.2)	67	(7.7)
Non-IP compliance	25	(5.7)	37	(8.4)	62	(7.1)
IP compliance	23	(5.3)	17	(3.9)	40	(4.6)
Eligibility and entry criteria	15	(3.4)	26	(5.9)	41	(4.7)
Withdrawal criteria	1	(0.2)	0	(0.0)	1	(0.1)

IP = investigational product; N = number of subjects in the Randomised Set; n = number of subjects with protocol deviations; PPS = Per-protocol Set.
Percentages were based on the number of subjects in the Randomised Set.
Source: Table 14.1-1.4

Table 18*: Number of major protocol deviations by region and treatment group,* **SB3-G31-BC** *(randomised set)*

	SB3	Herceptin	Total
Region 1 – Korea			
Number of subjects	37	37	74
No. with at least one major protocol deviations	8 (21.6%)	4 (10.8%)	12 (16.2%)
Excluded from PPS	0 (0.0%)	1 (2.7%)	1 (1.4%)
Region 2 – Malaysia, Mexico, Philippines, Vietnam			
Number of subjects	42	48	90
No. with at least one major protocol deviations	24 (57.1%)	32 (66.7%)	56 (62.2%)
Excluded from PPS	2 (4.8%)	2 (4.2%)	4 (4.4%)
Region 3 – Bosnia and Herzegovina, Ukraine			
Number of subjects	87	86	173
No. with at least one major protocol deviations	43 (49.4%)	44 (51.2%)	87 (50.3%)
Excluded from PPS	9 (10.3%)	5 (5.8%)	14 (8.1%)
Region 4 – Bulgaria, Czech Republic, France, Romania			
Number of subjects	41	39	80
No. with at least one major protocol deviations	31 (75.6%)	24 (61.5%)	55 (68.8%)
Excluded from the PPS	0 (0.0%)	2 (5.1%)	2 (2.5%)
Region 5 - Poland			
Number of subjects	72	71	143
No. with at least one major protocol deviations	45 (62.5%)	56 (78.9%)	101 (70.6%)
Excluded from the PPS	1 (1.4%)	3 (4.2%)	4 (2.8%)
Region 6 – India			
Number of subjects	52	52	104
No. with at least one major protocol deviations	30 (57.7%)	25 (48.1%)	55 (52.9%)
Excluded from the PPS	2 (3.8%)	2 (3.8%)	4 (3.8%)
Region 7 – Russian Federation			
Number of subjects	106	105	211

No. with at least one major protocol deviations	43 (40.6%)	34 (32.4%)	77 (36.5%)
Excluded from the PPS	3 (2.8%)	5 (4.8%)	8 (3.8%)

Due to regional issues in the Eastern Ukraine, it was decided before database lock to exclude 11 randomised subjects (6 received Ontruzant and 5 received Herceptin) from two sites from the PPS since it was impossible to conduct any source data verification activities for these subjects. No subjects from any other centres were excluded from the PPS due to issues with verifying the integrity of the data.

Baseline data

Demographic characteristics

Table 19*: Demographic characteristics (randomised set),* SB3-G31-BC

	SB3		Herceptin®		Total	
	N=437		N=438		N=875	
Age (years)						
n	437		437		874	
Mean (SD)	49.5	(9.51)	49.6	(9.38)	49.6	(9.44)
Median	51.0		50.0		51.0	
Min, Max	24	65	22	65	22	65
Age group n (%)						
< 30 years	9	(2.1)	12	(2.7)	21	(2.4)
30 ≤ and < 40 years	69	(15.8)	53	(12.1)	122	(13.9)
40 ≤ and < 50 years	123	(28.1)	144	(32.9)	267	(30.5)
50 ≤ and < 60 years	166	(38.0)	155	(35.4)	321	(36.7)
≥ 60 years	70	(16.0)	73	(16.7)	143	(16.3)
Missing	0	(0.0)	1	(0.2)	1	(0.1)
Gender n (%)						
Female	437	(100.0)	438	(100.0)	875	(100.0)
Male	0	(0.0)	0	(0.0)	0	(0.0)
Race, n (%)						
White	294	(67.3)	289	(66.0)	583	(66.6)
American Indian or Alaskan Native	0	(0.0)	0	(0.0)	0	(0.0)
Asian	134	(30.7)	138	(31.5)	272	(31.1)
Black or African American	0	(0.0)	0	(0.0)	0	(0.0)
Native Hawaiian or other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)
Other	9	(2.1)	11	(2.5)	20	(2.3)
Ethnicity n (%)						
Hispanic or Latino	1	(0.2)	2	(0.5)	3	(0.3)
Chinese	3	(0.7)	4	(0.9)	7	(0.8)
Indian (Indian subcontinent)	54	(12.4)	55	(12.6)	109	(12.5)
Japanese	0	(0.0)	0	(0.0)	0	(0.0)
Mixed ethnicity	2	(0.5)	0	(0.0)	2	(0.2)
Other	377	(86.3)	377	(86.1)	754	(86.2)
Height (cm)						
Mean (SD)	160.80	(7.207)	160.65	(7.286)	160.72	(7.243)
Median	162.00		161.00		162.00	
Min, Max	144.0	179.0	141.0	182.0	141.0	182.0

	SB3		Herceptin®		Total	
	N=437		N=438		N=875	
Weight (kg)						
Mean (SD)	68.71	(15.878)	69.64	(16.811)	69.18	(16.349)
Median	66.00		67.65		66.40	
Min, Max	35.1	128.0	35.0	150.0	35.0	150.0
BSA (m^2)						
Mean (SD)	1.742	(0.2145)	1.752	(0.2234)	1.747	(0.2189)
Median	1.720		1.740		1.730	
Min, Max	1.23	2.45	1.20	2.69	1.20	2.69
Childbearing potential n (%)						
Yes	198	(45.3)	193	(44.1)	391	(44.7)
No	239	(54.7)	245	(55.9)	484	(55.3)
Menopausal status n (%)						
Yes	220	(50.3)	216	(49.3)	436	(49.8)
No	217	(49.7)	222	(50.7)	439	(50.2)
ECOG performance status n (%)						
0	366	(83.8)	365	(83.3)	731	(83.5)
1	71	(16.2)	73	(16.7)	144	(16.5)
> 1	0	(0.0)	0	(0.0)	0	(0.0)
Left ventricular ejection fraction (%)						
Mean (SD)	65.29	(5.117)	65.18	(5.490)	65.24	(5.304)
Median	65.00		65.00		65.00	
Min, Max	55.0	80.0	55.0	85.0	55.0	85.0
ECG result n (%)						
Normal	287	(65.7)	288	(65.8)	575	(65.7)
Abnormal, NCS	144	(33.0)	140	(32.0)	284	(32.5)
Abnormal, CS	2	(0.5)	4	(0.9)	6	(0.7)
Missing	4	(0.9)	6	(1.4)	10	(1.1)

BSA = body surface area; CS = clinically significant; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; N = number of subjects in the Randomised Set; n = number of subjects; NCS = not clinically significant; SD = standard deviation.
Age was derived as the difference in years between the date of birth and the date of informed consent.
Body Surface Area (m^2) = (height (cm)*weight (kg)/3600)^(1/2)
Percentages were based on the number of subjects in the Randomised Set.
Source: Table 14.1-3.1

Baseline disease characteristics

Table 20*: Baseline disease characteristics (randomised set),* **SB3-G31-BC** *(DCO 8 March 2016)*

	SB3		Herceptin®		Total	
	N=437		N=438		N=875	
Number of breast tumour lesions, n (%)						
One	437	(100.0)	435	(99.3)	872	(99.7)
More than one	0	(0.0)	3	(0.7)	3	(0.3)
Histopathological tumour classification, n (%)						
Invasive ductal carcinoma NOS	417	(95.4)	421	(96.1)	838	(95.8)
Invasive lobular carcinoma	11	(2.5)	6	(1.4)	17	(1.9)
Other	9	(2.1)	11	(2.5)	20	(2.3)
Breast tumour size[a] (mm)						
n	421		422		843	
Median	37.00		38.20		38.00	
Min, Max	20.0	144.0	17.0	200.0	17.0	200.0
Clinical T stage, n (%)						
cT1	2	(0.5)	4	(0.9)	6	(0.7)
cT2	234	(53.5)	228	(52.1)	462	(52.8)
cT3	84	(19.2)	99	(22.6)	183	(20.9)
cT4	117	(26.8)	107	(24.4)	224	(25.6)
Clinical N stage, n (%)						
cN0	91	(20.8)	88	(20.1)	179	(20.5)
cN1	243	(55.6)	232	(53.0)	475	(54.3)
cN2	69	(15.8)	73	(16.7)	142	(16.2)
cN3	34	(7.8)	45	(10.3)	79	(9.0)
Clinical TNM staging[b], n (%)						
Stage IIA	65	(14.9)	62	(14.2)	127	(14.5)
Stage IIB	150	(34.3)	146	(33.3)	296	(33.8)
Stage IIIA	85	(19.5)	99	(22.6)	184	(21.0)
Stage IIIB	103	(23.6)	86	(19.6)	189	(21.6)
Stage IIIC	33	(7.6)	45	(10.3)	78	(8.9)
Stage IV	1	(0.2)	0	(0.0)	1	(0.1)

	SB3		Herceptin®		Total	
	N=437		N=438		N=875	
Breast cancer type[b], n (%)						
Operable	261	(59.7)	259	(59.1)	520	(59.4)
Locally advanced	160	(36.6)	164	(37.4)	324	(37.0)
Inflammatory	16	(3.7)	15	(3.4)	31	(3.5)
Hormone receptor status, n (%)						
ER+/PR+	179	(41.0)	170	(38.8)	349	(39.9)
ER+/PR-	78	(17.8)	73	(16.7)	151	(17.3)
ER-/PR+	9	(2.1)	8	(1.8)	17	(1.9)
ER-/PR-	171	(39.1)	187	(42.7)	358	(40.9)
Sentinel lymph node biopsy performed prior to treatment, n (%)	10	(2.3)	10	(2.3)	20	(2.3)
Result: Positive	3	(0.7)	5	(1.1)	8	(0.9)
Negative	7	(1.6)	5	(1.1)	12	(1.4)

ER: Oestrogen receptor; N = number of subjects in the Randomised Set; n = number of subjects
NOS: not otherwise specified; PR: Progesterone receptor; TNM = tumour, nodes, metastasis.
[a] Subjects with inflammatory breast carcinoma were not included in the analysis.
[b] Clinical TNM staging and breast cancer type were derived based on results of clinical T, N and M stage.
Source: Table 14.1-4.1 and Table 14.1-4.6

Medical/surgical history

A similar number of subjects in the Ontruzant and Herceptin groups (384 [87.9%] vs. 384 [87.7%], respectively) had medical and surgical histories and continuing medical conditions in any primary SOC. In general, the distribution of medical and surgical history and continuing medical conditions was comparable on the SOC level between the two treatment groups.

Prior and concomitant medication

A similar proportion of patients in the Ontruzant and EU Herceptin treatment groups (25.2% vs. 24.2% of patients, respectively) had taken medications which started and stopped prior to the study.

The use of concomitant medications by ATC drug class was comparable between the two treatment groups. All patients received at least one concomitant medication during the overall study period and during the neoadjuvant therapy period; during the adjuvant therapy period 88.8% in both treatment groups received concomitant medications.

Concomitant treatment for breast cancer

Surgery

Table 21*: Summary of primary surgery (randomised set),* SB3-G31-BC

Surgery Type Surgery Subtype	SB3 N=437 n (%)		Herceptin® N=438 n (%)		Total N=875 n (%)	
Primary surgery received	419	(95.9)	416	(95.0)	835	(95.4)
Breast surgery	419	(95.9)	416	(95.0)	835	(95.4)
Breast-conserving surgery	85	(19.5)	94	(21.5)	179	(20.5)
Mastectomy	331	(75.7)	321	(73.3)	652	(74.5)
Others[a]	3	(0.7)	1	(0.2)	4	(0.5)
Lymph node surgery	419	(95.9)	416	(95.0)	835	(95.4)
Axillary lymph node dissection (ALND)	342	(78.3)	344	(78.5)	686	(78.4)
Sentinel lymph node dissection with ALND	51	(11.7)	50	(11.4)	101	(11.5)
Sentinel lymph node dissection without ALND	17	(3.9)	14	(3.2)	31	(3.5)
No lymph node dissection	9	(2.1)	8	(1.8)	17	(1.9)

N = number of subjects in the Randomised Set; n = number of subjects
[a] Other breast surgery included quadrectomy, removal of part of breast tumour and mastectomy with breast reconstruction (2 subjects). Source: electronic case report form.
Source: Table 14.3-1.4

Radiation therapy

During the adjuvant therapy period, 227 (51.9%) patients in the Ontruzant treatment group and 219 (50.0%) patients in the EU Herceptin treatment group received at least one radiation therapy. The proportion of patients receiving whole breast radiation, whole chest wall radiation, and regional node radiation was comparable between the Ontruzant and EU Herceptin treatment groups.

Hormone therapy

Patients who were hormone-receptor positive received hormonal therapy after primary surgery. During the adjuvant therapy period, 185 (42.3%) patients in the Ontruzant treatment group and 169 (38.6%) patients in the EU Herceptin treatment group received hormone therapy. The various hormonal treatment options were well balanced between the two treatment groups. The most frequently received hormonal treatment was tamoxifen/tamoxifen citrate (130 [29.7%] subjects in the Ontruzant treatment group and 126 [28.8%] subjects in the Herceptin treatment group). Other frequently received hormonal treatments were letrozole (35 [8.0%] and 26 [5.9%], respectively) and anastrozole (20 [4.6%] and 17 [3.9%], respectively). Among the gonadotropin and analogues class, goserelin/goserelin acetate was the most frequently reported drug (20 [4.6%] subjects in the Ontruzant treatment group and 17 [3.9%] subjects in the Herceptin treatment group).

Numbers analysed

Table 22*: Data sets analysed (randomised set),* **SB3-G31-BC** *(DCO 8 March 2016)*

	SB3	Herceptin®	Total
	n (%)	n (%)	n (%)
Randomised	437 (100.0)	438 (100.0)	875 (100.0)
Full analysis set	437 (100.0)	438 (100.0)	875 (100.0)
Per-protocol set	402 (92.0)	398 (90.9)	800 (91.4)
Safety analysis set	437 (100.0)	438 (100.0)	875 (100.0)
Pharmacokinetic population	161 (36.8)	152 (34.7)	313 (35.8)

Outcomes and estimation

Primary efficacy results

The proportion of subjects achieving bpCR was 51.7% and 42.0% in the Ontruzant and Herceptin treatment groups, respectively, for the PPS.

For the FAS analysis set, 51.1% and 41.9% reached bpCR respectively.

The adjusted difference in bpCR rate for the PPS was 10.70% and the 95% CI of the difference was [4.13%, 17.26%], which was not contained within the pre-defined equivalence margin of [–13%, 13%].

The adjusted difference in bpCR rate for the FAS was 9.86% and the 95% CI of the difference was [3.41%, 16.31%], which was not contained within the pre-defined equivalence margin of [–13%, 13%].

***Table 23: Primary analysis of difference in bpCR Rate,* SB3-G31-BC**

Analysis Set	Treatment	n/n'	(%)	Adjusted Difference	95% CI
PPS	SB3 (N=402)	208/402	(51.7)	10.70%	[4.13%, 17.26%]
	Herceptin® (N=398)	167/398	(42.0)		
FAS	SB3 (N=437)	214/419	(51.1)	9.86%	[3.41%, 16.31%]
	Herceptin® (N=438)	174/415	(41.9)		

bpCR = breast pathological complete response; CI = confidence interval; FAS = Full Analysis Set; N = number of subjects in Analysis Set; n = number of responders; n' = number of subjects with available assessment results of pathological T category staging; PPS = Per-protocol Set.
Percentages were based on n'.
The adjusted difference and its 95% CI were analysed by a stratified Cochran-Mantel-Haenszel test with hormone receptor status, breast cancer type, and region as factors.
For the FAS, only available data were included in the analysis.

Sensitivity analysis of the primary efficacy endpoint

Table 24*: Primary Analysis of difference in bpCR Rate; Non-responder Analysis (FAS),* **SB3-G31-BC**

Treatment	n/n'	(%)	Adjusted difference	95% CI
SB3 (n=437)	214/437	(49.0)	9.59%	(3.26%, 15.91%)
Herceptin (n=438)	174/438	(39.7)		

Table 25*: Sensitivity Analysis of difference in bpCR Rate (PPS),* SB3-G31-BC

Treatment	n/n'	(%)	Log-linked binomial test	Chi-square test
			Adjusted difference (95% CI)	Crude difference (95% CI)
SB3 (n=402)	208/402	(51.7)	9.78% (2.90%, 16.66%)	9.78% (2.90%, 16.66%)
Herceptin (n=398)	167/398	(42.0)		

In order to establish the sensitivity of the primary efficacy outcomes, the same analyses for ratio and difference in imputed bpCR were performed for the FAS. In these analyses, subjects with a missing bpCR assessment were considered to be non-responders.

Using the non-responder analysis the proportion of subjects achieving bpCR was 49.0% for the Ontruzant and 39.7% for the Herceptin treatment groups.

Using the non-responder analysis the adjusted difference and its 95% CI in bpCR rate was 9.59% [3.26%, 15.91%], which was not contained within the pre-defined equivalence margin of [–13%, 13%].

Additionally the stratum-adjusted difference in bpCR rate between the two treatment groups and corresponding 95% CIs were calculated using a log-linked binomial model, including stratification factors of hormones receptor status, breast cancer type and region for the PPS.

The adjusted difference and its 95% CI in bpCR rate was 9.78% [2.90%, 16.66%] which fell outside the pre-defined equivalence margin for the difference in bpCR rates.

Finally crude differences and 95% CIs were calculated using Chi-square tests for the PPS. The crude difference and its 95% CI was 9.78% and [2.90%, 16.66%], which fell outside the predefined equivalence margin for the difference.

Given that all sensitivity analyses confirmed the primary analyses outcomes, the robustness in veracity of the latter is confirmed.

Total pathological clinical response

Analysis of difference in tpCR rate

The proportion of subjects achieving tpCR was 45.8% (175/382) and 35.8% (136/380) in the Ontruzant and Herceptin treatment groups, respectively, for the PPS.

For the FAS, the proportion of subjects achieving tpCR was 45.2% and 35.8% respectively.

Analysis of the FAS using the non-responder analysis saw the proportion of subjects achieving tpCR to be 41.2% and 32.4% respectively.

Thus the tpCR results confirmed the effects seen in the primary bpCR analyses.

Table 26*: Analysis of difference in tpCR rate,* SB3-G31-BC

Analysis Set	Treatment	n/n'	(%)	Adjusted Difference	95% CI
PPS	SB3 (N=402)	175/382	(45.8)	11.05%	[4.44%, 17.66%]
	EU Herceptin® (N=398)	136/380	(35.8)		
FAS	SB3 (N=437)	180/398	(45.2)	10.23%	[3.73%, 16.73%]
	EU Herceptin® (N=438)	142/397	(35.8)		

CI = confidence interval; FAS = Full Analysis Set; N = number of patients in Analysis Set; n = number of responders; n' = number of patients with available assessment results of pathological T category and N category in pN0 and pN+; PPS = Per-protocol Set; tpCR = total pathological complete response.
Percentages were based on n'.
The adjusted difference and its 95% CI were analysed by a stratified Cochran-Mantel-Haenszel test with hormone receptor status, breast cancer type, and region as factors.
For the FAS, only available data were included in the analysis.

Table 27*: Analysis of difference in tpCR rate; Non-responder analysis (FAS),* SB3-G31-BC

Treatment	n/n'	(%)	Adjusted Difference	95% CI
SB3 (N=437)	180/437	(41.2)	9.32%	[3.19%, 15.46%]
EU Herceptin® (N=438)	142/438	(32.4)		

CI = confidence interval; N = number of patients in the Full Analysis Set; n = number of responders;
n' = number of patients with available assessment results of pathological T category and N category in pN0 and pN+; tpCR = total pathological complete response.
Percentages were based on n'.

The adjusted difference and its 95% CI were analysed by a stratified Cochran-Mantel-Haenszel test with hormone receptor status, breast cancer type, and region as factors.
Patients with a missing tpCR assessment were considered to be non-responders.

Best overall response

The best overall response defined as the best response among cCR, cPR, cSD, and cPD assessed at the mapped visit (Cycle 5 and Pre-surgery).

Excluding subjects with inflammatory breast cancer or without a response assessment, a total of 757 subjects were eligible for BOR analysis in the PPS set.

Table 28*: Summary of best overall response (PPS),* SB3-G31-BC

	SB3 N=402		Herceptin® N=398		Total N=800	
	n/n'	(%)	n/n'	(%)	n/n'	(%)
Complete response	112/383	(29.2)	110/374	(29.4)	222/757	(29.3)
Partial response	257/383	(67.1)	231/374	(61.8)	488/757	(64.5)
Stable disease	14/383	(3.7)	32/374	(8.6)	46/757	(6.1)
Progression of disease	0/383	(0.0)	1/374	(0.3)	1/757	(0.1)

N = number of subjects in the Per-protocol Set; n = number of responders; n' = Number of subjects with best overall response during the neoadjuvant therapy period and without inflammatory breast carcinoma.
Percentages were based on n'.
Overall response was assessed and classified according to the modified Response Evaluation Criteria in Solid Tumours.

Overall response rate

In the FAS set 28.9% and 29.0% reached clinical complete response, respectively. The proportions of subjects with clinical partial response were 66.0% and 62.1% respectively.

Since measurement of breast tumour size was not available, subjects with inflammatory breast cancer were not included into the analysis population for clinical response evaluation. The proportion of these particular subjects with clinical disease progression was 6.7% in both treatment groups.

The results in the PPS set for the ratio and differences are provided in the table below.

Table 29*: Analysis of difference in overall response rate (PPS),* SB3-G31-BC

Treatment	Responder		Adjusted Difference	95% CI
	n/n'	(%)		
SB3 (N=402)	369/383	(96.3)	5.03%	[1.74%, 8.31%]
Herceptin® (N=398)	341/374	(91.2)		

CI = confidence interval; N = number of subjects in the Per-protocol Set; n = number of responders; n' = number of subjects with best overall response during the neoadjuvant therapy period and without inflammatory breast carcinoma.
Percentages were based on n'.
The adjusted difference and its 95% CI were analysed by a stratified Cochran-Mantel-Haenszel test with hormone receptor status, breast cancer type, and region as factors

In the FAS (available case analysis) the overall response rate was 94.9% (394/415) for the Ontruzant and 91.1% (368/404) for the Herceptin treatment groups, respectively. The adjusted difference in overall response rate was 3.68% and the 95% CI of the difference was [0.32%, 7.03%].

When the non-responder analysis was applied, the overall response rate was 93.6% (394/421) for the Ontruzant and 87.0% (368/423) for the Herceptin treatment groups, respectively. The adjusted difference in overall response rate was 5.94% and the 95% CI of the adjusted difference was [2.17%, 9.71%].

Event-free survival and Overall survival

The median follow-up duration was 437 days (range 94-593 days) in the Ontruzant treatment group and 438 days (range 24-651 days) in the Herceptin treatment group.

Table 30: ***Summary of Event-Free Survival and Overall Survival (Per-protocol Set),*** **SB3-G31-BC** ***(Final CSR)***

	SB3 N=402		Herceptin® N=398	
Event-Free Survival				
Number of subjects with event, n (%)	25	(6.2)	29	(7.3)
Number of subjects without event, n (%)	377	(93.8)	369	(92.7)
Event-free survival (months)				
Median [95% CI]	-	[-, -]	-	[-, -]
HR (SB3/Herceptin®) [95% CI]	0.86 [0.50, 1.49]			
p-value	0.5961			
Event-free survival rate at				
3 months	100.0%		99.7%	
6 months	98.8%		98.0%	
12 months	95.5%		94.9%	
Overall Survival				
Number of subjects died n (%)	0	(0.0)	2	(0.5)
Number of subjects alive n (%)	402	(100.0)	396	(99.5)
Overall survival (months)				
Median [95% CI]	-	[-, -]	-	[-, -]
HR (SB3/Herceptin®) [95% CI]	0.00 [0.00, -]			
p-value	0.9977			
Overall survival rate at				
3 months	100.0%		100.0%	
6 months	100.0%		100.0%	
12 months	100.0%		99.5%	

CI = confidence interval; HR = hazard ratio; N = number of subjects in the Per-protocol Set; n = number of responders.
Percentages were based on the number of subjects in the Per-protocol Set.
Median event-free survival and survival rate are Kaplan-Meier estimates.
HR, its 95% CI and p-value are calculated from a stratified cox proportional hazard model with hormone receptor status, disease stage and region as factors.
Source: Table 14.2-6.1 and Table 14.2-6.3

A total of 54 (6.8%) subjects experienced events (disease recurrence or progression [local, regional, distant or contralateral] or death); 25 (6.2%) subjects in the Ontruzant treatment group and 29 (7.3%) in the Herceptin treatment group. No subject in the Ontruzant treatment group and 2 subjects in the Herceptin treatment group died during the study. Twelve months after randomisation, 95.5% in the Ontruzant treatment group and 94.9% in the Herceptin treatment group were event-free.

Table 31: ***Summary of Event-Free Survival and Overall Survival,*** **SB3-G31-BC** ***(Full Analysis Set, from TLF of Final CSR)***

	SB3	EU Herceptin®
	N = 437	N = 438
Event-Free Survival		
Number of patients with event, n (%)	34 (7.8)	37 (8.4)
Number of patients without event, n (%)	403 (92.2)	401 (91.6)
HR (SB3/EU Herceptin®) [95% CI]	0.94 [0.59, 1.51]	
p-value	0.8065	
Event-free survival rate at		
3 months	99.3%	99.5%
6 months	97.0%	96.7%
12 months	93.7%	93.4%
Overall Survival		
Number of patients died, n (%)	1 (0.2)	5 (1.1)
Number of patients alive, n (%)	436 (99.8)	433 (98.9)
HR (SB3/EU Herceptin®) [95% CI]	0.23 [0.03, 1.97]	
p-value for overall survival (months)	0.1798	
Overall survival rate at		
3 months	99.8%	99.8%
6 months	99.8%	99.3%
12 months	99.8%	98.8%

CI = confidence interval; HR = hazard ratio; N = number of patients in the Full Analysis Set.
Percentages were based on the number of patients in the Full analysis set.
Event-free survival rate and overall survival rate are Kaplan-Meier estimates.

Ancillary analyses

Breast pathological complete response subgroup analyses

By ADA status

As the overall incidence of ADA was markedly low in both Ontruzant and Herceptin treatment groups (only 3 patients, all in the Ontruzant group, up to cycle 9 had an overall positive ADA result) the relationship between immunogenicity and treatment efficacy could not be statistically analysed.

By demographics (PPS)

Table 32*: Region (EU vs Non-EU),* **SB3-G31-BC**

			Responder	Adjusted difference (SB3 / Herceptin)	
Subgroup	Treatment	n'	n (%)	Difference (%)	95% CI
EU	SB3 (N=108)	108	53 (49.1)	3.44%	(-9.63%, 16.51%)
	Herceptin (N=98)	98	44 (44.9)		
Non-EU	SB3 (N=294)	294	155 (52.7)	13.18%	(5.59%, 20.77%)
	Herceptin (N=300)	300	123 (41.0)		

Table 33*: Age group (<45y and ≥45 y)*, SB3-G31-BC

			Responder		Adjusted difference (SB3 / Herceptin)	
Subgroup	Treatment	n'	n (%)		Difference (%)	95% CI
<45 years	SB3 (N=121)	121	59 (48.8)		9.20%	(-3.08%, 21.48%)
	Herceptin (N=119)	119	48 (40.3)			
>=45 years	SB3 (N=281)	281	149 (53.0)		11.51%	(3.76%, 19.26%)
	Herceptin (N=279)	279	119 (42.7)			

Table 34*: Race (Asian, white and other)*, SB3-G31-BC

			Responder		Adjusted difference (SB3 / Herceptin)	
Subgroup	Treatment	n'	n (%)		Difference (%)	95% CI
Asian	SB3 (N=124)	124	68 (54.8)		15.52%	(4.27%, 26.78%)
	Herceptin (N=124)	124	51 (41.1)			
White	SB3 (N=269)	269	135 (50.2)		8.45%	(0.28%, 16.62%)
	Herceptin (N=264)	264	112 (42.4)			
Other	SB3 (N=9)	9	5 (55.6)		16.13%	(-25.32%, 57.58%)
	Herceptin (N=10)	10	4 (40.0)			

Table 35*: Menopausal status*, SB3-G31-BC

			Responder		Adjusted difference (SB3 / Herceptin)	
Subgroup	Treatment	n'	n (%)		Difference (%)	95% CI
Yes	SB3 (N=198)	198	105 (53.0)		7.65%	(-1.33%, 16.64%)
	Herceptin (N=198)	198	92 (46.5)			
No	SB3 (N=204)	204	103 (50.5)		12.97%	(3.81%, 22.14%)
	Herceptin (N=200)	200	75 (37.5)			

By history of breast cancer

As expected, the bpCR rate in the Ontruzant and Herceptin treatment groups was higher in subjects who were ER and PR negative (60.1% and 53.0% in the Ontruzant and Herceptin treatment group, respectively) than subjects who were ER and/or PR positive (46.9% vs. 33.9% in the Ontruzant and Herceptin treatment group, respectively). The bpCR rate was slightly higher in subjects with locally advanced breast cancer (54.7% and 43.8% in the Ontruzant and Herceptin treatment group, respectively) than in subjects with operable breast cancer (49.8% and 40.8% in the Ontruzant and Herceptin treatment group, respectively).

Summary of main study

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

Table 36: Summary of efficacy for trial SB3-G31-BC

Title: A Phase III Randomised, Double-Blind, Parallel Group, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB3 and Herceptin in Women with Newly Diagnosed HER2 Positive Early or Locally Advanced Breast Cancer in Neoadjuvant Setting		
Study identifier	SB3-G31-BC	
Design	A 1:1 randomised phase III, double-blind, parallel group, multicentre biosimilarity study, with SB3 as the IP and Herceptin as the comparator.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	54 weeks not applicable 4 weeks (safety follow-up)
Hypothesis	Equivalence	
Treatments groups	SB3	8mg/kg loading followed by 6 mg/kg every 3 weeks for a total of 8 neoadjuvant and 10 adjuvant cycles, IV Concurrent neoadjuvant 75 mg/m^2 IV docetaxel every 3 weeks for 4 cycles, followed by 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2 given intravenously every 3 weeks for 4 cycles Adjuvant hormonal therapy possible according to local practice for HR+ BC patients
	Herceptin	8mg/kg loading followed by 6 mg/kg every 3 weeks for a total of 8 neoadjuvant and 10 adjuvant cycles, IV Concurrent neoadjuvant 75 mg/m^2 IV docetaxel every 3 weeks for 4 cycles, followed by 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m2 given intravenously every 3 weeks for 4 cycles Adjuvant hormonal therapy possible according to local practice for HR+ BC patients

Endpoints and definitions	Primary endpoint	bpCR	No histological evidence of residual invasive tumour cells in the breast specimen removed at surgery. Non-invasive breast residuals were allowed and the pathological examination of axillary lymph nodes was not to be considered. Similarity analysis: Difference of bpCR rate: similarity if 95% CI within [-13%, 13%] equivalence margin.
	Secondary endpoint	tpCR	Absence of invasive residual tumour cells in both breast and lymph nodes. Similar analysis as primary
	Secondary endpoint	Best ORR	Best response among cCR, cPR, cSD and cPD assessed at the mapped visit (Cycle 5 and Pre-surgery as defined in the Statistical Analysis Plan) during neoadjuvant therapy Subjects with inflammatory breast cancer were excluded from analysis
	Secondary endpoint	ORR	Percentage of subjects achieving cCR or cPR for the best overall response during the neoadjuvant therapy period Similar analysis as primary
	Secondary endpoint	Event-free survival	Time from the date of randomisation to the date where an event occurred.
	Secondary endpoint	OS	Time from the date of randomisation to the date of death, regardless of the cause of death. Subjects who were alive at the time of analysis were censored at the date of the last follow-up assessment.
Database lock	22 March 2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol and Full analysis set (non-responder analysis) After completion of 8 cycles of neoadjuvant therapy		
Descriptive statistics and estimate variability	Treatment group	SB3	Herceptin
	Number of subject	437	438
	bpCR (%) PPS	208/402 (51.7)	167/398 (42.0)

	FAS	214/437 (49.0)	174/438 (39.7)
	tpCR (%) PPS	175/382 (45.8)	136/380 (35.8)
	FAS	180/437 (41.2)	142/438 (32.4)
	ORR (%) PPS FAS	369/383 (96.3) 394/421 (93.6)	341/374 (91.2) 368/423 (87.0)
Effect estimate per comparison	Primary endpoint **bpCR (%)** PPS	Comparison groups	SB3 vs. Herceptin
		Adjusted difference	10.70%
		95% CI	4.13%, 17.26%
		Test	-13% < CI < +13%
	Primary endpoint **bpCR (%)** FAS	Comparison groups	SB3 vs. Herceptin
		Adjusted difference	9.59%
		95% CI	3.26%, 15.91%
		Test	-13% < CI < +13%
	Secondary endpoint **tpCR (%)** PPS	Comparison groups	SB3 vs. Herceptin
		Adjusted difference	11.05%
		95% CI	4.44%, 17.66%
	Secondary endpoint **tpCR (%)** FAS	Comparison groups	SB3 vs. Herceptin
		Adjusted difference	9.32%
		95% CI	3.19%, 15.46%
	Secondary endpoint **ORR (%)** PPS	Comparison groups	SB3 vs. Herceptin
		Adjusted difference	5.03%
		95% CI	1.74%, 8.31%
	Secondary endpoint **ORR (%)** FAS	Comparison groups	SB3 vs. Herceptin
		Adjusted difference	5.94%
		95% CI	2.17%, 9.71%
	Secondary endpoint **OS (%)** PPS	Comparison groups	SB3 vs. Herceptin
		Hazard Ratio (95% CI)	0.00 (0.00, -)
		p-value	0.9977
	Secondary endpoint **OS (%)** FAS	Comparison groups	SB3 vs. Herceptin
		Hazard Ratio (95% CI)	0.23 (0.03,1.97)
		p-value	0.1798
	Secondary endpoint **EFS (%)** PPS	Comparison groups	SB3 vs. Herceptin
		Hazard Ratio (95% CI)	0.86 (0.50, 1.49)
		p-value	0.5961
	Secondary endpoint **EFS (%)** FAS	Comparison groups	SB3 vs. Herceptin
		Hazard Ratio (95% CI)	0.94 (0.59, 1.51)
		p-value	0.8065

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

No cross-trial analysis was provided.

Clinical studies in special populations

No studies in special populations were provided.

Supportive information

Antibody-dependent cellular cytotoxicity (ADCC) is mediated by tumor cell surface binding of trastuzumab and its interaction with Fc-gamma (Fcγ) receptors on immune cells. As the binding of trastuzumab to FcγRIIIa is correlated to the degree of fucosylation in the antibody's Fc part, this effect can be controlled through the testing of afucosylated (aFuc) glycan content. A large body of non-clinical evidence has demonstrated the key role that the core fucose on glycans plays in *in vitro* ADCC activity. The absence of the core fucose imparts higher ADCC activity to the antibody (Shields et al. 2002, Shinkawa et al. 2003). Afucosylated trastuzumab (100%) had significantly enhanced ADCC, compared with the fucosylated antibody, when tested using peripheral blood mononucleated cells (PBMCs) from either normal donors or breast cancer patients (Suzuki et al. 2007). Recent studies have demonstrated, using mouse models of HER2 amplified breast cancer, that afucosylated trastuzumab has increased ADCC and more than doubled the median progression-free survival in mice, when compared with conventional trastuzumab (i.e., low in afucoslyated glycan forms) (Junttila et al. 2010).

After similarity assessment between Ontruzant and EU Herceptin was completed, additional Herceptin lots were analysed by the applicant for monitoring purposes. During this analysis, it was noted that for many of the more recent batches of EU Herceptin (starting from the lots with expiry dates of Oct 2018) and US Herceptin (lots with expiry dates from Aug 2018), apparent shifts were found in terms of ADCC activity.

The overall contribution of ADCC activity versus antiproliferative effects through inhibition of ligand-independent HER2 signalling on the therapeutic benefit of trastuzumab is not known. However, the apparent shift in ADCC activity might have contributed to the small observed differences in the efficacy of Ontruzant compared to EU Herceptin.

For a better understanding of these effects an analysis by ADCC status was conducted using bpCR results stratification approach, the results of which are shown in Table 39.

Table 39: bpCR Response Rate by ADCC Status (Per-Protocol Set), SB3-G31-BC

ADCC Status	Treatment	N'	N(%)
Not exposed to lot with shifted ADCC	SB3 (N=402)	402	208 (51.7%)
	EU Herceptin (N=186)	186	82 (44.1%)
Exposed to lot with shifted ADCC	EU Herceptin (N=212)	212	85 (40.1%)

Note: Patients exposed to at least one IP kit from shifted ADCC lot during neoadjuvant period (from Cycle 1 to Cycle 8) were considered as "Exposed to lot with shifted ADCC". N': Number of patients with available assessment with subgroup: percentage were based on N'. Exposed to lot with shifted ADCC was based on expiry date.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme to assess biosimilarity in terms of efficacy and safety between Ontruzant and Herceptin is based on a single Phase III study in women with newly diagnosed HER2 positive early or locally advanced breast cancer in the neoadjuvant setting.

The choice of EB/LABC in neo- and adjuvant setting for the comparability study is considered a sensitive population and sufficient homogeneity is expected in an early clinical setting. The choice of the indication, the clinical setting, the primary and secondary endpoints and the equivalence margin were endorsed in CHMP Scientific Advice. This clinical model was considered sufficiently sensitive to enable the detection of differences between the two products.

The protocol defined inclusion criteria prevented men from participating in the study. Breast cancer in males is very rare and there is evidence that this population has a different clinical profile versus female breast cancer. Therefore, including them in the trial would have impacted the homogeneity of the study.

The applicant selected the same sequential combination chemotherapy regimen as used in the HannaH study which investigated the comparability of SC trastuzumab and IV trastuzumab in neoadjuvant setting in patients with operable, locally advanced or inflammatory breast cancer (Ismael, 2012). The chemotherapy backbone was also identical to HannaH study and was chosen based on reported pCR rates. There were no universal consensus for chemotherapy regimen and several clinical studies have been conducted to investigate the role of trastuzumab in neoadjuvant setting. The choice of docetaxel instead of paclitaxel is viewed as acceptable alternative in Europe and its dose was reduced from the registered dose of 100 mg/m² to 75 mg/m² to improve tolerability. A potential impact on pCR due to lower dose used would occur to a similar extent in both treatment arms and is acceptable for comparability purposes. The co-administration of anthracyclines with trastuzumab was justified by the fact that in contrast to the early experiences in MBC, simultaneous neoadjuvant therapy with anthracyclines and Herceptin appears to have an acceptable cardiac toxicity profile

The pCR is generally regarded as a sensitive endpoint for similarity comparisons. The primary efficacy endpoint in the pivotal study was the proportion of patients achieving bpCR. The choice of bpCR was justified by a possible occurrence of more confounding factors in determining tpCR rate and such approach was considered acceptable given that tpCR was included as secondary endpoint in this study.

Five global amendments and 4 country-specific amendments were made to the original protocol (dated Nov 08, 2013). Under Amendment 4.1, determination of sample size and its rationale was updated as a result of newly found literature and references added to the bibliography and recommendations of regulatory authorities. The tightening of the equivalence margin from 95% CI within [-15%, 15%] to 95% CI within [-13%, 13%] resulted in more stringent criteria to claim similarity. The chosen equivalence margin (95% CI within [-13%, 13%]) was deemed acceptable following CHMP scientific advice if quality, non-clinical and PK data did not indicate any difference between Ontruzant and Herceptin.

The number of patients with major protocol deviation was relatively balanced across the treatment groups. A total of 37 (4.2%) subjects were excluded from the PPS due to major protocol deviations.

Six patients having received Ontruzant and five having received Herceptin, all enrolled and treated at 2 centres in the Ukraine, were excluded from the PPS as source data verification was impossible and thus data integrity could not be ensured. No other subjects from any other centre presented with similar data issues. The decision to exclude the patients from these 2 centres is endorsed as the number of patients

enrolled in these centres represent a very small portion of the total study population and is also balanced across the 2 treatment groups.

The routine GCP inspection that was conducted on this study concluded that the results of this trial can be used for evaluation and assessment of the MAA.

Efficacy data and additional analyses

Baseline patient demographics and disease characteristics were well balanced across treatment arms.

The proportion of patients achieving bpCR in the subset of EU Herceptin group never exposed to ADCC-shifted Herceptin was 44.1%, while that of the 212 excluded patients was 40.1%. This small difference possibly associated with shifts in ADCC activity is viewed as not being clinically significant given the small magnitude and the unlikely impact of small changes in bpCR on clinically relevant time-dependent clinical endpoints.

In the case of Ontruzant, it is likely that the apparent difference is confounded by the shift in ADCC activity. The shift may have added variability in the estimation of the treatment difference and is thought to have contributed to the apparent superiority of Ontruzant in terms of bpCR and the upper limit of the confidence interval slightly exceeding the pre-specified equivalence margins (95% CI: 4.13%, 17.26%; equivalence margins: -13%, 13%). Thus, the magnitude of the differences observed can be in part attributed to other factors and the true difference is considered likely to fall within the equivalence margins and of no clinical relevance. In conclusion, Ontruzant is not considered superior to Herceptin in terms of efficacy and equivalence in efficacy is considered sufficiently established.

The applicant provided OS and EFS data at 1 year of treatment. No statistical difference in these endpoints was observed between the Ontruzant and Herceptin groups. Furthermore, there were no clinically meaningful differences in safety profile identified in the safety population which and this provides further reassurance in regard to similarity between Ontruzant and EU Herceptin. The Applicant will follow up events (disease recurrence or death) over 5 years after end of study (EOS) as part of the extension study for cardiac safety (SB3-G31-BC-E) (see RMP).

2.5.4. Conclusions on the clinical efficacy

Given the data submitted and the consideration above, similarity between Ontruzant and Herceptin in terms of efficacy is considered sufficiently established.

Herceptin is authorised in the treatment of HER2-positive MBC, early breast cancer, and metastatic gastric cancer. The mechanism of action of trastuzumab is the same in all three indications and the target receptor involved is also the same in early breast cancer, metastatic gastric cancer and MBC (i.e., HER2). Results of the physico-chemical, structural, and biological characterisation studies together with the evidence from non-clinical studies and PK study SB3-G11-NHV support extrapolation to the other oncology indications.

2.6. Clinical safety

Key safety information is derived from the clinical Phase III study (SB3-G31-BC) in EBC or LABC patients, supported by the safety/tolerability profile from the clinical Phase I study (SB3-G11-NHV) in healthy male subjects. The main study was completed (1 year data).

Patient exposure

Study SB3-G31-BC

In this randomised phase III study, women with HER2-positive early breast cancer (EBC) or LABC were randomised in a 1:1 ratio to receive either Ontruzant or Herceptin in a neoadjuvant setting for 8 cycles concurrently with 8 cycles of chemotherapy (4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/cyclophosphamide - FEC). Subjects then underwent surgery. After surgery, subjects received a further 10 cycles of adjuvant Ontruzant or Herceptin as per randomisation to complete 1 year of therapy.

All randomised subjects who received at least one infusion of Ontruzant or Herceptin were included in the safety set: 437 in the Ontruzant arm and 438 in the Herceptin arm.

In Ontruzant and Herceptin arms, similar proportion of patients completed the 8 cycles of neoadjuvant therapy, surgery, the 10 cycles of adjuvant therapy and completed the study.

Table 37: Subject disposition by Treatment Group – Enrolled set (SB3-G31-BC - Final CSR)

Number of subjects	SB3 n (%)	Herceptin n (%)
Screened		
Screening failures		
Reasons for screening failure		
Does not meet inclusion criteria		
Does meet exclusion criteria		
Subject lost to follow up		
Withdraw consent		
Other		
Randomised	437	438
Completed 8 cycles of neoadjuvant therapy	427 (97.7)	420 (95.9)
Completed surgery	419 (95.9)	416 (95.0)
Completed 8 cycles of neoadjuvant therapy and surgery	419 (95.9)	416 (95.0)
Withdrew before surgery	18 (4.1)	22 (5.0)
Main reasons for withdrawal		
Progressive disease/disease recurrence	6 (1.4)	4 (0.9)
Adverse events	2 (0.5)	7 (1.6)
Withdrawal of consent (refusal for study participation)	5 (1.1)	6 (1.4)
Lost to follow-up (loss of contact with subject)	1 (0.2)	1 (0.2)
Death	1 (0.2)	3 (0.7)
Administrative or other reasons	3 (0.7)	1 (0.2)
Completed 10 cycles of adjuvant therapy	381 (87.2)	384 (87.7)
Withdrew during adjuvant therapy	38 (8.7)	32 (7.3)
Main reasons for withdrawal		
Progressive disease/disease recurrence	17 (3.9)	18 (4.1)
Adverse events	11 (2.5)	5 (1.1)
Protocol violation (eligibility criteria or study procedure)	1 (0.2)	0 (0.0)
Withdrawal of consent (refusal for study participation)	5 (1.1)	3 (0.7)
Lost to follow-up (loss of contact with subject)	3 (0.7)	3 (0.7)
Death	0 (0.0)	2 (0.5)
Administrative or other reasons	1 (0.2)	1 (0.2)
Completed study	380 (87.0)	384 (87.7)
Incomplete EOS visit after adjuvant therapy	1 (0.2)	0 (0.0)
Lost to follow-up (loss of contact with subject)	1 (0.2)	0 (0.0)

Table 38: Summary of administration of IP by treatment group – Safety set (SB3-G31-BC, Final CSR)

	SB3 N=437	Herceptin N=438
Dose intensity of neoadjuvant IP (mg/kg/day)		
n	437	438
Mean	0.292	0.292
SD	0.0096	0.0140
Median	0.294	0.294
Min, Max	0.25, 0.33	0.25, 0.38
Dose intensity of adjuvant IP (mg/kg/day)		
n	413	410
Mean	0.294	0.293
SD	0.0101	0.0098
Median	0.294	0.294
Min, Max	0.25, 0.38	0.25, 0.40
Dose intensity of overall IP (mg/kg/day)		
n	437	438
Mean	0.293	0.293
SD	0.0073	0.0119
Median	0.293	0.293
Min, Max	0.26, 0.33	0.25, 0.38
Cumulative dose of IP (mg)		
n	437	438
Mean	7339.51	7395.71
SD	2104.342	2292.194
Median	7266.00	7434.00
Min, Max	483.0, 14490.0	441.0, 16842.0
Cycle delay of IP	199 (45.5)	210 (47.9)
Adverse events	116 (26.5)	117 (26.7)
Other	133 (30.4)	131 (29.9)
Dose interruption of IP	9 (2.1)	12 (2.7)
RDI of neoadjuvant IP (%)		
n	437	438
Mean	98.08	97.76
SD	3.175	3.685
Median	98.69	98.54
Min, Max	84.2, 105.8	82.8, 108.2
RDI of adjuvant IP (%)		
n	413	410
Mean	99.33	99.12
SD	2.461	2.602
Median	99.49	99.36
Min, Max	84.6, 110.0	83.8, 104.3
RDI of overall IP (%)		
n	437	438
Mean	98.65	98.37
SD	2.426	2.824
Median	98.85	98.95
Min, Max	84.2, 107.5	84.2, 106.0

Table 39: Summary of exposure to study treatment – Safety set (SB3-G31-BC, Final CSR)

	SB3	EU Herceptin®
	N = 437	N = 438
Number of cycle completed		
n	437	438
Mean (SD)	17.0 (2.90)	17.0 (3.28)
Min, Max	2, 18	1, 18
Number of patients who completed cycle N infusion, n (%)		
Cycle 1	437 (100.0)	438 (100.0)
Cycle 2	437 (100.0)	434 (99.1)
Cycle 3	436 (99.8)	432 (98.6)
Cycle 4	436 (99.8)	432 (98.6)
Cycle 5	432 (98.9)	430 (98.2)
Cycle 6	430 (98.4)	425 (97.0)
Cycle 7	427 (97.7)	422 (96.3)
Cycle 8	427 (97.7)	420 (95.9)
Cycle 9	413 (94.5)	410 (93.6)
Cycle 10	411 (94.1)	409 (93.4)
Cycle 11	408 (93.4)	407 (92.9)
Cycle 12	405 (92.7)	406 (92.7)
Cycle 13	402 (92.0)	404 (92.2)
Cycle 14	396 (90.6)	397 (90.6)
Cycle 15	393 (89.9)	393 (89.7)
Cycle 16	389 (89.0)	392 (89.5)
Cycle 17	384 (87.9)	390 (89.0)
Cycle 18	381 (87.2)	384 (87.7)
Neoadjuvant IP exposure duration (days)		
n	437	438
Mean (SD)	170.5 (12.97)	168.8 (20.25)
Min, Max	42, 217	21, 211
Adjuvant IP exposure duration (days)		
n	413	410
Mean (SD)	204.4 (30.16)	206.8 (26.12)
Min, Max	21, 273	21, 273
Overall IP exposure duration (days)		
n	437	438
Mean (SD)	363.7 (61.56)	362.4 (70.35)
Min, Max	42, 443	21, 479

Source: Attachment 5

Table 40: Summary of administration of non-IP by treatment group – Safety set (SB3-G31-BC, Final CSR)

	SB3	Herceptin®
	N=437	N=438
Dose intensity of docetaxel (mg/m²/day)		
n	437	438
Mean (SD)	3.480 (0.1868)	3.481 (0.2056)
Min, Max	2.58, 3.71	1.86, 3.78
Dose intensity of 5-fluorouracil (mg/m²/day)		
n	432	430
Mean (SD)	22.967 (1.4369)	22.987 (1.3965)
Min, Max	14.14, 25.64	16.19, 25.97
Dose intensity of epirubicin (mg/m²/day)		
n	432	430
Mean (SD)	3.445 (0.2147)	3.446 (0.2110)
Min, Max	2.12, 3.85	2.43, 3.90
Dose intensity of cyclophosphamide (mg/m²/day)		
n	432	430
Mean (SD)	22.980 (1.4229)	22.980 (1.3993)
Min, Max	14.14, 25.64	16.19, 25.97
Cycle delay of non-IP n (%)	142 (32.5)	144 (32.9)
Adverse events	100 (22.9)	108 (24.7)
Other	61 (14.0)	52 (11.9)
Dose modification of non-IP n (%)	49 (11.2)	43 (9.8)
Adverse events	49 (11.2)	39 (8.9)
Other	1 (0.2)	5 (1.1)
RDI of non-IP (%)		
Docetaxel from cycle 1 to cycle 4		
n	437	438
Mean (SD)	97.43 (5.231)	97.48 (5.758)
Min, Max	72.4, 103.8	51.9, 105.8
FEC from cycle 5 to cycle 8		
n	432	430
Mean (SD)	96.48 (5.989)	96.51 (5.867)
Min, Max	59.4, 107.8	68.0, 109.1

FEC = 5-fluorouracil, epirubicin, cyclophosphamide; IP = Investigational Product; Max = maximum; Min = minimum; N = number of subjects in the Safety Set; n = number of subjects
RDI = Relative Dose Intensity; SD=standard deviation.
Dose intensity = cumulative actual dose level administered/duration of exposure; RDI= actual dose intensity/planned dose intensity*100%
More than one reason may be applied for cycle delay of non-IP.

Table 41: Summary of Cumulative Exposure to Non-IP (mg) – Safety set (SB3-G31-BC)

Non-IP	Statistics	SB3 N=437	EU Herceptin® N=438
Docetaxel	n	437	438
	Mean	514.70	513.59
	SD	67.126	81.269
	Median	512.20	516.00
	Min, Max	184.2, 732.0	110.0, 808.0
5-Fluorouracil	n	432	430
	Mean	3431.54	3434.40
	SD	500.825	543.902
	Median	3425.00	3460.00
	Min, Max	700.0, 4900.0	705.0, 5380.0
Epirubicin	n	432	430
	Mean	514.62	515.16
	SD	75.090	81.166
	Median	513.20	519.20
	Min, Max	110.0, 736.0	106.0, 808.0
Cyclophosphamide	n	432	430
	Mean	3434.10	3434.65
	SD	504.908	532.775
	Median	3430.00	3460.00
	Min, Max	700.0, 4800.0	705.0, 5100.0

n = number of subjects who contributed to analysis

Study SB3-G11-NHV (supportive study)

Double-blind, three-arm, parallel group, single-dose study that aimed to demonstrate similarity in PK, safety/tolerability and immunogenicity profiles between three presentations (Ontruzant, EU sourced Herceptin, and US sourced Herceptin) in healthy male subjects. In each arm, all subjects received a single dose (6 mg/kg) of either Ontruzant, EU sourced Herceptin, or US sourced Herceptin by intravenous (IV) infusion for 90 minutes (1 single cycle).

A total of 109 healthy subjects were randomised to receive a single trastuzumab infusion, with 36 subjects from Ontruzant and US Herceptin treatment groups and 37 subjects from EU Herceptin treatment group. However, a total of 108 subjects were exposed to IP with 36 subjects in each treatment group. One subject withdrew informed consent right before start of infusion after randomisation and was replaced by a new subject. This subject was excluded from the Safety set and from the PK population. A total of 108 subjects (36 subjects in each treatment) were included in the safety set and in the PK population. The safety set comprised all subjects who received at least one dose of the study drug. The data cut-off (end of study) was April 24, 2014.

Adverse events

Study SB3-G31-BC

Overall study

Table 42: Summary of All Treatment-emergent Adverse Events during the Overall Study Period – Safety set (SB3-G31-BC, Final CSR)

Treatment	SB3 N=437			Herceptin® N=438		
Number of subjects experiencing	**n**	**(%)**	**E**	**n**	**(%)**	**E**
TEAEs	426	(97.5)	5433	421	(96.1)	5245
TEAE severity						
Grade 1	19	(4.3)	2844	25	(5.7)	2805
Grade 2	82	(18.8)	1729	81	(18.5)	1598
Grade 3	119	(27.2)	533	129	(29.5)	527
Grade 4	205	(46.9)	326	181	(41.3)	310
Grade 5	1	(0.2)	1	5	(1.1)	5
TEAEs of special interest	76	(17.4)	113	70	(16.0)	98
Infusion-related reaction	37	(8.5)	53	44	(10.0)	64
Left ventricular systolic dysfunction (asymptomatic)	11	(2.5)	14	8	(1.8)	9
Congestive heart failure	3	(0.7)	3	1	(0.2)	1
Pulmonary events	35	(8.0)	43	23	(5.3)	24
TEAEs leading to IP discontinuation	15	(3.4)	19	14	(3.2)	14
TEAEs leading to non-IP discontinuation	6	(1.4)	9	8	(1.8)	8
Serious TEAEs	56	(12.8)	98	58	(13.2)	79
Deaths	1	(0.2)		5	(1.1)	

E = frequency of adverse events; IP = investigational product; N = number of subjects in the Safety Set; n = number of subjects with TEAEs; TEAE = treatment-emergent adverse event;
Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities Version 16.1.
Severity assessment was classified in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 with the exception of febrile neutropenia and left ventricular systolic dysfunction which were classified according to v4.03 and v3.0, respectively.

The most frequently affected SOCs for both arms in terms of TEAEs were blood and lymphatic system disorders (76% in the Ontruzant vs. 71.9% in the Herceptin treatment groups), skin and subcutaneous tissue disorders (73.9% vs. 70.8%, respectively) and gastrointestinal disorders (48.3% vs. 46.8%, respectively).

Table 43: TEAE with Incidence > 5% by Preferred Term during the Overall Study Period – Safety set (SB3-G31-BC)

	SB3			EU Herceptin®		
	N = 437			N = 438		
	n	(%)	E	n	(%)	E
Alopecia	299	(68.4)	349	283	(64.6)	324
Neutropenia	294	(67.3)	661	282	(64.4)	639
Nausea	144	(33.0)	363	135	(30.8)	388
Leukopenia	125	(28.6)	259	114	(26.0)	238
Anaemia	96	(22.0)	183	95	(21.7)	198
Diarrhoea	92	(21.1)	148	67	(15.3)	93
Fatigue	88	(20.1)	186	80	(18.3)	183
Alanine aminotransferase increased	84	(19.2)	150	83	(18.9)	150
Aspartate aminotransferase increased	68	(15.6)	102	63	(14.4)	110
Myalgia	63	(14.4)	150	66	(15.1)	138
Vomiting	62	(14.2)	111	52	(11.9)	89
Stomatitis	61	(14.0)	108	51	(11.6)	88
Asthenia	58	(13.3)	146	55	(12.6)	162
Neutrophil count decreased	56	(12.8)	144	57	(13.0)	169
Arthralgia	48	(11.0)	74	47	(10.7)	70
Radiation skin injury	48	(11.0)	48	38	(8.7)	47
Rash	47	(10.8)	61	45	(10.3)	62
Upper respiratory tract infection	44	(10.1)	67	40	(9.1)	64
Cough	41	(9.4)	46	27	(6.2)	34
Decreased appetite	40	(9.2)	78	41	(9.4)	103
Procedural pain	39	(8.9)	41	53	(12.1)	54
Pyrexia	39	(8.9)	51	39	(8.9)	50
Infusion related reaction	37	(8.5)	53	44	(10.0)	64
Lymphorrhoea	32	(7.3)	58	30	(6.8)	51
Headache	31	(7.1)	55	32	(7.3)	51
Peripheral sensory neuropathy	30	(6.9)	42	23	(5.3)	40
Febrile neutropenia	28	(6.4)	39	34	(7.8)	40
Joint range of motion decreased	27	(6.2)	33	20	(4.6)	21
Postoperative wound complication	27	(6.2)	27	21	(4.8)	21
Dyspepsia	26	(5.9)	39	22	(5.0)	27
Oropharyngeal pain	25	(5.7)	28	19	(4.3)	22
White blood cell count decreased	25	(5.7)	69	32	(7.3)	71
Bone pain	23	(5.3)	39	24	(5.5)	39
Blood alkaline phosphase increased	22	(5.0)	40	29	(6.6)	43
Nail disorder	22	(5.0)	23	23	(5.3)	23
Oedema peripheral	18	(4.1)	27	31	(7.1)	34

TEAE = treatment-emergent adverse event; E: Frequency of TEAEs.
Adverse events were coded to preferred term using the MedDRA Version 16.1 coding dictionary.
Percentages were based on the number of patients in the Safety set.
Preferred terms were sorted in descending order of patient frequency in SB3. If the frequency of the preferred term was tied, the preferred terms were sorted alphabetically.
Source: Attachment 4

Table 44: TEAE relationship to IP and non-IP, and TEAE outcome during Overall Study Period

Number of subjects experiencing	SB3 N=437 n	(%)	E	Herceptin N=438 n	(%)	E
TEAE Relationship with IP						
Related	146	(33.4)	620	145	(33.1)	601
Not related	280	(64.1)	4813	276	(63.0)	4644
TEAE Relationship with Non-IP						
Related	407	(93.1)	3592	402	(91.8)	3550
Not related	19	(4.3)	1841	19	(4.3)	1695
TEAE Outcome						
Recovered/Resolved			4898			4723
Recovered/Resolved with sequelae			134			93
Not recovered/Not resolved			378			402
Fatal			1			5
Unknown			22			22

Neoadjuvant therapy period

Table 45: Summary of All Treatment-emergent Adverse Events during the neoadjuvant therapy period – Safety set (SB3-G31-BC)

Treatment	SB3 N=437			Herceptin® N=438		
Number of subject experiencing	**n**	**(%)**	**E**	**n**	**(%)**	**E**
TEAEs	422	(96.6)	4336	417	(95.2)	4220
TEAE severity						
Grade 1	21	(4.8)	2143	27	(6.2)	2129
Grade 2	85	(19.5)	1367	83	(18.9)	1289
Grade 3	113	(25.9)	502	122	(27.9)	491
Grade 4	202	(46.2)	323	182	(41.6)	308
Grade 5	1	(0.2)	1	3	(0.7)	3
TEAEs of special interest	63	(14.4)	85	59	(13.5)	81
Infusion-related reaction	36	(8.2)	51	44	(10.0)	64
Left ventricular systolic dysfunction (asymptomatic)	4	(0.9)	5	3	(0.7)	3
Congestive heart failure	2	(0.5)	2	0	(0.0)	0
Pulmonary events	25	(5.7)	27	14	(3.2)	14
TEAEs leading to IP discontinuation	4	(0.9)	7	7	(1.6)	7
TEAEs leading to non-IP discontinuation	6	(1.4)	9	8	(1.8)	8
Serious TEAEs	46	(10.5)	81	47	(10.7)	64
Deaths	1	(0.2)		3	(0.7)	

E = frequency of adverse events; IP = investigational product; N = number of subjects in the Safety Set; n = number of subjects with TEAEs; TEAE = treatment-emergent adverse event;
Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities Version 16.1.

The most frequently affected SOCs were blood and lymphatic system disorders (73.9% in the Ontruzant treatment group vs. 71.5% in the Herceptin treatment group), skin and subcutaneous tissue disorders (71.9% vs. 67.8%, respectively) and gastrointestinal disorders (46.7% vs. 45.7%, respectively).

Table 46: Number (%) of Subjects with TEAEs and Number of Events by Preferred Term

Treatment	SB3 N=437			Herceptin® N=438		
Preferred term	n	(%)	E	n	(%)	E
Alopecia	299	(68.4)	349	283	(64.6)	324
Neutropenia	294	(67.3)	661	282	(64.4)	639
Nausea	144	(33.0)	363	135	(30.8)	388
Leukopenia	125	(28.6)	259	114	(26.0)	238
Anaemia	96	(22.0)	183	95	(21.7)	198
Diarrhoea	92	(21.1)	148	67	(15.3)	93
Fatigue	88	(20.1)	186	80	(18.3)	183
Alanine aminotransferase increased	84	(19.2)	150	83	(18.9)	150
Aspartate aminotransferase increased	68	(15.6)	102	63	(14.4)	110
Myalgia	63	(14.4)	150	66	(15.1)	138
Vomiting	62	(14.2)	111	52	(11.9)	89
Stomatitis	61	(14.0)	108	51	(11.6)	88
Asthenia	58	(13.3)	146	55	(12.6)	162
Neutrophil count decreased	56	(12.8)	144	57	(13.0)	169
Arthralgia	48	(11.0)	74	47	(10.7)	70
Radiation skin injury	48	(11.0)	48	38	(8.7)	47
Rash	47	(10.8)	61	45	(10.3)	62
Upper respiratory tract infection	44	(10.1)	67	40	(9.1)	64
Cough	41	(9.4)	46	27	(6.2)	34
Decreased appetite	40	(9.2)	78	41	(9.4)	103
Procedural pain	39	(8.9)	41	53	(12.1)	54
Pyrexia	39	(8.9)	51	39	(8.9)	50
Infusion related reaction	37	(8.5)	53	44	(10.0)	64
Lymphorrhoea	32	(7.3)	58	30	(6.8)	51
Headache	31	(7.1)	55	32	(7.3)	51
Peripheral sensory neuropathy	30	(6.9)	42	23	(5.3)	40
Febrile neutropenia	28	(6.4)	39	34	(7.8)	40
Joint range of motion decreased	27	(6.2)	33	20	(4.6)	21
Postoperative wound complication	27	(6.2)	27	21	(4.8)	21
Dyspepsia	26	(5.9)	39	22	(5.0)	27
Oropharyngeal pain	25	(5.7)	28	19	(4.3)	22
White blood cell count decreased	25	(5.7)	69	32	(7.3)	71
Bone pain	23	(5.3)	39	24	(5.5)	39
Blood alkaline phosphatase increased	22	(5.0)	40	29	(6.6)	43
Nail disorder	22	(5.0)	23	23	(5.3)	23
Oedema peripheral	18	(4.1)	27	31	(7.1)	34

E = frequency of the adverse events; N = number of subjects in the Safety Set; n = number of subjects with

In the Ontruzant treatment group during the neoadjuvant therapy period, 444 TEAEs were reported to be related to the IP in 118 (27.0%) subjects and in the Herceptin treatment group, 423 TEAEs were reported to be related to the IP in 117 (26.7%) subjects. In the Ontruzant treatment group, 3498 TEAEs were reported to be related to the non-IP in 407 (93.1%) subjects and in the Herceptin treatment group, 3473 TEAEs were reported to be related to the non-IP in 402 (91.8%) subjects. Most of the TEAE recovered/resolved without sequelae in both arms: 4078 events in Ontruzant and 3926 events in Herceptin.

Adjuvant therapy period

Table 47: Summary of All Treatment-emergent Adverse Events during the adjuvant therapy period – Safety set (SB3-G31-BC)

Treatment	SB3			Herceptin®		
	N=437			N=438		
Number of subjects experiencing	**n**	**(%)**	**E**	**n**	**(%)**	**E**
TEAEs	246	(56.3)	1043	241	(55.0)	977
TEAE severity						
Grade 1	93	(21.3)	664	80	(18.3)	644
Grade 2	126	(28.8)	345	125	(28.5)	293
Grade 3	24	(5.5)	31	32	(7.3)	36
Grade 4	3	(0.7)	3	2	(0.5)	2
Grade 5	0	(0.0)	0	2	(0.5)	2
TEAEs of special interest	20	(4.6)	24	15	(3.4)	17
Infusion-related reaction	2	(0.5)	2	0	(0.0)	0
Left ventricular systolic dysfunction (asymptomatic)	8	(1.8)	9	5	(1.1)	6
Congestive heart failure	1	(0.2)	1	1	(0.2)	1
Pulmonary events	10	(2.3)	12	9	(2.1)	10
TEAEs leading to IP discontinuation	11	(2.5)	12	7	(1.6)	7
Serious TEAEs	15	(3.4)	17	14	(3.2)	15
Deaths	0	(0.0)		2	(0.5)	

E = frequency of adverse events; IP = investigational product; N = number of subjects in the Safety Set; n = number of subjects with TEAEs; TEAE = treatment-emergent adverse event;
Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities Version 16.1.
Severity assessment was classified in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 with the exception of febrile neutropenia and left ventricular systolic dysfunction which were classified according to v4.03 and v3.0, respectively.
Percentages were based on the number of subjects in the Safety Set.
If a subject had multiple events of the same severity or relationship, then they were counted only once in that severity or relationship. If a subject had multiple events with different severity or relationship, then the subject was counted only once for more severe adverse events or related adverse events.
Source: Table 14.3.1-3.1a

The most frequently affected SOCs were injury, poisoning and procedural complications (30.9% in the Ontruzant vs. 30.6% in the EU Herceptin treatment groups), musculoskeletal and connective tissue disorders (18.1% vs. 14.6%), general disorders and administration site conditions (15.6% vs. 13.5%) and infections and infestations (14.4% vs. 14.8%).

Table 48: Number (%) of Subjects with TEAEs and Number of Events by Preferred Term that Occurred during the Adjuvant Period in > 5% of Subjects in Any Treatment Group (Safety Set)

Treatment	SB3 N=437			Herceptin® N=438		
Preferred term	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Radiation skin injury	48	(11.0)	48	36	(8.2)	45
Procedural pain	38	(8.7)	40	53	(12.1)	54
Fatigue	37	(8.5)	43	31	(7.1)	32
Lymphorrhoea	32	(7.3)	57	30	(6.8)	51
Anaemia	28	(6.4)	41	20	(4.6)	37
Joint range of motion decreased	26	(5.9)	32	20	(4.6)	21
Postoperative wound complication	26	(5.9)	26	21	(4.8)	21
Upper respiratory tract infection	25	(5.7)	33	21	(4.8)	28

E = frequency of the adverse events; N = number of subjects in the Safety Set; n = number of subjects with TEAEs; TEAE = treatment-emergent adverse event
Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities Version 16.1.
Percentages were based on the number of subjects in the Safety Set.
Preferred terms were sorted in descending order of subject frequency in the SB3 treatment group. If the frequencies of the PTs were the same, the PTs were sorted alphabetically.

TEAE relationship to IP and non-IP, and TEAE outcome are shown in Table 55.

Table 49: TEAE relationship to IP and non-IP, and TEAE outcome during the adjuvant Study Period (Safety Set - Final CSR: table 14.3.1-3.1)

Number of subjects experiencing	SB3 N=437 n	(%)	E	Herceptin N=438 n	(%)	E
TEAE Relationship with IP						
Related	58	(13.3)	173	67	(15.3)	168
Not related	188	(43.0)	870	174	(39.7)	809
TEAE Outcome						
Recovered/Resolved			785			757
Recovered/Resolved with sequelae			33			18
Not recovered/Not resolved			212			191
Fatal			0			2
Unknown			13			9

Around only 75% of the TEAE recovered/resolved without sequelae at the data cut-off in both arms, and 20% of the TEAE not recovered/resolved in both arms, and patients had TEAE mostly unrelated to IP (41% of the treated patients).

Study SB3-G11-NHV (supportive study)

Table 50: Summary of Frequency, Severity and Causality of all TEAEs and the Number of Events by PT that Occurred in ⩾ 5% of Subjects in Any Treatment Group (Safety Set, Study SB3-G11-NHV)

Treatment	SB3 N=36		EU Herceptin® N=36		US Herceptin® N=36	
Preferred Term	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**
Any TEAEs	25 (69.4)	69	23 (63.9)	42	25 (69.4)	64
Severity						
Grade 1 (Mild)	22 (61.1)	54	21 (58.3)	32	20 (55.6)	48
Grade 2 (Moderate)	10 (27.8)	13	8 (22.2)	10	12 (33.3)	16
Grade 3 (Severe)	2 (5.6)	2	0 (0.0)	0	0 (0.0)	0
Causality						
Not related	22 (61.1)	47	12 (33.3)	18	18 (50.0)	29
Related	13 (36.1)	22	16 (44.4)	24	22 (61.1)	35
Preferred Term (PT)						
Infusion related reaction	9 (25.0)	9	8 (22.2)	8	16 (44.4)	16
Headache	9 (25.0)	12	4 (11.1)	4	5 (13.9)	5
Nasopharyngitis	4 (11.1)	4	4 (11.1)	4	8 (22.2)	8
Fatigue	3 (8.3)	4	1 (2.8)	1	3 (8.3)	3
Oral herpes	1 (2.8)	2	3 (8.3)	3	2 (5.6)	2
Back pain	2 (5.6)	2	0 (0.0)	0	3 (8.3)	3
Epistaxis	4 (11.1)	6	0 (0.0)	0	0 (0.0)	0
Diarrhoea	2 (5.6)	3	1 (2.8)	1	1 (2.8)	1
Myalgia	3 (8.3)	3	0 (0.0)	0	1 (2.8)	1
Rash	0 (0.0)	0	1 (2.8)	1	3 (8.3)	3
Rhinitis	2 (5.6)	3	0 (0.0)	0	2 (5.6)	2
Acne	0 (0.0)	0	1 (2.8)	1	2 (5.6)	2
Toothache	1 (2.8)	1	2 (5.6)	2	0 (0.0)	0
Upper respiratory tract infection	2 (5.6)	2	1 (2.8)	1	0 (0.0)	0
Dizziness	2 (5.6)	2	0 (0.0)	0	0 (0.0)	0
Vision blurred	0 (0.0)	0	0 (0.0)	0	2 (5.6)	2

N = number of subjects in the Safety set; Subjects n = number of subjects who experienced each event; Events n = number of events experienced.
Percentages were Subjects n divided by N.

The majority of TEAEs were Grade 1 (mild) to Grade 2 (moderate) in severity, and transient. Two subjects (both receiving Ontruzant) experienced Grade 3 (severe) TEAEs; these were 1 event of IRR and 1 event of chondropathy reported from each subject.

The TEAEs seen in the study were as expected for this class of drug and recovered without any sequelae, except for 3 events following Ontruzant treatment (ankle fracture, myalgia, and the SAE of

chondropathy). All of these events were assessed by the Investigator not to be related to the IP. Moreover, after the data cut-off, follow-up information was obtained per phone call and an end-date (after the data cut-off) was confirmed for the 3 TEAEs. The SAE of chondropathy recovered with sequelae.

The proportion of subjects who experienced TEAEs considered to be related to the IPs were 36.1% of the subjects after Ontruzant administration, 44.4% of the subjects after EU sourced Herceptin administration and 61.1% of the subjects after US sourced Herceptin administration. The most frequently reported TEAE suspected to be IP related was IRR (9 in Ontruzant, 8 in EU sourced Herceptin, and 16 in US sourced Herceptin). All other TEAEs suspected to be IP related occurred in two or less subjects per treatment group.

Adverse events of special interest

Based on the Herceptin safety profile to this date, infusion-related reactions, CHF (Congestive Heart Failure), left ventricular systolic dysfunction and pulmonary toxicity are also a recognised AE of special interest for Ontruzant.

The total number of AESI was 113 in the Ontruzant and 98 in the EU Herceptin treatment group.

Infusion-Related Reactions

The incidence of common symptoms of infusion-related reactions was balanced across both treatment groups: 53 TEAEs associated with infusion-related reaction were reported in 37 (8.5%) patients in the Ontruzant treatment group, and 64 events in 44 (10.0%) patients in the EU Herceptin treatment group.

The most frequently reported signs and symptoms were in the SOCs of general disorders and administration site conditions (27 events in 14 [3.2%] patients in the Ontruzant arm, 33 events in 20 [4.6%] patients in the EU Herceptin arm) and respiratory, thoracic and mediastinal disorders (13 events in 11 [2.5%] patients in the Ontruzant arm, 16 events in 13 [3.0%] patients in the EU Herceptin arm). The most common symptoms of infusion-related reactions reported in the PT were dyspnoea (10 and 15 events, respectively), chest discomfort (9 and 7 events, respectively), chills (7 and 13 events, respectively), and pyrexia (4 and 8 events, respectively).

The majority of infusion-related reactions were Grade 1 (4.1% [18/437] of patients and 4.6% [20/438] of patients in the Ontruzant and EU Herceptin treatment groups, respectively) and Grade 2 (4.3% [19/437] and 4.6% [20/438] of patients, respectively). In the Ontruzant treatment group, there were no severe infusion-related reactions (grade ≥ 3). However, in the Herceptin treatment group, there were 3 grade 3 infusion-related reactions in 3 (0.7%) subjects, and 1 grade 4 infusion-related reaction reported in 1 (0.2%) subject (no grade 5 infusion-related reactions). In both arm, around 30% of the IRR were related to IP, and 70% to non-IP.

Overall, the time pattern was comparable. The incidence of infusion-related reactions was highest during the first two treatment cycles for both treatment groups, and the incidence decreased over time in both treatment groups.

Cardiac toxicity

Left Ventricular Ejection Fraction Assessment

The baseline cardiac status, as shown by LVEF, was similar in the two treatment groups. At baseline, the median LVEF value was 65.0% in both treatment groups (range 55%-80% and 55%-85% in the Ontruzant and EU Herceptin treatment groups, respectively).

A similar proportion of patients in each treatment group had a significant decrease in LVEF of ≥ 10% points from baseline and resulting LVEF < 50% (16 [3.7%] patients in the Ontruzant treatment group and 12 [2.8%] patients in the EU Herceptin treatment group).

Left Ventricular Systolic Dysfunction

In the Ontruzant treatment group, 14 left ventricular systolic dysfunction events were reported in 11 (2.5%) patients and, in the EU Herceptin treatment group, 9 left ventricular systolic dysfunction events were reported in 8 (1.8%) patients (Final CSR: table 14.3.1-1.1).

Most of them were grade 1 or 2 in both arms. In the Ontruzant treatment group, 13 left ventricular systolic dysfunction events were reported as Grade 1-2 and 1 left ventricular systolic dysfunction event was reported as Grade 3. In the Herceptin treatment group, 7 left ventricular systolic dysfunction events were reported as Grade 1-2 and 2 left ventricular systolic dysfunction events were reported as grade 3; there were no Grade 4 or 5 events.

The majority were related to the IP: 12 IP-related events in the Ontruzant arm and 7 IP-related events in the EU Herceptin. There were also 4 non-IP related events in the Ontruzant arm and 1 non-IP related events in the Herceptin arm.

Congestive Heart Failure

In the Ontruzant treatment group, 2 (0.5%) patients had class II CHF (related to IP) and 1 (0.2%) patient had class IV CHF (not-related to IP). One event was Grade 2, and 2 were Grade 3 (Final CSR: table 14.3.1-1.1).

In the Herceptin arm, 1 (0.2%) patient had class II CHF (Grade 3, non-IP related).

Overall Cardiac Safety

Cardiac TEAEs at the SOC level were cardiac disorders (65 events in 46 [10.5%] patients in the Ontruzant, and 75 events in 53 [12.1%] patients in the EU Herceptin treatment groups) and investigations (4 events in 4 [0.9%] patients in the Ontruzant, and 3 events in 3 [0.7%] patients in the EU Herceptin treatment groups) (Final CSR: table 14.3.1-1.2).

The most common reported cardiac TEAEs at the PT level were sinus tachycardia (15 events in 13 [3%] patients in Ontruzant arm, and 21 events in 20 [4.6%] patients in Herceptin arm), Left ventricular dysfunction (14 events in 11 [2.5%] patients in the Ontruzant, and 9 events in 8 [1.8%] patients, respectively) and tachycardia (13 events in 9 [2.1%] patients, and 6 events in 6 [1.4%] patients, respectively).

These cardiac TEAEs were mainly Grade 1 or 2.

In each arm, 5 severe cardiac TEAE were reported in 5 (1.1%) patients. All were Grade 3 events with the exception of one Grade 5 event of myocardial infraction in the EU Herceptin treatment group.

In addition, 5 serious cardiac TEAEs were reported: 4 (0.9%) patients reported 4 events in the Ontruzant treatment group and 1 (0.2%) patient reported 1 event in the EU Herceptin treatment group. In the Ontruzant treatment group, 3 subjects had cardiac failure congestive and 1 subject had supraventricular tachycardia. In the Herceptin treatment group, 1 subject had fatal myocardial infarction.

Pulmonary toxicity

According to the Herceptin SmPC, severe pulmonary events have been reported with the use of Herceptin in the post-marketing setting.

Table 51: Summary of Pulmonary Events during the Overall Study Period (Safety Set); revision of Final Clinical Study Report Table 12-4

Treatment	SB3			Herceptin®		
	N=437			N=438		
Number of subjects experiencing	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Any TEAE of special interest (pulmonary events)	35	(8.0)	43	23	(5.3)	24
TEAE severity						
Grade 1	19	(4.3)	25	11	(2.5)	12
Grade 2	11	(2.5)	12	8	(1.8)	8
Grade 3	5	(1.1)	6	3	(0.7)	3
Grade 4	0	(0.0)	0	0	(0.0)	0
Grade 5	0	(0.0)	0	1	(0.2)	1
TEAEs leading to IP discontinuation	0	(0.0)	0	0	(0.0)	0
TEAEs leading to IP dose delay	4	(0.9)	5	5	(1.1)	5
TEAEs leading to IP dose interruption	0	(0.0)	0	0	(0.0)	0
TEAEs leading to non-IP discontinuation	0	(0.0)	0	0	(0.0)	0
TEAEs leading to Non-IP dose delay/modification	3	(0.7)	4	4	(0.9)	4
TEAEs leading to Non-IP dose interruption	0	(0.0)	0	0	(0.0)	0
Serious TEAEs	5	(1.1)	6	3	(0.7)	3
TEAE Outcome						
Recovered/Resolved			38			21
Recovered/Resolved with sequelae			0			0
Not recovered/Not resolved			4			0
Fatal			0			1
Unknown			1			2

E = frequency of adverse events; IP = investigational product; N = number of subjects in the Safety Set; n = number of subjects with TEAEs; TEAE = treatment-emergent adverse event; Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities Version 16.1. Severity assessment was classified in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 with the exception of febrile neutropenia and left ventricular systolic dysfunction which were classified according to v4.03 and v3.0, respectively.

Percentages were based on the number of subjects in the Safety Set. If a subject had multiple events of the same severity or relationship, then they were counted only once in that severity or relationship. If a subject had multiple events with different severity or relationship, then the subject was counted only once for more severe adverse events or related adverse events. Source: Table 14.3.1-1.1a and Listing 14.3.2-1.3a

Table 52: Table TEAEs of Special Interest (Pulmonary Events) by System Organ Class and Preferred Term during the Overall Study Period (Safety Set)

Treatment	SB3 N=437			Herceptin® N=438		
System organ class Preferred term	n	(%)	E	n	(%)	E
Any TEAE of special interest (pulmonary events)	35	(8.0)	43	23	(5.3)	24
Infections and infestations	18	(4.1)	20	12	(2.7)	12
Bronchitis	10	(2.3)	10	5	(1.1)	5
Pneumonia	6	(1.4)	7	3	(0.7)	3
Lower respiratory tract infection	1	(0.2)	1	0	(0.0)	0
Lung infection	1	(0.2)	2	1	(0.2)	1
Bronchopneumonia	0	(0.0)	0	1	(0.2)	1
Lobar pneumonia	0	(0.0)	0	2	(0.5)	2
Respiratory, thoracic and mediastinal disorders	17	(3.9)	23	12	(2.7)	12
Dyspnoea	11	(2.5)	16	8	(1.8)	8
Pleural effusion	3	(0.7)	3	1	(0.2)	1
Pulmonary fibrosis	2	(0.5)	2	1	(0.2)	1
Dyspnoea exertional	1	(0.2)	1	0	(0.0)	0
Hydrothorax	1	(0.2)	1	0	(0.0)	0
Lower respiratory tract inflammation	0	(0.0)	0	1	(0.2)	1
Pneumonitis	0	(0.0)	0	1	(0.2)	1

E = frequency of adverse events; N = number of subjects in the Safety Set; n = number of subjects with TEAEs; TEAE = treatment-emergent adverse event. Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities Version 16.1.

Percentages were based on the number of subjects in the Safety Set. System organ classes were presented alphabetically. Preferred terms were sorted within the system organ class in descending order of subject frequency in the SB3 treatment group. If the frequencies of the preferred terms were the same, the preferred terms were sorted alphabetically.

Source: Table 14.3.1-1.24

Severe (Grade ≥ 3) Pulmonary Events

The majority of pulmonary events were grade 1 or 2 in severity in the two treatment groups. Ten severe (grade ≥ 3) TEAEs were reported; 5 (1.1%) subjects reported 6 events in the Ontruzant treatment group and 4 (0.9%) subjects reported 4 events in the Herceptin treatment group.

In the Ontruzant treatment group, 1 event of bronchitis grade 3, 1 event of pleural effusion grade 3 and 4 events of pneumonia grade 3 (in 3 subjects) were reported. In the Herceptin treatment group, 1 event each of pneumonitis grade 5, bronchitis grade 3, bronchopneumonia grade 3 and lobar pneumonia grade 3 were reported. All events except for the event of grade 5 pneumonitis were resolved without sequelae. One event of grade 3 bronchitis (one subject from the Ontruzant treatment group) was considered by the Investigator to be related to the investigational product.

Serious Adverse Events (Pulmonary Events)

Overall, 9 serious pulmonary events were reported; 6 events for 5 (1.1%) subjects in the Ontruzant treatment group and 3 events for 3 (0.7%) subjects in the Herceptin treatment group.

In the Ontruzant treatment group, 1 event of bronchitis and 5 events of pneumonia (in 4 subjects) were reported; all events were grade 3 except for 1 event of pneumonia which was grade 2. In the Herceptin

treatment group, 1 event each of pneumonitis, bronchopneumonia and lobar pneumonia were reported. Pneumonitis was grade 5 (fatal) and the other events were grade 3. All events except for the grade 5 pneumonitis were resolved without sequelae. One serious adverse event of bronchitis grade 3 (1 subject from the Ontruzant treatment group) was considered by the Investigator to be related to the investigational product.

Neoadjuvant therapy period

In the Ontruzant treatment group, 85 TEAEs of special interest were reported in 63 (14.4) patients: 51 infusion-related reactions in 36 (8.2%) subjects, 5 events of left ventricular systolic dysfunction in 4 (0.9%) subjects, 2 events of CHF in 2 (0.5%) subjects and 27 pulmonary events in 25 (5.7%) subjects. In the Herceptin treatment group, 81 TEAEs of special interest were reported in 59 (13.5%) patients: 64 infusion-related reactions in 44 (10.0%) subjects, 3 events of left ventricular systolic dysfunction in 3 (0.7%) subjects, no events of CHF and 14 pulmonary events in 14 (3.2%) patients were reported.

The profile of the IRR reported in the neoadjuvant therapy period was similar to that of the overall study in terms of the most common AEs and respective SOCs (please Cf. overall duration therapy). The most frequently reported signs and symptoms were in the SOCs of general disorders and administration site conditions and respiratory, thoracic and mediastinal disorders. The most common symptoms of infusion-related reactions reported in the PT were dyspnoea, chest discomfort, chills, and pyrexia. The incidence of common symptoms of IRR was balanced across both treatment groups. The majority were grade 1 or 2, not-related to IP, but related to non-IP.

Adjuvant therapy period

During the adjuvant period, a very low number of TEAEs of special interest were reported (Table 53):

- 24 in the Ontruzant arm in 20 subjects (4.6%): 2 IRR in 2 (0.5%) subjects (influenza-like illness and pyrexia), 9 left ventricular systolic dysfunction in 8 (1.8%) subjects, 1 CHF in 1 (0.2%) subject and 12 pulmonary events in 10 (2.3%) subjects.

- 17 in the Herceptin arm in 15 subjects (3.4%): no IRR, 6 left ventricular systolic dysfunction in 5 (1.1%) subjects, 1 CHF in 1 (0.2%) subject and 10 pulmonary events in 9 (2.1%) subjects.

The majority were grade 1 or 2, and related to IP.

Study SB3-G11-NHV (supportive study)

Infusion-Related Reactions

In the clinical Phase I study, a total of 33 subjects reported 33 events of IRR (9 [25.0%], 8 [22.2%] and 16 [44.4%] subjects from Ontruzant, EU Herceptin and US Herceptin treatment groups, respectively). Among them, 2 subjects had infusion interruptions but completed the infusion. The majority of IRR were Grade 1 (n=18) to Grade 2 (n=14). The 1 severe IRR occurred in a subject receiving Ontruzant. Reaction onset was 48 minutes after infusion start, with a symptom constellation of back pain, muscle spasms, dizziness, fatigue, hyperhidrosis, pallor, headache and pyrexia. The symptoms of IRR were treated with paracetamol 500 mg after onset and resolved within 1 day.

The most frequently reported symptoms of IRR were feeling cold (21 subjects; 7 in Ontruzant, 3 in EU-Herceptin, and 11 in US-Herceptin), headache (17 subjects; 3 in Ontruzant, 5 in EU-Herceptin, and 9

in US-Herceptin), pyrexia (13 subjects; 4 in Ontruzant, 4 in EU-Herceptin, and 5 in US-Herceptin), and chills (13 subjects; 5 in Ontruzant, 3 in EU-Herceptin, and 5 in US-Herceptin).

Cardiac toxicity

ECG measures and change from baseline of heart rate, RR interval, PQ interval, PR interval, QRS interval, QT interval, QTcF interval and QTcB interval were followed. Mean and median values of all parameters of ECG did not show any relevant changes over time. Minor alterations are similar to those usually observed in healthy subjects.

No subject had a QTcF interval > 450 msec at any time point during the study.

QTcF changes > 60 msec were not observed in any of the subjects.

Interpretation of ECG recordings showed some abnormalities, but most of these abnormalities did not reach clinical relevance as judged by the Investigator. Atrial fibrillation with arrhythmia observed on Day 3 for one Subject from EU-Herceptin group was assessed by the Investigator as a clinically significant abnormality; on Day 4 and all subsequent assessments, the ECG recordings for this subject was normal.

Serious adverse event / deaths

Study SB3-G31-BC

Overall study

Table 53: Summary of serious TEAE during the overall therapy Period – Safety set (SB3-G31-BC)

	SB3 N=437		Herceptin N=438	
Number of subjects experiencing	n (%)	E	n (%)	E
Serious TEAEs	56 (12.8)	98	58 (13.2)	79
Serious TEAE Severity				
Grade 1	2 (0.5)	2	2 (0.5)	3
Grade 2	5 (1.1)	10	5 (1.1)	7
Grade 3	27 (6.2)	52	31 (7.1)	43
Grade 4	21 (4.8)	33	15 (3.4)	21
Grade 5	1 (0.2)	1	5 (1.1)	5
Serious TEAE Relationship with IP				
Related	11 (2.5)	12	9 (2.1)	10
Not related	45 (10.3)	86	49 (11.2)	69
Serious TEAE Relationship with Non-IP				
Related	37 (8.5)	68	34 (7.8)	43
Not related	19 (4.3)	30	24 (5.5)	36
Serious TEAE Outcome				
Recovered/Resolved		94		73
Recovered/Resolved with sequelae		1		1
Not recovered/Not resolved		2		0
Fatal		1		5
Unknown		0		0

The most frequently occurring SAEs at the SOC level were blood and lymphatic system disorders (24 events in 18 [4.1%] patients in the Ontruzant treatment group and 21 events in 18 [4.1%] patients in the EU Herceptin treatment group), and infection and infestations (15 events in 13 [3%] subjects in both treatment groups).

Table 54: Serious Treatment-Emergent Adverse Events by System Organ Class (> 1% in Any Treatment Group) and Preferred Term during the Overall Study Period (Safety Set)

Treatment	SB3 N=437			Herceptin® N=438		
System organ class						
Preferred term	**n**	**(%)**	**E**	**n**	**(%)**	**E**
Any serious TEAE	56	(12.8)	98	58	(13.2)	79
Blood and lymphatic system disorders	18	(4.1)	24	18	(4.1)	21
Febrile neutropenia	10	(2.3)	11	13	(3.0)	14
Neutropenia	7	(1.6)	7	5	(1.1)	5
Anaemia	2	(0.5)	3	0	(0.0)	0
Thrombocytopenia	1	(0.2)	3	0	(0.0)	0
Haemolytic anaemia	0	(0.0)	0	1	(0.2)	1
Leukopenia	0	(0.0)	0	1	(0.2)	1
Gastrointestinal disorders	8	(1.8)	11	6	(1.4)	7
Diarrhoea	3	(0.7)	5	3	(0.7)	3
Gastrooesophageal reflux disease	2	(0.5)	2	0	(0.0)	0
Abdominal pain upper	1	(0.2)	1	0	(0.0)	0
Nausea	1	(0.2)	1	0	(0.0)	0
Stomatitis	1	(0.2)	1	0	(0.0)	0
Vomiting	1	(0.2)	1	2	(0.5)	2
Gastritis	0	(0.0)	0	1	(0.2)	1
Haemorrhoids	0	(0.0)	0	1	(0.2)	1
Infections and infestations	13	(3.0)	15	13	(3.0)	15
Pneumonia	4	(0.9)	5	0	(0.0)	0
Urinary tract infection	2	(0.5)	2	0	(0.0)	0
Bronchitis	1	(0.2)	1	0	(0.0)	0
Cellulitis	1	(0.2)	1	1	(0.2)	1
Furuncle	1	(0.2)	1	0	(0.0)	0
Gastroenteritis	1	(0.2)	1	1	(0.2)	1
Neutropenic sepsis	1	(0.2)	1	1	(0.2)	1
Soft tissue infection	1	(0.2)	1	0	(0.0)	0
Tuberculosis	1	(0.2)	1	0	(0.0)	0
Upper respiratory tract infection	1	(0.2)	1	0	(0.0)	0
Bronchopneumonia	0	(0.0)	0	1	(0.2)	1
Dengue fever	0	(0.0)	0	2	(0.5)	2
Erysipelas	0	(0.0)	0	1	(0.2)	1
Influenza	0	(0.0)	0	2	(0.5)	2
Intraspinal abscess	0	(0.0)	0	1	(0.2)	1
Lobar pneumonia	0	(0.0)	0	1	(0.2)	1
Neutropenic infection	0	(0.0)	0	1	(0.2)	1
Postoperative wound infection	0	(0.0)	0	1	(0.2)	1
Wound infection	0	(0.0)	0	1	(0.2)	2
Injury, poisoning and procedural complications	3	(0.7)	3	7	(1.6)	7
Facial bones fracture	1	(0.2)	1	0	(0.0)	0
Radiation necrosis	1	(0.2)	1	0	(0.0)	0
Radiation pneumonitis	1	(0.2)	1	0	(0.0)	0
Hand fracture	0	(0.0)	0	1	(0.2)	1
Infusion-related reaction	0	(0.0)	0	2	(0.5)	2
Post-procedural complication	0	(0.0)	0	1	(0.2)	1
Post-procedural haemorrhage	0	(0.0)	0	2	(0.5)	2
Radiation mucositis	0	(0.0)	0	1	(0.2)	1
Investigations	8	(1.8)	20	4	(0.9)	7
Neutrophil count decreased	8	(1.8)	20	4	(0.9)	7
Nervous system disorders	1	(0.2)	1	6	(1.4)	6
Polyneuropathy	1	(0.2)	1	0	(0.0)	0
Carpal tunnel syndrome	0	(0.0)	0	1	(0.2)	1
Convulsion	0	(0.0)	0	2	(0.5)	2
Haemorrhagic stroke	0	(0.0)	0	1	(0.2)	1
Ischaemic stroke	0	(0.0)	0	1	(0.2)	1
Transient ischaemic attack	0	(0.0)	0	1	(0.2)	1

E = frequency of the adverse events; N = number of subjects in the Safety Set; n = number of subjects with TEAEs; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities Version 16.1.
Percentages were based on the number of subjects in the Safety Set.
System organ classes were presented alphabetically. Preferred terms were sorted within the SOC in descending order of subject frequency in the SB3 treatment group. If the frequencies of the PTs were the same, the PTs were sorted alphabetically.

6 deaths were reported; none were considered to be related to the IP. One was in the Ontruzant arm (0.2% of the patients): completed suicide (neoadjuvant period); and 5 in the Herceptin arm (1.1% of the patients): myocardial infarction (neoadjuvant period), sudden death (neoadjuvant period, unknown cause of death), pulmonary embolism (neoadjuvant period, clinical diagnosis without definite evidence), haemorrhagic stroke (adjuvant period, clinical diagnosis without imaging evidence), and pneumonitis (adjuvant period).

Neoadjuvant therapy period

During the neoadjuvant therapy period, 81 SAEs were reported in 46 (10.5%) Ontruzant subjects, and 64 events in 47 (10.7%) Herceptin subjects, respectively.

The most frequently occurring SAEs at the PT level were febrile neutropenia (11 events in 10 [2.3%] subjects in the Ontruzant arm, and 14 events in 13 [3%] subjects in the Herceptin arm), neutrophil count decreased (20 events in 8 [1.8%] subjects, and 7 events in 4 [0.9%] subjects, respectively), neutropenia (7 events in 7 [1.6%] subjects, and 5 events in 5 [1.1%] subjects, respectively) and diarrhoea (5 events in 3 [0.7%] subjects and 3 events in 3 [0.7%] subjects, respectively).

Most of the SAE were grade 3 or 4 in severity, and most of the patients had grade 3 or 4 SAEs: 41 grade 3 SAE in 21 patients in Ontruzant arm and 31 grade 3 SAE in 22 patients in Herceptin arm; 30 grade 4 SAE in 18 patients and 20 grade 4 SAE in 15 patients, respectively. Finally, the number of SAE related to IP was equivalent in both arm (2.1% of the subjects), and the number of SAEs related to non-IP was similar in both arms (8.2% versus 7.8%, respectively). Most of them recovered/resolved without sequelae (80 SAE in Ontruzant arm and 61 events in Herceptin arm).

Adjuvant therapy period

Table 55: Serious TEAE grade, relationship to IP and non-IP, and outcome during the adjuvant Period – Safety set

	SB3 N=437		Herceptin N=438	
Number of subjects experiencing	n	(%)	n	(%)	E
Serious TEAEs	15	(3.4)	17	14	(3.2)	15
Serious TEAE Severity						
Grade 1	0	(0.0)	0	0	(0.0)	0
Grade 2	3	(0.7)	3	0	(0.0)	0
Grade 3	9	(2.1)	11	11	(2.5)	12
Grade 4	3	(0.7)	3	1	(0.2)	1
Grade 5	0	(0.0)	0	2	(0.5)	2
Serious TEAE Relationship with IP						
Related	2	(0.5)	2	0	(0.0)	0
Not related	13	(3.0)	15	14	(3.2)	15
Serious TEAE Outcome						
Recovered/Resolved			14			12
Recovered/Resolved with sequelae			1			1
Not recovered/Not resolved			2			0
Fatal			0			2
Unknown			0			0

The SOC with the most SAE were infections and infestations (6 SAE in 6 patients – 1.4% in Ontruzant, and 7 SAE in 6 patients – 1.4%), injury, poisoning and procedural complications (3 SAE in 3 patients – 0.7% in Ontruzant, and 4 SAE in 4 patients – 0.9%), and respiratory, thoracic and mediastinal disorders (2 SAE in 2 patients – 0.5% in each arm). The most frequently occurring SAE at the PT level was pneumonia (2 [0.5%] subjects in the Ontruzant treatment group and no subject in the Herceptin treatment group); the remaining SAEs were reported for one subject each in one of the 2 treatment groups.

Study SB3-G11-NHV (supportive study)

No deaths occurred during the study period.

One SAE was reported in 1 subject in the Ontruzant treatment group, as follows: chondropathy. The event of chondropathy was assessed by the Investigator to be of Grade 3 severity with outcome 'recovered with sequelae and not related to the IP.

Laboratory findings

Study SB3-G31-BC

Haematology

The pattern of laboratory abnormalities of haematology parameters (haemoglobin, absolute neutrophil count, platelet count and white blood cell count) observed was similar between the Ontruzant and EU Herceptin treatment groups during the overall study period (Table 62).

Table 56: Summary of Worst CTCAE Grade for Haematology Parameters during the Overall Study Period– Safety set (SB3-G31-BC – Final CSR: table 14.3-2.1)

Time period CTCAE Grade	SB3 N=437	Herceptin N=438
Parameter: Haemoglobin (g/L)		
Overall Study Period		
n'	437	436
Grade 0	75 (17.2)	72 (16.5)
Grade 1	253 (57.9)	268 (61.5)
Grade 2	100 (22.9)	88 (20.2)
Grade 3	9 (2.1)	8 (1.8)
Grade 4	0 (0.0)	0 (0.0)
Parameter: Total WBC (×10E9/L)		
Overall Study Period		
n'	437	436
Grade 0	52 (11.9)	52 (11.9)
Grade 1	64 (14.6)	64 (14.7)
Grade 2	113 (25.9)	127 (29.1)
Grade 3	186 (42.6)	176 (40.4)
Grade 4	22 (5.0)	17 (3.9)
Parameter: Absolute Neutrophil Count (×10E9/L)		
Overall Study Period		
n'	429	429
Grade 0	42 (9.8)	41 (9.6)
Grade 1	28 (6.5)	42 (9.8)
Grade 2	45 (10.5)	45 (10.5)
Grade 3	100 (23.3)	103 (24.0)
Grade 4	214 (49.9)	198 (46.2)
Parameter: Platelet Count (×10E9/L)		
Overall Study Period		
n'	437	436
Grade 0	323 (73.9)	326 (74.8)
Grade 1	107 (24.5)	105 (24.1)
Grade 2	3 (0.7)	3 (0.7)
Grade 3	3 (0.7)	2 (0.5)
Grade 4	1 (0.2)	0 (0.0)

A total of 1613 neutropenia events in 665 (76.0%) of patients were reported. In both arms, the most common Grade 3-4 TEAE was neutropenia.

In both arms, the most common Grade 3-4 TEAE was neutropenia.

Table 57: Treatment-Emergent Adverse Events of Neutropenia and Severity Group by System Organ Class and Preferred Term, Safety Set

System organ class / Preferred term	Severity	SB3 N=437 n	(%)	E	Herceptin N=438 n	(%)	E	Total N=875 n	(%)	E
Any TEAE of Neutropenia	Overall	342	(78.3)	805	323	(73.7)	808	665	(76.0)	1613
	Grade 1-2	50	(11.4)	250	46	(10.5)	253	96	(11.0)	503
	Grade 3-4	292	(66.8)	555	277	(63.2)	555	569	(65.0)	1110
	Grade 5	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Blood and lymphatic system disorders	Overall	294	(67.3)	661	282	(64.4)	639	576	(65.8)	1300
	Grade 1-2	45	(10.3)	212	40	(9.1)	201	85	(9.7)	413
	Grade 3-4	249	(57.0)	449	242	(55.3)	438	491	(56.1)	887
	Grade 5	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Neutropenia	Overall	294	(67.3)	661	282	(64.4)	639	576	(65.8)	1300
	Grade 1-2	45	(10.3)	212	40	(9.1)	201	85	(9.7)	413
	Grade 3-4	249	(57.0)	449	242	(55.3)	438	491	(56.1)	887
	Grade 5	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0

- TEAE: Treatment-Emergent Adverse Event; E: Frequency of TEAEs of Neutropenia
- TEAEs with preferred term of Neutropenia and Neutrophil count decreased were included.
- Adverse events were coded to system organ class and preferred term using the MedDRA Version 16.1 coding dictionary.
- Severity assessment was done in accordance with NCI-CTCAE v4.0. Exceptionally, febrile neutropenia and LV systolic dysfunction was done according to v4.03 and v3.0 respectively.
- Percentages were based on the number of subjects in the Safety set.
- If a subject had more than one adverse event, more than one adverse event within a system organ class or more than one adverse event within a preferred term, they were only counted once for the maximum severity for the relevant row of the table.
- System organ classes (SOCs) were presented alphabetically; preferred terms were sorted within system organ class in descending order of subject frequency in SB3. If the frequency of the preferred term was tied, the preferred terms were sorted alphabetically.
- Subjects with missing severity were counted for both categories with maximum severity and missing category.

In both arms, other commonly (incidence > 5% in either treatment group) reported haematology-related TEAEs were:

- Leukopenia (259 events were reported in 125 [28.6%] patients in Ontruzant, and 238 events in 114 [26%] patients in Herceptin).

- Anaemia (183 events were reported in 96 [22%] patients in Ontruzant, and 198 events in 95 [21.7%] patients in Herceptin).

- Febrile neutropenia (39 events were reported in 28 [6.4%] patients in Ontruzant, and 40 events in 34 [7.8%] patients in Herceptin).

- WBC decreased (69 events were reported in 25 [5.7%] patients in Ontruzant, and 71 events in 32 [7.3%] patients in Herceptin).

Biochemistry

The pattern of laboratory abnormalities of biochemistry parameters (alkaline phosphatase, Alanine transaminase, aspartate transaminase, total bilirubin, serum creatinine) observed was similar between the 2 arms (

Table **64**).

Table 58: Summary of Worst CTCAE Grade for biochemistry Parameters during the Overall Study Period– Safety set (SB3-G31-BC – Final CSR: table 14.3-2.2)

Time period CTCAE Grade	SB3 N=437	Herceptin N=438
Parameter: Alkaline phosphatase (IU/L)		
Overall Study Period		
n'	437	436
Grade 0	276 (63.2)	284 (65.1)
Grade 1	155 (35.5)	148 (33.9)
Grade 2	6 (1.4)	4 (0.9)
Grade 3	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)
Parameter: Serum creatinine (umol/L)		
Overall Study Period		
n'	437	436
Grade 0	344 (78.7)	360 (82.6)
Grade 1	87 (19.9)	73 (16.7)
Grade 2	5 (1.1)	2 (0.5)
Grade 3	0 (0.0)	1 (0.2)
Grade 4	1 (0.2)	0 (0.0)
Parameter: SGPT (ALT) (IU/L)		
Overall Study Period		
n'	437	436
Grade 0	130 (29.7)	128 (29.4)
Grade 1	259 (59.3)	261 (59.9)
Grade 2	31 (7.1)	35 (8.0)
Grade 3	17 (3.9)	12 (2.8)
Grade 4	0 (0.0)	0 (0.0)
Parameter: SGOT (AST) (IU/L)		
Overall Study Period		
n'	437	436
Grade 0	162 (37.1)	166 (38.1)
Grade 1	256 (58.6)	252 (57.8)
Grade 2	12 (2.7)	14 (3.2)
Grade 3	7 (1.6)	4 (0.9)
Grade 4	0 (0.0)	0 (0.0)
Parameter: Total bilirubin (umol/L)		
Overall Study Period		
n'	437	436
Grade 0	377 (86.3)	380 (87.2)
Grade 1	49 (11.2)	45 (10.3)
Grade 2	11 (2.5)	9 (2.1)
Grade 3	0 (0.0)	2 (0.5)
Grade 4	0 (0.0)	0 (0.0)

In both arms, the most commonly reported biochemistry-related TEAEs were:

- ALT increased (150 events were reported in 84 [19.2%] patients in Ontruzant, and 150 events were reported in 83 [18.9%] patients in Herceptin).
- AST increased (102 events were reported in 68 [15.6%] patients in Ontruzant, and 110 events were reported in 63 [14.4%] patients in Herceptin).

Urinalysis

The collection of urinalysis results included urine haemoglobin, ketones, leukocytes, nitrite, pH, specific gravity, bilirubin, glucose, protein, and urobilinogen at three different time points: baseline, cycle 5, and pre-surgery.

All parameters were mostly normal at baseline in both treatment groups (range from 81.1% to 99.0% and from 78.1% to 98.7% in the Ontruzant and EU Herceptin group, respectively), and the baseline results were not significantly changed at cycle 5 and presurgery.

Overall, there was no significant difference in urinalysis results between the treatment groups.

Study SB3-G11-NHV (supportive study)

Haematology, Biochemistry, Urinalysis, and Cardiac markers parameters

Mean and median values of all parameters did not show any significant change over time. A few subjects had shifts from normal values at baseline to values outside the normal range. However, there were no significant changes from baseline in the values in any treatment group.

Safety in special populations

Not applicable.

Immunological events

Study SB3-G31-BC

In the clinical Phase III study, the immunogenicity profile was evaluated as one of the secondary endpoints in terms of the incidence of ADA and NAbs. Blood samples for determination of immunogenicity were collected at pre-dose of Cycle 1, 5, 9, 14 and 30 days after the last dose of IP.

Table 59: Incidence of Anti-Drug Antibody and Neutralising Antibodies by Visit, Overall Study Period– Safety set (SB3-G31-BC)

Timepoint	Parameter	Assessment	SB3 N = 437			EU Herceptin® N = 438		
			n'	n	(%)	n'	n	(%)
Cycle 1 (BL)	ADA	Positive	425	4	(0.9)	430	4	(0.9)
		Negative	425	421	(99.1)	430	426	(99.1)
	NAb	Positive	4	0	(0.0)	4	0	(0.0)
		Negative	4	4	(100.0)	4	4	(100.0)
Cycle 5	ADA	Positive	422	3	(0.7)	426	1	(0.2)
		Negative	422	419	(99.3)	426	425	(99.8)
	NAb	Positive	3	2	(66.7)	1	0	(0.0)
		Negative	3	1	(33.3)	1	1	(100.0)
Cycle 9	ADA	Positive	410	0	(0.0)	406	1	(0.2)
		Negative	410	410	(100.0)	406	405	(99.8)

	NAb	Positive	0	0	(-)	1	0	(0.0)
		Negative	0	0	(-)	1	1	(100.0)
Cycle 14	ADA	Positive	397	1	(0.3)	394	0	(0.0)
		Negative	397	396	(99.7)	394	394	(100.0)
	NAb	Positive	1	0	(0.0)	0	0	(-)
		Negative	1	1	(100.0)	0	0	(-)
End of Study	ADA	Positive	377	2	(0.5)	377	3	(0.8)
		Negative	377	375	(99.5)	377	374	(99.2)
	NAb	Positive	2	0	(0.0)	3	2	(66.7)
		Negative	2	2	(100.0)	3	1	(33.3)
Cycle 9 Overall	ADA	Positive	423	3	(0.7)	426	0	(0.0)
		Negative	423	416	(98.3)	426	422	(99.1)
		Inconclusive	423	4	(0.9)	426	4	(0.9)
End of Study Overall	ADA	Positive	423	3	(0.7)	426	3	(0.7)
		Negative	423	416	(98.3)	426	419	(98.4)
		Inconclusive	423	4	(0.9)	426	4	(0.9)

Overall ADA result was defined as Positive for a patient with treatment-induced or treatment-boosted ADA where, treatment-induced ADA indicated at least one positive result after pre-dose of Cycle 1 for patients with negative ADA at pre-dose of Cycle 1, and treatment-boosted ADA indicated at least one positive result with higher titre level compared with the baseline after pre-dose of Cycle 1 for patients with positive ADA at pre-dose of Cycle 1.
Overall ADA result is defined as Negative for a patient with negative ADA at baseline and no positive results up to the time point.
Overall ADA result is defined as Inconclusive for a patient with positive ADA at baseline and no positive result with higher titre level observed after baseline up to the time point.
Source: Attachment 10, Attachment 11

Titre evolution by visit for each ADA positive patient

Overall ADA results, up to the relevant timepoint, were defined as positive when patients with a negative ADA at pre-dose Cycle 1 had at least one positive result after the dose at Cycle 1, and when patients with a positive ADA at pre-dose Cycle 1 had at least one positive result after the dose at Cycle 1 with a higher titre level compared with baseline (Cycle 1).

In the final CSR, the number of patients with an overall ADA positive result was 3 (0.7%) in both Ontruzant and EU Herceptin treatment groups. In terms of neutralising antibody (NAb), 2 out of 3 ADA positive patients in each treatment group has also detectable NAb.

ADA impact on clinical outcome

In the Ontruzant treatment group, 3 patients had ADA-positive results, with PK data available for one patient.

In the EU Herceptin treatment group, 3 patients had overall ADA-positive results, with no PK information available.

Clinical relevance of TEAE

During the overall study period, for the 3 subjects with an overall positive ADA result in each arm, a total of 23 TEAE were reported in Ontruzant and 25 TEAE in Herceptin (

Table **66**).

Table 60: TEAE for <u>overall positive ADA</u> result by System Organ Class and Preferred Term, Overall Study Period– Safety set (SB3-G31-BC)

System organ class Preferred term	SB3 N=3 n (%)	E	Herceptin N=3 n (%)	E
Any TEAE	3 (100.0)	23	3 (100.0)	25
Blood and lymphatic system disorders	1 (33.3)	1	0 (0.0)	0
Anaemia	1 (33.3)	1	0 (0.0)	0
Cardiac disorders	1 (33.3)	1	0 (0.0)	0
Left ventricular dysfunction	1 (33.3)	1	0 (0.0)	0
Gastrointestinal disorders	0 (0.0)	0	2 (66.7)	19
Abdominal pain upper	0 (0.0)	0	1 (33.3)	1
Nausea	0 (0.0)	0	2 (66.7)	17
Stomatitis	0 (0.0)	0	1 (33.3)	1
General disorders and administration site conditions	1 (33.3)	2	1 (33.3)	1
Fatigue	1 (33.3)	2	0 (0.0)	0
Asthenia	0 (0.0)	0	1 (33.3)	1
Infections and infestations	1 (33.3)	1	0 (0.0)	0
Bronchitis	1 (33.3)	1	0 (0.0)	0
Injury, poisoning and procedural complications	0 (0.0)	0	1 (33.3)	1
Radiation mucositis	0 (0.0)	0	1 (33.3)	1
Investigations	3 (100.0)	13	1 (33.3)	1
Neutrophil count decreased	2 (66.7)	6	0 (0.0)	0
Alanine aminotransferase increased	1 (33.3)	2	1 (33.3)	1
Aspartate aminotransferase increased	1 (33.3)	1	0 (0.0)	0
White blood cell count decreased	1 (33.3)	4	0 (0.0)	0
Musculoskeletal and connective tissue disorders	1 (33.3)	1	0 (0.0)	0
Bone pain	1 (33.3)	1	0 (0.0)	0
Reproductive system and breast disorders	0 (0.0)	0	1 (33.3)	1
Reproductive system and breast disorders (cont.)				
Breast pain	0 (0.0)	0	1 (33.3)	1
Respiratory, thoracic and mediastinal disorders	1 (33.3)	1	0 (0.0)	0
Cough	1 (33.3)	1	0 (0.0)	0
Skin and subcutaneous tissue disorders	3 (100.0)	3	2 (66.7)	2
Alopecia	3 (100.0)	3	2 (66.7)	2

Study SB3-G11-NHV (supportive study)

See clinical pharmacokinetics

Discontinuation due to adverse events

Study SB3-G31-BC

Adverse events leading to IP or non-IP discontinuation

Overall period

During the overall study period, the incidence of TEAEs affecting IP or non-IP discontinuation was comparable between the Ontruzant and Herceptin treatment group. A summary of TEAEs affecting IP or non-IP administration is presented in Table 67.

Table 61: Summary of Adverse Events Affecting IP or non-IP Administration during the Overall Study Period– Safety set (SB3-G31-BC)

Number of subjects experiencing	SB3 N=437 n	(%)	E	Herceptin N=438 n	(%)	E
TEAEs leading to IP discontinuation	15	(3.4)	19	14	(3.2)	14
TEAEs leading to IP dose delay	127	(29.1)	225	128	(29.2)	226
TEAEs leading to IP dose interruption	9	(2.1)	9	12	(2.7)	16
TEAEs leading to Non-IP discontinuation	6	(1.4)	9	8	(1.8)	8
TEAEs leading to Non-IP dose delay/modification	142	(32.5)	265	142	(32.4)	253
TEAEs leading to Non-IP dose interruption	19	(4.3)	24	30	(6.8)	38

The most common reasons by SOC for IP discontinuation in the 2 arms were events in cardiac disorders: 12 events in 11 (2.5%) patients in Ontruzant vs. 6 events in 6 (1.4%) patients in Herceptin. In the Ontruzant treatment group, the most frequently reported TEAEs at the PT level were left ventricular dysfunction (9 events in 8 subjects) and cardiac failure congestive (2 events in 2 subjects). In the Herceptin treatment group, the most frequently reported TEAE reported was left ventricular dysfunction (5 events in 5 subjects). TEAEs leading to non-IP (docetaxel) discontinuation were reported in 4 subjects (0.9%) in the Herceptin treatment group (no subject in the Ontruzant treatment group). The 3 TEAEs leading to non-IP discontinuation were infusion-related reaction (2 events), peripheral motor neuropathy (1 event) and ALT increased (1 event).

TEAEs leading to non-IP (FEC) discontinuation were reported in 6 subjects (1.4%) in the Ontruzant treatment group (9 events) and 4 subjects (0.9%) in the Herceptin treatment group (4 events). In the Ontruzant arm, the 9 TEAEs leading to non-IP discontinuation were: febrile neutropenia, cardia failure congestive, diarrhoea, vomiting, fatigue, cellulitis, WBC decreased, suicide, and renal failure acute. In the Herceptin arm, they were: neutropenia, fatigue, myalgia and hypotension.

Neoadjuvant therapy period

The pattern of events that led to affecting IP or non-IP discontinuation was comparable between the Ontruzant and Herceptin treatment groups during the neoadjuvant therapy period (

Table **68**).

Table 62: Summary of Adverse Events Affecting IP or non-IP Administration during the neoadjuvant Period– Safety set (SB3-G31-BC)

Number of subjects experiencing	SB3 N=437 n	(%)	E	Herceptin N=438 n	(%)	E
TEAEs leading to IP discontinuation	4	(0.9)	7	7	(1.6)	7
TEAEs leading to IP dose delay	110	(25.2)	186	116	(26.5)	204
TEAEs leading to IP dose interruption	8	(1.8)	8	12	(2.7)	16
TEAEs leading to Non-IP discontinuation	6	(1.4)	9	8	(1.8)	8
TEAEs leading to Non-IP dose delay/modification	142	(32.5)	265	140	(32.0)	251
TEAEs leading to Non-IP dose interruption	19	(4.3)	24	30	(6.8)	38

TEAEs leading to IP discontinuation were reported in 4 subjects (0.9%) in the Ontruzant treatment group (7 events) and 7 subjects (1.6%) in the Herceptin treatment group (7 events). As seen in the overall therapy period, cardiotoxicity TEAE were also the most common reasons for IP discontinuation in the neoadjuvant period. In the Ontruzant treatment group, the cardiotoxicity TEAEs leading to IP discontinuation were left ventricular dysfunction (2 events), cardiac failure congestive (1) and supraventricular tachycardia (1). In the Herceptin treatment group, the cardiotoxicity TEAEs were left ventricular dysfunction (2).

TEAEs leading to non-IP discontinuation were reported in 6 (1.4%) subjects in the Ontruzant treatment group and 8 (1.8%) subjects in the Herceptin treatment group.

Adjuvant therapy period

The pattern of events that led to IP discontinuation was comparable between the Ontruzant and Herceptin treatment groups during the adjuvant therapy period (Table 69).

Table 63: Summary of Adverse Events Affecting IP Administration during the adjuvant Period– Safety set (SB3-G31-BC)

Number of subjects experiencing	SB3 N=437 n	(%)	E	Herceptin N=438 n	(%)	E
TEAEs leading to IP discontinuation	11	(2.5)	12	7	(1.6)	7
TEAEs leading to IP dose delay	29	(6.6)	39	20	(4.6)	22
TEAEs leading to IP dose interruption	1	(0.2)	1	0	(0.0)	0

As noticed in the overall and neoadjuvant therapy period, cardiotoxicity TEAE were also the most common reasons for IP discontinuation in the neoadjuvant and the adjuvant period. In the Ontruzant treatment group, the cardiotoxicity TEAEs leading to IP discontinuation were left ventricular dysfunction (7 events) and cardiac failure congestive (1). In the Herceptin treatment group, the cardiotoxicity TEAEs were left ventricular dysfunction (3) and cardiac failure congestive (1).

Adverse events leading to IP dose delay/interruption

Overall period

The pattern of events that led to IP delay/interruption was comparable between the Ontruzant and Herceptin treatment groups.

During the overall period, TEAEs leading to IP dose delay were reported in 127 subjects (29.1%) in the Ontruzant treatment group (225 events) and 128 subjects (29.2%) in the Herceptin treatment group (226 events). The most common reasons by SOC for IP dose delay in the 2 treatment groups were events in blood and lymphatic system disorders (102 events in 69 patients (15.8%) in Ontruzant and 112 events in 71 patients (16.2%) in Herceptin), mainly due to the number of neutropenia (91 events in 65 patients (14.9%) in Ontruzant and 95 events in 68 patients (15.5%) in Herceptin) and investigations.

TEAEs leading to IP dose interruption at the PT level were reported in 9 subjects (2.1%) in the Ontruzant treatment group (9 events) and 12 subjects (2.7%) in the Herceptin treatment group (16 events). The most common reasons for IP dose interruption in the 2 treatment groups were infusion-related reactions: 9 events in 9 [2.1%] subjects in Ontruzant, 12 events in 10 [2.3%] subjects in Herceptin.

Neoadjuvant therapy period

The pattern of events that led to IP delay/interruption was comparable between the Ontruzant and Herceptin treatment groups (

Table **68**). Moreover, similar profiles were observed during overall and neoadjuvant period for both arms.

Adjuvant therapy period

During the adjuvant therapy period, TEAEs leading to IP dose delay were reported in 29 subjects (6.6%) in the Ontruzant treatment group (39 events) and in 20 subjects (4.6%) in the Herceptin treatment group (22 events) (Table 69).

A slight numerical higher patients with TEAEs leading to IP dose delay were noted in the Ontruzant treatment groups with blood and lymphatic system disorders (8 events in Ontruzant and 1 event in Herceptin), gastrointestinal disorders (4 versus none, respectively), and investigations (4 versus none, respectively) of PT terms, whereas higher number of patients with TEAEs leading to IP dose delay were observed in the Herceptin treatment groups with cardiac disorders (1 versus 3, respectively) of PT terms. Although slight difference exists in IP dose delay between the two treatment groups, dose intensity and relative dose intensity of adjuvant IP (investigational product) are comparable between the two treatment groups. Therefore, slightly different number of TEAE leading to IP dose delay during the adjuvant period is not considered clinically relevant.

Only 1 subject had an IP dose interruption in the Ontruzant arm due to infusion related reaction (no subject in the Herceptin arm).

Adverse events leading to non-IP dose delay/modification/interruption

Overall period

The pattern of events that led to non-IP delay/modification/interruption was comparable between the Ontruzant and Herceptin treatment groups (Table 67).

TEAEs leading to non-IP (docetaxel) dose delay/modification were reported in 57 subjects (13.0%) in the Ontruzant treatment group (94 events) and 53 subjects (12.1%) in the Herceptin treatment group (69 events). The most common reasons by SOC in the 2 treatment groups were events in blood and lymphatic system disorders (29 events in Ontruzant and 23 events in Herceptin) and investigations (34 events in Ontruzant and 16 events in Herceptin). In the Ontruzant treatment group, the most frequently reported TEAEs at the PT level were ALT increased (20 [4.6%] subjects), febrile neutropenia (16 [3.7%] subjects) and neutropenia (8 [1.8%] subjects). In the Herceptin treatment group, the TEAEs were febrile neutropenia (17 [3.9%] subjects), ALT increased (8 [1.8%] subjects) and neutropenia (5 [1.1%] subjects).

TEAEs leading to non-IP (FEC) dose delay/modification were reported in 105 subjects (24.0%) in the Ontruzant treatment group (171 events) and 110 subjects (25.1%) in the Herceptin treatment group (187 events). The most common reasons by SOC in the 2 treatment groups were events in blood and lymphatic system disorders (98 events in Ontruzant and 110 events in Herceptin) and investigations (27 events in Ontruzant and 28 events in Herceptin). In the Ontruzant treatment group, the most frequently reported TEAEs at the PT level were neutropenia (64 [14.6%] subjects) and ALT increased and neutrophil count decreased (7 [1.6%] subjects). In the Herceptin treatment group, the TEAEs were neutropenia (67 [15.3%] subjects), leukopenia (11 [2.5%] subjects) and ALT increased (10 [2.3%] subjects) (Final CSR – table 14.3.1-1.15).

TEAEs leading to non-IP (docetaxel) dose interruption were reported in 18 subjects (4.1%) in the Ontruzant treatment group (23 events) and 28 subjects (6.4%) in the Herceptin treatment group (36 events). In the Ontruzant treatment group, the TEAEs at the PT level were infusion-related reaction (17

[3.9%] subjects) and extravasation (1 [0.2%] subject). In the Herceptin treatment group, the TEAEs were infusion-related reaction (28 [6.4%] subjects) and myalgia (1 [0.2%] subject) (Final CSR: table 14.3.1-1.16).

FEC dose interruption was less common event than docetaxel dose interruption: none in the Ontruzant arm, and 2 subjects (0.5%) in the Herceptin arm (2 events: 1 neutropenia and 1 infusion related reaction) (Final CSR: table 14.3.1-1.16).

Neoadjuvant therapy period

Similarly to the overall period, during the neoadjuvant therapy period, the pattern of events that led to non-IP delay/modification/interruption was comparable between the Ontruzant and Herceptin treatment groups (

Table **68**).

TEAEs leading to non-IP (docetaxel) dose delay/modification were reported in 57 subjects (13.0%) in the Ontruzant treatment group (94 events) and 52 subjects (11.9%) in the Herceptin treatment group (68 events) (Final CSR: table 14.3.1-2.15).

TEAEs leading to non-IP (FEC) dose delay/modification were reported in 105 subjects (24.0%) in the Ontruzant treatment group (171 events) and 109 subjects (24.9%) in the Herceptin treatment group (186 events) (Final CSR: table 14.3.1-2.15).

TEAEs leading to non-IP (docetaxel) dose interruption were reported in 18 subjects (4.1%) in the Ontruzant treatment group (23 events) and 28 subjects (6.4%) in the Herceptin treatment group (36 events) (Final CSR: table 14.3.1-2.16).

FEC dose interruption was less common event than docetaxel dose interruption: none in the Ontruzant arm, and 2 subjects (0.5%) in the Herceptin arm (2 events: 1 neutropenia and 1 infusion related reaction) (Final CSR: table 14.3.1-2.16).

Study SB3-G11-NHV (supportive study)

No subjects were discontinued from the study due to AEs.

2.6.1. Discussion on clinical safety

Trastuzumab has been widely used in clinical practice with a well-characterised safety profile from published clinical studies and a large amount of post-marketing safety data. As Ontruzant is a proposed biosimilar to Herceptin, the safety/tolerability of trastuzumab from Ontruzant has been compared against the safety/tolerability profile of Herceptin to show similarity. Key safety information was derived from the clinical Phase III study (SB3-G31-BC) in EBC or LABC patients, supported by the clinical Phase I study (SB3-G11-NHV) in healthy subjects.

In study SB3-G31-BC, the median duration of safety observation was 437 days (range 94–593 days) in the Ontruzant treatment group and 438 days (range 24–651 days) in the Herceptin treatment group.

Slightly less patients withdraw before surgery in the Ontruzant arm compared to Herceptin (4.1% and 5%, respectively), and slightly more patients withdraw during adjuvant therapy (8.7% and 7.3%, respectively). This last difference was mainly due to more adverse events (2.5% and 1.1%, respectively).

IP exposure was comparable between the 2 arms with similar: exposure duration (during the neoadjuvant, adjuvant and overall therapy period), dose intensity of IP (during the neoadjuvant, adjuvant and overall therapy period), cumulative dose of IP, cycle delay of IP, dose interruption of IP, and relative dose intensity (during the neoadjuvant, adjuvant and overall therapy period) (

Table 44). A similar number of cycles was completed in each arm, with a similar number of subjects who completed each cycle

The non-IP exposure was also similar between the 2 arms: similar dose intensity, relative dose intensity, exposure duration and cumulative dose of docetaxel from cycle 1 to cycle 4, and of FEC regimen from cycle 5 to cycle 8.

In terms of adverse events in the overall study period, although the number of reported TEAEs was higher in Ontruzant group (5433) compared to Herceptin group (5245), the number of patients reporting a TEAE of any grade at any point during the study was comparable: 426 (97.5%) and 421 (96.1%) patients in the Ontruzant and EU Herceptin treatment groups, respectively. The numerical difference of 188 TEAE was

derived from the large variation in the number of AEs reported in each patient; a small number of patients reported a relatively high number of AEs, up to 65 events, and the same AEs were reported repeatedly in the same patients.

Most of the patients had grade 3 or 4 TEAE in both groups. The incidence of severe (Grade ≥ 3) TEAEs during overall study period was comparable between the two treatment groups: 860 TEAE in 325 (74.4%) patients in Ontruzant and 842 TEAE in 315 (71.9%) patients in EU Herceptin. However, most of the TEAE were Grade 1 or 2 in both groups: 2844 grade 1 TEAE and 1729 grade 2 TEAE in Ontruzant, and 2805 grade 1 TEAE and 1598 grade 2 TEAE in Herceptin. In both treatment groups, most of the TEAEs were recovered/resolved without sequelae, and patients had TEAE mostly unrelated to IP (average of 63.5% of the TEAE), but related to non-IP (average of 92.5% of the TEAE).

The most common adverse events with Ontruzant, including alopecia, neutropenia, nausea, leukopenia and anaemia, were in line with those of Herceptin in pivotal clinical studies and in the post-marketing setting. The most frequently occurring TEAEs was alopecia (68.4% in Ontruzant and 64.6% in EU Herceptin), known to be associated with using docetaxel. Although slightly higher in Ontruzant, the incidence of the most of the common TEAE was, overall, comparable with less than 5% difference between the 2 treatment groups. Diarrhoea was the event which differed by more than 5% between the two treatment groups (21.1% of patients in Ontruzant and 15.3% of patients in EU Herceptin treatment group), however the number of patients with severe diarrhoea was the same, 6 in each treatment group.

In terms of serious adverse events, although the number of reported serious TEAEs was higher in Ontruzant group (98) compared to Herceptin group (79), the number of patients reporting a serious TEAE during the study was comparable: 56 (12.8%) patients for Ontruzant and 58 (13.2%) patients for EU Herceptin. The numerical difference of 19 in the incidence of SAEs was derived from a small number of patients who reported up to 12 SAEs. In both treatment groups, most of the patients had Grade 3 or 4 SAEs. The SAEs were, for the majority, unrelated to IP (average of 10.75%) but related to non-IP (average of 8.15%). Most of them recovered/resolved without sequelae.

The most frequently occurring severe TEAEs were neutropenia (57.0% in the Ontruzant treatment group and 55.3% in the Herceptin treatment group), leukopenia (17.6% and 14.2%, respectively), neutrophil count decreased (11.2% and 10.3%, respectively), febrile neutropenia (6.4% and 7.8%, respectively) and ALT increased (3.2% and 2.5%, respectively). While the frequency of neutropenia and leukopenia was slightly higher in the Ontruzant group, it was not considered significant.

6 deaths were reported (one was in the Ontruzant arm and 5 in the Herceptin arm); none were considered to be related to the IP.

Incidences of TEAEs of special interest (infusion-related reaction, congestive heart failure (CHF), left ventricular systolic dysfunction and pulmonary toxicity) were also comparable between Ontruzant and the EU Herceptin treatment groups.

The incidence of common symptoms of infusion-related reactions was balanced across both treatment groups. Overall, the time pattern was comparable. The incidence of infusion-related reactions was highest during the first two treatment cycles for both treatment groups, and the incidence decreased over time in both treatment groups.

Cardiac toxicity is the most concerning adverse effect of trastuzumab usually characterised as cumulative toxicity and manifesting as an asymptomatic decline in left ventricular ejection fraction (LVEF) rather than symptomatic congestive heart failure (CHF). The overall incidence of cardiac toxicity was comparable between treatment arms and comparable to that reported for trastuzumab combination with anthracyclines. There was also no indication of any clinically relevant differences between Ontruzant and the reference product. A phase III Long-term Follow-up Study for Cardiac Safety SB3-G31-BC-E was

initiated by the applicant prior to the submission of the MAA. The purpose of this study is to observe the incidence of symptomatic CHF NYHA class II, III, and IV and asymptomatic significant LVEF decrease in patients who participated in the SB3-G31-BC study and treated with Ontruzant (proposed trastuzumab biosimilar) or Herceptin as neoadjuvant and adjuvant treatment. An additional objective of this study will be to observe the long term effectiveness of Ontruzant compared to Herceptin (see discussion in the efficacy part).

Although there were numerically more pulmonary events in the Ontruzant treatment group (35 patients) [8%] vs 23 patients [5.3%]), the proportion of patients with severe (Grade ≥ 3) pulmonary TEAEs were similar in two treatment groups (5 (1.1%) patients in Ontruzant and 4 (0.9%) patients in EU Herceptin treatment group).

The overall incidence of TEAEs affecting IP or non-IP administration was comparable between the 2 treatment groups: 15 (3.4%) and 14 (3.2%) patients reported IP discontinuation; 127 (29.1%) and 128 (29.2%) patients reported IP dose delay; 9 (2.1%) and 12 (2.7%) patients reported IP dose interruption in Ontruzant and EU Herceptin treatment groups; and 6 (1.4%) and 8 (1.8%) patients reported non-IP discontinuation respectively.

In summary, the incidence, severity and outcome of reported TEAEs (including SAEs and TEAEs of special interest) were generally comparable between the Ontruzant and EU Herceptin treatment groups in the adjuvant, the neoadjuvant and the overall study periods. All the AEs reported during study were within the expected ranges for this population and treatment, and no new or unexpected safety findings were observed.

With regards to immunogenicity, the incidence of ADA to trastuzumab was similar in Ontruzant and EU Herceptin treatment groups at each timepoint (low immunogenicity) (Table 65) for up to 1 year. Antidrug antibodies against trastuzumab have been observed transiently during the study in <1% of patients and in very low titres. Although interpretation are limited due to the low incidence of positive ADA results, no significant clinical impact of ADA-positive results were found in terms of efficacy, PK, and safety profiles in both treatment groups.

With regards to the supportive study (Study SB3-G11-NHV) in healthy volunteers, although its value for comparability exercise is limited from safety point of view given single dose administered, small sample size and healthy volunteers enrolled, safety/tolerability and immunogenicity between the 3 presentations (Ontruzant, EU Herceptin, and US Herceptin) was comparable.

There were no significant changes from baseline in the values in any treatment group for haematology, biochemistry, urinalysis and cardiac markers parameters.

There have been no exposures during pregnancy in the SB3 Phase III study. Oligohydramnios is a complication in approximately 4.5% of all pregnancies and severe oligohydramnios is a complication in 0.7% of pregnancies. Similarly to Herceptin, Ontruzant should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. Section 4.6 of the SmPC warns about the risk of oligohydramnios and foetal harm.

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

The applicant claimed the same therapeutic indications for the biosimilar Ontruzant as granted for Herceptin for intravenous administration in the EU. Ontruzant showed similarity to Herceptin in terms of safety based on available data up to 52 weeks in in EBC or LABC patients. The results are comparable to data published for the reference product. Overall, no clinically meaningful differences were observed

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

Considering Herceptin is also marketed for subcutaneous administration and the Applicant applied only for intravenous administration, a risk of medication error was identified. Adequate risk minimisation measures to avoid the potential route of administration error have been included in the RMP.

2.6.2. Conclusions on the clinical safety

The main data relevant for comparability exercise in terms of safety comes from the completed 1-year study SB3-G31-BC on women with HER2-positive early breast cancer (EBC) or LABC. The overall safety profile as reflected by the most frequently reported TEAEs, severity of the TEAEs and number reported as related, appears broadly similar between Ontruzant and Herceptin and in line with those expected on the basis of the EU Herceptin SmPC. The immunogenicity profiles were also comparable in terms of overall ADA incidences and neutralising antibodies between the Ontruzant and EU Herceptin treatment groups.

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

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Cardiac dysfunction Administration related reactions Haematotoxicity Oligohydramnios Pulmonary Disorders
Important potential risks	Infections Medication Error
Missing information	Treatment in male patients (breast cancer indications only)

Pharmacovigilance plan

Ongoing and planned studies in the PhV development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
SB3-G31-BC-E A long-term follow up study for cardiac safety in patients with HER2 positive early or locally advanced breast cancer who have completed the SB3-G31-BC (Category 3)	Primary Objective: To observe the incidence of symptomatic CHF NYHA class II, III and IV and asymptomatic significant LVEF decrease in patients who participated in the SB3-G31-BC study and were treated with SB3 or Herceptin as neoadjuvant and adjuvant treatment. Secondary Objectives: To observe the incidence of cardiac death and other significant cardiac conditions To observe the long term efficacy of SB3 compared to Herceptin by - event-free survival - overall survival	Cardiac dysfunction	Started: Apr 28, 2016	Final report: 1Q 2022 (planned)

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Cardiac Dysfunction	Warning in section 4.4 of the SmPC concerning the risk of cardiac dysfunction and the need for caution in patients with increased cardiac risk. Recommendations concerning cardiac assessment and monitoring before, during and after treatment with trastuzumab. Criteria for discontinuing or interrupting treatment with trastuzumab based on LVEF. The need to institute CHF treatment. Cardiac undesirable effects listed in section 4.8 of the SmPC including Ejection fraction decreased, Cardiac failure congestive, Cardiogenic	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	shock, Acute pulmonary oedema, Pulmonary oedema and Orthopnoea. Prescription only medicine.	
Administration-related Reactions	Section 4.2 of the SmPC describes the correct method of administration for the first and subsequent infusions and the recommended observation times following these infusions. The need to be prepared for managing anaphylaxis and possible actions including interrupting or slowing the infusion rate if infusion-related reactions occur are also described. Section 4.4 warns about the risk of infusion-related-reactions and informs that patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. This section also provides information concerning pre-medication and treatment for these reactions and warns about the possibility of delayed reactions. Section 4.8 of the SmPC lists the following undesirable effects: Infusion related reaction, Erythema, Rash, Swelling face, Wheezing, Dyspnoea, Cough and Lip swelling, Hypersensitivity, Maculopapular rash, Pruritus, Asthma and Hypotension, Urticaria, Anaphylactic reaction, Anaphylactic shock, Angioedema, Respiratory distress, Respiratory failure, Bronchospasm and Laryngeal oedema. Prescription only medicine.	None
Haematotoxicity	The following undesirable effects are listed in section 4.8 of the SmPC: Febrile neutropenia, Anaemia, Neutropenia, White blood cell count decreased/leukopenia and Thrombocytopenia. Prescription only medicine.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Oligohydramnios	Section 4.6 of the SmPC warns about the risk of oligohydramnios and foetal harm and advises that women of childbearing potential should use effective contraception during treatment and for 7 months after treatment with trastuzumab. It also states that trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. If a pregnant woman is treated with trastuzumab, or if a patient becomes pregnant while receiving trastuzumab or within 7 months following the last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable. Section 4.8 of the SmPC lists the following undesirable effects: Oligohydramnios, Pulmonary hypoplasia and Renal hypoplasia. Prescription only medicine.	None
Pulmonary Disorders	Section 4.3 contraindicates use of trastuzumab in patients with severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy. Section 4.4 warns about the risk of severe pulmonary events including interstitial lung disease together with associated risk factors. These events may occur as part of an infusion-related reaction or with a delayed onset. Section 4.8 of the SmPC lists the following undesirable effects: Pulmonary fibrosis, Lung infiltration and Interstitial lung disease. Prescription only medicine.	None
Infections	Section 4.8 of the SmPC lists the following undesirable effects: Infection, Nasopharyngitis, Neutropenic sepsis, Cystitis, Herpes zoster, Influenza, Sinusitis, Skin	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	infection, Rhinitis, Upper respiratory tract infection, Urinary tract infection, Erysipelas, Cellulitis, Pharyngitis and Sepsis. Prescription only medicine.	
Medication Error	Section 4.2 of the SmPC states that Ontruzant treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy. It emphasises the importance of checking the product label to avoid medication errors and stresses that Ontruzant intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only. Prescription only medicine	None
Treatment in male patients (breast cancer indications only)	Prescription only medicine.	None

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

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Ontruzant is developed as a biosimilar to Herceptin. The approval is sought for intravenous use in all approved indications of the reference product: treatment of adult patients with HER2 positive metastatic breast cancer, early breast cancer and metastatic gastric cancer.

3.1.2. Main studies

From the quality perspective, a comprehensive similarity study has been performed to assess the biosimilar comparability of Ontruzant with Herceptin, including characterisation of structural, physicochemical and biological properties of Ontruzant clinical material and PVR batches, in side-by-side assays with the EU Herceptin (Reference Product).

The non-clinical comparability programme consisted in a series of *in vitro* PD studies assessing the biological activity of Ontruzant compared to EU or US Herceptin using various cell-based and binding assays. An *in vivo* study assessing the therapeutic efficacy of Ontruzant compared to EU Herceptin and US Herceptin in the orthotopic BT-474 human breast cancer cell xenograft mouse model was also submitted as supportive information.

The clinical trial programme conducted to assess biosimilarity between Ontruzant and Herceptin was based on two trials:

- Study SB3-G11-NHV, Phase I PK study in male healthy volunteers.
- Study SB3-G31-BC, Phase III study comparing the efficacy and safety of Ontruzant and Herceptin in women with newly diagnosed HER2 positive early or locally advanced breast cancer.

3.2. Favourable effects

From a quality perspective, it is considered that similarity between Ontruzant and EU Herceptin was shown by characterisation of structural, physicochemical and biological properties in side-by-side assays. Results from primary, secondary and tertiary structures of the trastuzumab molecule showed that these were comparable. Minor differences were observed (slightly lower levels of N-terminal pyroglutamate, slightly higher C-terminal lysine and C-terminal α-amidated Pro content in Ontruzant batches which are not expected to impact safety/ efficacy and minor differences in methionine oxidation and deamidation profiles which did not impact biological activity). In addition, biosimilarity also encompassed evaluation of

the glycosylation profile (only minor differences in the relative content of N-glycans; degradation profile; charge variants, HER2 binding and anti-proliferation activity; ADCC activity; binding affinity to Fc receptors (FcγRIa, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb and FcRn) and the complement component C1q (genotype for FcγRIIIa requested); additional biological assays (HER2 ECD shedding, surface HER2 expression, inhibition of AKT, angiogenesis, combination with chemotherapy and CDC assay).

From a non-clinical perspective, the *in vitro* assays performed on an appropriate number of batches have shown similarity between Ontruzant and the EU Herceptin reference product in terms of HER2 binding, inhibition of proliferation, ADCC, ADCP, C1q binding, Fc receptor binding. HER2 expression level, HER2 ECD shedding, inhibition of AKT phosphorylation. *In vitro* angiogenesis and combination treatment with chemotherapy completed the in vitro similarity assessment.

From a pharmacokinetics perspective, comparability between Ontruzant and Herceptin has been demonstrated in study SB3-G11-NHV since the ratios (90% CI) of geometric means for both primary PK endpoints AUC0-last and C_{max} were within the acceptability range of 80-125%. In study SB3-G31-BC, a statistical comparison for the C_{trough} concentrations pre-dose of Cycle 8 support similarity for the C_{trough} concentrations between treatments. The minimum target concentration of 20 µg/ml was reached at cycle 3 for both products and steady state appeared to be reached at Cycle 7.

Based on the efficacy results of the phase III study in patients with HER2 positive EBC/LABC, Ontruzant was concluded to be equivalent to Herceptin. Results for other efficacy endpoints (EFS and OS) are still immature but do not suggest significant differences at one year time point. Although the difference in bpCR was slightly outside the pre-specified equivalence range in the upper bound limit, this observation was considered at least in part confounded by a small shift in ADCC activity in a number of the EU Herceptin batches used in the pivotal trial. Overall it is doubtful that a small shift as the one observed would have any significant impact in terms of clinical outcomes although numerically it is thought to have contributed to a more extreme location of the point estimate and upper bound of the confidence interval, shifting the latter beyond the pre-specified equivalence margin. Based on additional analysis and considering the evidence of similarity provided in terms of quality, non-clinical, PK, clinical efficacy and safety, biosimilarity has been sufficiently shown for Ontruzant compared to the reference product Herceptin.

3.3. Uncertainties and limitations about favourable effects

The exact magnitude of the effect of the observed ADCC shift for Herceptin on bpCR and clinical important endpoints is not known but the effect is likely to be small and not of clinical relevance. In view of the totality of the data, this remaining uncertainty does not question the biosimilarity between Ontruzant and Herceptin.

3.4. Unfavourable effects

Safety data were provided from the clinical studies in healthy volunteers and women with HER2-positive early breast cancer (EBC) or LABC (randomised phase III study SB3-G31-BC).

The main data for comparability exercise in terms of safety comes from the study SB3-G31-BC (1-year data). The overall incidences of TEAEs and their severity were generally comparable between the test and the reference product and in line with those expected on the basis of the Herceptin SmPC.

The most frequently reported ADRs corresponded to blood and lymphatic system disorders (76.0% in the Ontruzant and 71.9% in the Herceptin treatment groups), skin and subcutaneous tissue disorders (73.9% and 70.8%, respectively) and gastrointestinal disorders (48.3% and 46.8%, respectively).

The most frequently occurring TEAEs were alopecia, neutropenia, nausea, leukopenia, anaemia (and diarrhoea, with comparable incidence and severity observed.

Incidences of TEAEs of special interest (infusion-related reactions, CHF, left ventricular systolic dysfunction) were comparable between the Ontruzant and EU Herceptin treatment groups. Pulmonary toxicity which is considered also as AESI was comparable in both groups.

No increased immunogenicity has been observed with Ontruzant compared with EU Herceptin. The overall incidence of ADA to trastuzumab up to end of study was low in both treatment groups (3 [0.7%] subjects in each group).

In conclusion, there were no clinically meaningful differences in safety profiles between the Ontruzant treatment group and EU Herceptin treatment groups in EBC or LABC patients up to data cut-off date (Feb 14, 2017). Furthermore, other than safety issues identified from the use of Herceptin, no additional safety issues were identified during the study period.

There is no indication from the observed safety profile that efficacy finding in terms of apparent higher bpCR rates in the Ontruzant arm are associated with worsening of the safety profile up to one year of observation.

3.5. Uncertainties and limitations about unfavourable effects

There are no remaining uncertainties regarding the comparability of the clinical safety of Ontruzant with Herceptin. While there was also no indication of any clinically relevant differences between Ontruzant and the reference product in terms of cardiac toxicity, a Phase III long-term follow-up study initiated by the Applicant (SB3-G31-BC-E) is currently ongoing and will provide relevant safety information on cardiac dysfunction (see RMP).

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

From a quality and non-clinical perspective, *in vitro* and *in vivo* functional assays such as HER 2 binding, inhibition of proliferation, ADCC, ADCP, C1q binding and Fc receptor binding have demonstrated that Ontruzant is similar to Herceptin.

Similarity of Ontruzant and Herceptin was also shown from a PK perspective. PD, with the exception those provided with exploratory analyses for the potential impact of the ADCC quality shift, data have not been provided and this is justified by the absence of validated biomarkers.

Ontruzant can be considered similar in terms of efficacy to the reference product Herceptin.

The descriptive comparison of safety, immunogenicity, efficacy (EFS and OS), and tolerability profile of Ontruzant and Herceptin given in combination with a taxane did not reveal any clinically relevant differences between both treatments up to 1 year.

3.6.2. Balance of benefits and risks

Biosimilarity of Ontruzant to Herceptin has been shown based on the provided quality, non-clinical and clinical comparability data from study SB3-G31-BC comparing the efficacy and safety of Ontruzant and

Herceptin conducted in women with newly diagnosed HER2 positive early or locally advanced breast cancer.

Ontruzant was also shown similar to Herceptin in terms of safety based on available data from SB3-G31-BC up to 24 weeks. The results are comparable to data published for the reference product. While some differences in terms of clinical safety have been reported between indications, these are likely to be the result of the use of concomitant medication and other factors aforementioned rather than differences related to trastuzumab.

3.6.3. Additional considerations on the benefit-risk balance

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

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

3.7. Conclusions

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

Breast cancer

Metastatic breast cancer

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

(MBC):

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

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

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

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

Early breast cancer

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

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

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

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

- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

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

Metastatic gastric cancer

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

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

4. Recommendations

Outcome

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

Breast cancer

Metastatic breast cancer

Ontruzant 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

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

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- 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 Ontruzant therapy, for locally advanced (including inflammatory) disease or tumours >2 cm in diameter (see sections 4.4 and 5.1).

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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