25 July 2024
EMA/CHMP/367870/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tuznue

International non-proprietary name: trastuzumab

Procedure No. EMEA/H/C/006252/0000

Note

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

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Table of contents

List of abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATF	Alternating tangential flow
AUC	Area Under Curve
bpCR	Breast Pathological Complete Response
BSE	Bovine spongiform encephalopathy
CAPA	Corrective and Preventive Action
CD	Circular dichroism
CDC	Complement dependent cytotoxicity
CE	Capillary electrophoresis
CEX-HPLC	Cation exchange
CEX-HPLC	Cation exchange high performance liquid chromatography
CI	Confidence Interval
cIEF	Capillary isoelectric focusing
CL	Rate of Clearance
CMA	Critical material attributes
Cmax	Maximum concentration
CMO	Contract manufacturer organisation
COA	Certificate of analysis
CPU	Clinical Pharmacology Unit
CR	Complete Response
CRO	Clinical Research Organization
CSR	Clinical Study Report
Ctrough	Through Concentration
CV	Coefficient of Variation
DLS	Dynamic light scattering
DP	Drug product
DS	Drug substance
DSP	Downstream Process
DSC	Differential scanning calorimetry
EBC	Early Breast Cancer
ECG	Electrocardiogram
eCRF	Electronica case reprot form
EFS	Event-Free Survival
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ER	Estrogen Receptor
FAS	Full Analysis Set
FISH	Fluorensence in Situ Hybridization
FTIR	Fourier transform infrared spectroscopy
GS/MS	Gas chromatography mass spectrometry
HER2	Human Epidermal Growth Factor Receptor 2
HMW	High molecular weight
HOQ	Higher limit of quantitation
HPAEC-PAD	High performance anion exchange chromatography with pulsed amperometric detection

HPLC	High performance liquid chromatography
i.v. / IV	Intravenous
ICP-OES	Inductively-coupled plasma optical emission spectroscopy
IHC	Immunohistochemistry
IPC	In-process controls
LC-MS	Liquid chromatography mass spectrometry
LMW	Low molecular weight
LOQ	Lower limit of quantitation
MBC	Metastatic Breast Cancer
MBR	Master batch record
MCB	Master cell bank
mFAS	Modified Full Analysis Set
MGC	Metastatic Gastric Cancer
Nab	Neutralising Antibody
NF	National formulary
NGH	Non-glycosylated heavy chain
NPN	N-phenyl-1-napthylamine
OD	Optimal density
ORR	Overall Response Rate
OS	Overall Survival
PACM	Post approval change management
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
PNPP	p-nitrophenyl phosphate
PPP	Per Protocol Population
PPS	Per Protocol Set
PR	Partial Response
PT	Preferred Term
PW	Purified water
QA	Quality assurance
QC	Quality Control
QRD	Quality control research and development
QTPP	Quality target product profile
RH	Relative humidity
RMP	Reference medicinal product
RP-HPLC	Reverse phase liquid chromatography
rPPS	Restricted per population set
RSP	Reference standard dilution
RT	Retention time
SAE	Serious Adverse Event
SD	Standard deviation
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SE	Size exclusion
SE-HPLC	Size exclusion high precision liquid chromatography
SISH	Silver in Situ Hybridization
SOC	System Organ Class
SOP	Standard operating procedure
SPR	Surface plasma resonance
SUB	Single use bioreactor

T1/2	Terminal Half-life
TEAE	Treatment Emergent Adverse Event
TIC	Total ion chromatogram
tpCR	Total Pathological Complete Response
TSE	Transmitting animal spongiform encephalopathy
UF/DF	Ultrafiltration/diafiltration
ULN	Upper limit of normal
USP	Upstream Process
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
VI	Virus inactivation
Vss	Volume of Distribution at Steady State
WCB	Working cell bank
WFI	Water for injection
ypN0	Post treatment pathological lymph node complete response

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Prestige Biopharma Belgium submitted on 31 July 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Tuznue, 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:

Metastatic breast cancer (MBC)

For the treatment of adult patients with HER2-positive MBC:

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

Early breast cancer (EBC)

For the treatment of adult patients with HER2-positive EBC:

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant HD201 therapy, for locally advanced (including inflammatory) disease or tumours >2 cm in diameter.

HD201 should only be used in patients with MBC or EBC whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

Metastatic gastric cancer (MGC)

In combination with capecitabine or 5-fluorouracil and cisplatin 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.

HD201 should only be used in patients with MGC whose tumours have HER2 overexpression as defined by Immunohistochemistry (IHC) 2+ and a confirmatory silver-enhanced in situ hybridisation (SISH) or fluorescence in situ hybridisation (FISH) result, or by an IHC 3+ result. Accurate and validated assay methods should be used.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

The chosen reference product is: Herceptin.

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

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

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

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

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

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

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

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

Date	Reference	SAWP co-ordinators
9 November 2009	EMEA/H/SA/2212/1/FU/2017/II	David Brown and Joao Manuel Lopes de Oliveira
17 November 2017	EMEA/H/SA/2212/1/2011/III	David Brown and Olli Tenhunen

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

- the comparability testing programme to support the claim of biosimilarity to Herceptin; the specifications for the drug substance and drug product; the stability programme;
- the comparative PD programme to assess biosimilarity against the reference products; the in vivo non-clinical studies to assess the comparative PK and toxicity profiles;
- the design of the Phase I study in healthy volunteers;
- the design of the Phase III study in patients with HER2+ MBC to compare the efficacy and safety profile of HD201 to Herceptin, in particular: the choice of the patient population, the primary endpoint (ORR after 8 cycles of treatment), the equivalence margins;
- the MAA submission strategy, including the strategy to extrapolate safety and efficacy data to the other therapeutic indications, to characterise the immunogenicity profile, and size of the safety database.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Christian Gartner

The application was received by the EMA on	31 July 2023
The procedure started on	17 August 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 November 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint	06 May 2024

Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	30 May 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 July 2024
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 Tuznue on	25 July 2024

2. Scientific discussion

2.1. Problem statement

Not applicable.

2.2. About the product

HD201 (Tuznue) has been developed as a similar biological medicinal product to the reference medicinal product Herceptin (Roche Registration Limited).

Trastuzumab (Herceptin) is currently authorised for the treatment of breast cancer and gastric cancer. Herceptin is available as a 150 mg powder for concentrate for solution for infusion for intravenous (IV) use and as a 600 mg solution for injection (SC) for subcutaneous use (EPAR Herceptin).

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody targeted against the human epidermal growth factor receptor 2 (HER2). Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and thereby inhibits the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of ADCC and ADCP. The same therapeutic indications as granted for Herceptin for intravenous administration in the EU (EU/1/00/145/001) is proposed for HD201.

HD201 is supplied in 2 presentations containing 150 mg or 420 mg per single-use vials. The finished product is intended for reconstitution with 7.2 mL (150 mg) or 20 mL (420 mg) of sterile water for Injection (SWI). Upon reconstitution, each vial contains approximately 21 mg/mL of trastuzumab, and the reconstituted product is intended for dilution in saline (0.9% sodium chloride) for intravenous administration.

The formulation, dosage, strength upon reconstitution, and administration are the same as for the reference product, Herceptin, and the same formulation of HD201 was used throughout the clinical development program. However, HD201 is intended only for intravenous use and the Applicant did not apply for the subcutaneous route of administration (authorised for Herceptin -600 mg strength, solution for injection pharmaceutical form). The 420 mg strength (powder for concentrate for solution for injection) is not currently authorised for Herceptin.

HD201 is a powder for concentrate for solution for infusion containing 150 mg or 420 mg of trastuzumab per single-use vials.

The same therapeutic indications, dosage and route of administration as granted for Herceptin for intravenous administration in the EU (EU/1/00/145/001) are proposed for HD201, in the treatment of HER2-positive metastatic breast cancer (MBC), early breast cancer (EBC), and metastatic gastric cancer (MGC)

2.3. Type of application and aspects on development

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

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

2.4. Quality aspects

2.4.1. Introduction

Tuznue (company code HD201) has been developed as biosimilar to Herceptin. The formulation, dosage, strength upon reconstitution, and administration are the same as for Herceptin.

The finished product (FP) is presented as powder for concentrate for solution for infusion, available in two presentations containing 150 mg and 420 mg of trastuzumab as active substance (AS). Other ingredients are: L-histidine hydrochloride monohydrate, L-histidine, α,α-trehalose dihydrate, and polysorbate 20.

The product is available in 20 mL (150 mg presentation) and 50 mL (420 mg presentation) clear glass type I vials with butyl rubber stopper. Each carton contains one vial.

2.4.2. Active substance

2.4.2.1. General information

The active substance trastuzumab is a humanised monoclonal antibody (mAb). The recombinant glycoprotein consists of four polypeptides; 2 light chains and 2 heavy chains with an approximate molecular weight of 148 kDa. There are 214 amino acids in a light chain and 449 amino acids in a heavy chain. The light and heavy chains are linked by 4 inter- and 12 intra-chain disulfide bonds. Each heavy chain contains N-linked glycans at the consensus glycosylation site at Asn^{300}.

The murine complementarity-determining region of the antibody binds directly to the extracellular domain of the HER2 receptor, inhibiting ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism.

Prevention of HER2 mediated signalling ultimately results in the inhibition of proliferation in tumours that overexpress HER2. Additionally, trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).

2.4.2.2. Manufacture, characterisation and process controls

HD201 AS is manufactured at Prestige Biologics CO., Ltd. South Korea. Proof of GMP compliance is provided. The site was inspected by AEMPS and the GMP certificate was issued.

The active substance trastuzumab is expressed in genetically modified CHO-K1 cells. Definitions of batch and scale are provided; traceability of active substance batches is ensured by a unique batch code. The upstream process involves thawing of working cell bank (WCB) vials, seed expansion, and harvest by filtration. The seed culture broth is transferred into a bioreactor. The cell culture process is tightly controlled by process parameters (PP). IPCs and IPTs are defined with adequate acceptance criteria. Clarified harvest is further processed by downstream manufacturing.

The downstream processing consists of clarified harvest purification through a series of purification steps, virus filtration, final formulation, and filling.

HD201 AS manufactured in South Korea will be shipped to the finished product manufacturer in Spain in bulk format.

The Applicant provided a detailed description of the manufacturing process steps that is accompanied by flow charts and tables listing process parameters and in-process controls (IPCs) with their classification and acceptable ranges/acceptance criteria/action limits.

Control of materials

The raw materials used to manufacture HD201 AS are listed. All materials with Certificates of Analysis (CoA) were purchased from qualified suppliers and tested according to established procedures available in the European (Ph. Eur.) and United States Pharmacopoeias (USP) or according to in-house standards prior to release for use. Tests and acceptance criteria are presented for raw materials tested according to in-house standards. No animal derived materials are used in the manufacture of HD201. Acceptable in-house acceptance criteria are provided for the non-compendial raw materials. The composition of the cell culture media and feed solutions is described. The excipients, i.e. histidine, histidine monohydrochloride monohydrate, trehalose dihydrate, polysorbate 20, comply with Ph. Eur. The provided information is considered sufficient.

The production strain for HD201 was derived from CHO-K1 (Chinese Hamster Ovary-K1) cell line. A two-tiered cell banking system, consisting of a Master cell bank (MCB) and a Working cell bank (WCB) was established for HD201 and characterised according to ICH Guidelines Q5A (R1), Q5B and Q5D.

Control of critical steps and intermediates

To ensure a robust and consistent manufacturing process, control strategies are established based on comprehensive understanding of the process and product to maintain critical quality attributes (CQA) within their action limits. The process parameters and normal operating ranges (NOR) were defined based on knowledge from developmental studies and experience gained during process validation. A risk matrix was established and design of experiments (DoE) studies were performed to confirm the classification of the parameters, such as CPP or non-CPP, depending on their impacts on the CQAs and whether the NOR of each parameter was appropriate. CPPs have NORs and action limits. Exceeding the action limit for a CPP triggers the filing of a deviation. The control strategy implemented for the manufacturing process is considered acceptable. The process is run under narrow NOR conditions. The classification pf process parameters (inputs) and process controls (outputs) is considered acceptable.

Process validation and/or evaluation

Based on the results from the process validation (PV) of eight consecutive batches for the upstream main cell culture processes the quality control activities confirmed that the quality aspects met the acceptance criteria which is sufficient.

The results for process validation of eight consecutive batches for the downstream purification process confirmed that the quality aspects of the final formulated AS met the acceptance criteria. Process-related impurities are monitored and controlled through release testing of HD201. Efficient removal of impurities was demonstrated. Product-related impurities are controlled by release testing.

A protocol for UF/DF membrane re-usage is presented by the Applicant and respective IPCs/IPTs are defined for this process step. The lifetime of the resin was validated through repeated use of the chromatography resin in the downstream process of HD201. Resin lifetimes and potential carry-over have been investigated in a qualified scale down model. In terms of product quality and performance attributes the presented data show consistent performance of the resins (CEX, HIC, AEX), and would support the proposed target resin lifetimes. No carry-over was observed showing that the column sanitization procedures are effective.

Validation of process hold times was conducted on three batches of HD201 AS.

HD201 AS is shipped from South Korea to Spain in bulk format). The bags are packed into boxes and transported in temperature-controlled containers.

Manufacturing process development

The quality attributes (QAs) were evaluated for their criticality according to ICH Q9 using a risk-based approach determined by impact score and uncertainty. The QAs were assessed based on impact on efficacy, pharmacokinetics, immunogenicity and safety. The attributes were ranked into high, moderate, and low and assigned to three different tiers. Attributes with a direct influence on the mechanism of action were assigned to Tier 1, attributes with moderate criticality were assigned to Tier 2 and attributes with low criticality were assigned to Tier 3. The information on the CQA assessment and ranking of critical quality attributes is satisfactory. Overall, criticality ratings and their justification appear reasonable.

Twenty-six lots of HD201 AS have been manufactured, starting from the production of early development lots in October 2010 up until process validation lots in July 2021. The manufacture of HD201 AS involves four different processes. Process A represents the initial stages of development for early development studies, and Processes B, C, and D represent later stages of development used in the generation of pivotal comparative data (i.e., pivotal clinical studies, and analytical biosimilarity data). Process D is the intended commercial manufacturing process. To demonstrate comparability between clinical and intended commercial material, AS lots from process B, C, and D were evaluated in a comparability study.

Analytical comparability studies included batch release testing, extended characterisation, and forced degradation studies.

The initial assessment concluded that AS material used in pivotal clinical studies, mostly derived from process B and C, could not be considered comparable to the material produced by the proposed commercial manufacturing process, process D. Notably, comparability between process B and process D material (lower % afucosylation + high mannose and % afucosylation in process B material) as well as between process C and process D material (higher % afucosylation + high mannose and % afucosylation in process C material) was not shown. A major objection was raised with regard to the comparability between clinical and commercial material. Specifically, the applicant was asked to address the following points:

1. Justify that the differences in the quality profile of the clinical and the commercial batches do not impact efficacy and/or safety.
2. Whereas intentional changes were introduced between process B and C to better match the QTPP of the reference product, the reasons for the observed differences between Process C and Process D material required further explanation.
3. Total mass and higher order structural data (fluorescence excitation, FT-IR analysis), raised uncertainties with respect to the molecular structure of HD201 in comparison to the reference product as well as between HD201 AS manufactured with process B, process C and process D.

In response to point 1 the applicant summarised previously presented data from functional and binding assays, where the observed variations in afucosylation levels were demonstrated to have no impact on biological activities relevant to the mode of action. Both FcγRIIIa-binding affinity and ADCC activity show comparability of clinical and commercial material. Other critical quality attributes related to clinical PK, efficacy and safety including binding to HER2 and FcRn, as well as ADCP, and anti-proliferation activity were demonstrated to be comparable. In addition, data from additional ADCC assays using peripheral blood mononuclear cells (PBMCs) and natural killer (NK) cells as effector cells were provided, in order to verify the relevance of afucosylation variations in a more clinically relevant

setting. Comparable ADCC activity demonstrated previously by reporter assay was confirmed in human PBMC and NK cell ADCC assays. Overall, the data support the justification that the variations between processes B, C and D are sufficiently minor and can be expected to have no significant effect on clinical activity.

In response to point 2, the applicant provided an in depth analysis of the upstream results including in-process controls and tests for all batches manufactured using processes C and D. This revealed some differences between process C and Process D which could explain the observed differences in afucosylation levels. Overall, the data explains the observed minor differences between Process C and Process D performance. In addition, comparable ADCC activity was observed in all employed ADCC assays (reporter assay and PBMC and NK cell assay), consistently demonstrating that process C derived material has comparable ADCC activity to process D material.

With regard to point 3, the applicant attributes the differences seen in total mass (specifically, intact mass major glycoform abundances for G0F(1)/G1F(1) and G0F(2)), and higher order structure data obtained by fluorescence and FT-IR to differences in instruments/methods employed during original data generation. The Applicant therefore re-analysed process B and C material the same way as process D and Herceptin material. Data generated in the re-analysis by FT-IR, LC-MS, and Fluorescence spectroscopy confirm comparability of lots manufactured across the different processes, as well as Herceptin material.

In conclusion, the Applicant provided additional data and justifications to address the points raised and the major objection was considered adequately resolved.

Characterisation

HD201 is being developed as biosimilar to Herceptin, therefore a comprehensive comparability exercise comparing HD201 to the originator Herceptin regarding essential quality attributes is performed and is further discussed in the "biosimilarity" section. The primary structure of HD201 is assessed using both direct and indirect methods. Higher-order structures of HD201, glycosylation profiles, functional properties, antiproliferative activity, ADCC activity, ADCP activity induced by HD201, and binding affinities of HD201 to FcγRIIa, FcγRIIIa, FcγRIIb, FcγRIIIb, and FcRn were evaluated.

Impurities

Product-related impurities consist of molecular and charge variants, and modifications such as deamidation, oxidation, isomerisation and sialylation which were characterized and included in the overall control strategy if applicable. Process-related impurities (HCP, residual DNA, rInsulin) are efficiently removed by the purification process and are monitored and controlled through release testing. It is noted that the purification process also efficiently removes endotoxins, and after virus filtration step, endotoxin level of all three PV batches met the acceptance criteria. The initial levels of endotoxins in these batches were rather high which is unexpected considering the well characterised expression system and the «closed » manufacturing system. The applicant attributed the elevated levels to the raw materials used to manufacture HD201 AS but emphasises that the purification process efficiently reduces the endotoxins to acceptable levels after the virus filtration step. Measurements are in place to reduce the entrance of endotoxins. Furthermore, the Applicant is planning to implement additional endotoxin testing, which will be included in a post-approval variation. Endotoxin levels will be monitored at various stages.

2.4.2.3. Specification

HD201 AS specifications are set in accordance with ICHQ6B. The release specification for HD201 active substance comprises tests for general attributes (colour, clarity, pH, osmolality), identity, quantity,

purity and impurities, potency, process-related impurities, polysorbate 20, and microbiological safety (bacterial endotoxins and bioburden).

Identity is confirmed by peptide mapping, isoelectric point analyses by cIEF, molecular weight (SE-HPLC), and isoform charge distribution (CEX-HPLC). Quantity is based on protein content determined by UV-spectrometry. Purity and product variants are determined by complementary methods, i.e. monomer and HMW variants by SEC, main peak and impurities by automated electrophoreses, and charge variants by CEX as well as N-glycosylation variants. Potency is determined by a relevant potency assay (anti-proliferation assay and ADCC). Polysorbate 20 concentration is determined by HPLC. Residual HCP is quantified using a process-specific ELISA, residual DNA and insulin are determined by qPCR or ELISA, respectively. General attributes colour, clarity, pH, and osmolality as well as microbiological attributes are determined according to compendial methods. In summary, the set of quality attributes tested at release and during shelf life, mostly complies with ICH Q6B, Ph. Eur. 0784, and EMA/CHMP/BWP/532517/2008 and is acceptable.

Analytical methods

The commercial HCP ELISA method has been validated and is used for routine analysis. Overall the commercial antibody kit is considered suitable for determination of residual HCPs derived from the HD201 manufacturing process. Validation of analytical methods was performed in accordance with ICH Q2A principles. Appearance, pH, and osmolality tests for AS are general test methods, which were verified. The validated ADCC reporter bioassay consists of a genetically engineered cell line expressing the FcγRIIIa-F receptor for ADCC-F variant.

Batch analysis

HD201 AS batch analyses data are presented for five batches manufactured using process A, process B, and process C, and batches at commercial scale at the intended commercial manufacturing site Prestige Biologics. All results comply with the specifications valid at time of testing and with the proposed commercial specifications (if applicable). In summary, the presented results demonstrate that the manufacturing process reliably delivers active substance with consistent quality.

Reference Material

The history of reference standards used during development is provided. It is outlined that a two-tiered reference standard system has been established. The applicant clearly described the currently valid reference standard system and the qualification results and provided the CoA for both the primary and secondary reference standard. Further, it is noted that since 2021 a WHO International Standard (1st International Standard for the biological activities of Trastuzumab, NIBSC code: 19/108) is available. The Applicant commits to adopting the WHO International Standard as the future primary reference standard. Respective protocols will be submitted as a post-approval variation, which is accepted. The proposed testing panel for primary reference standard and in-house development reference standard qualification is considered sufficient.

Container closure system

The primary container closure system intended for commercial use of HD201 AS is widely used for storage of biological active substances and complies with Ph. Eur. 3.1.7., Ph. Eur. 3.2.2., and USP Class VI. Results of extractable and leachable studies did not identify significant amounts of compounds of toxicological concern. Thus, the primary container closure is suitable for storage of HD201 AS.

2.4.2.4. Stability

Thirteen batches of HD201 AS were tested in long-term storage conditions.

Specifications and test methods used in the stability program are identical to those used for release.

Long-term studies have been completed for all batches and results for all batches were within specifications, demonstrating that HD201 AS remains stable while stored in the proposed container closure system at the proposed storage conditions.

For the accelerated stability studies all parameters tested were within their acceptance criteria, apart from main peak % area when tested for purity in two Process A batches and one Process D batch at the 6-month time point. A trend analysis of the data was performed, and a linear regression trend line was obtained for main peak % area which remained within specifications. Thus, stability under accelerated storage conditions up to 6 months is supported for all batches tested.

Stress studies were conducted using three Process D batches. Results showed significant changes in the charge profile of all three batches when tested for identity and purity, falling out of specification from the 7-day time point and continuing to degrade until the study concluded. All other parameters tested remained within specifications throughout the study.

Photostability was assessed Results of the studies showed changes in charge variants indicating that HD201 AS is sensitive to light. Results from long-term storage conditions, accelerated storage conditions, stress storage conditions, and exposure to visible and UV light support the proposed HD201 AS shelf life claim when stored protected from light.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

HD201 finished product (FP) is a sterile, preservative-free lyophilised powder, available as 150 mg and 420 mg powder for concentrate for solution for infusion.

Each vial of HD201 150 mg FP is packaged as a single-dose use, including a 4% overfill to ensure that the labelled dose can be withdrawn from each vial. The finished product is intended for reconstitution with 7.2 mL of sterile water for injection (not supplied) to yield a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab at a pH of approximately 6.0.

Each vial of HD201 420 mg FP is packaged as a single-dose use, including a 4.8% overfill to ensure that the labelled dose can be withdrawn from each vial. The finished product is intended for reconstitution with 20 mL of sterile water for injection (not supplied) to yield a 20.6 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab at a pH of approximately 6.0.

Tuznue is intended for administration via intravenous infusion only.

Well established compendial excipients are used to manufacture HD201 FP. The excipients, their reference standards, and their specifications are provided. No excipients of human or animal origin are used in the manufacture of HD201 FP.

Pharmaceutical development

The excipients used to manufacture HD201 150 mg FP are identical to the reference medicinal product, Herceptin. L-histidine monohydrochloride monohydrate and L-histidine are to maintain HD201 are buffering agents. α,α-trehalose dihydrate is used to prevent denaturation of proteins during the freeze-

drying process. Polysorbate 20 is used to prevent surface adsorption and serve as a stabiliser against protein aggregation.

The manufacturing process development of HD201 150 mg FP involves 4 processes. Processes 1 and 2-I represent early development while processes 2-II and 2-III represent later stages of development used in the generation of pivotal comparative data (i.e., pivotal clinical studies, and analytical biosimilarity data). Process 2-III is the intended 150 mg FP commercial manufacturing process.

Process 2-II lots were manufactured for use in pivotal Phase 1 (TROIKA-1) and Phase 3 (TROIKA) clinical studies, stability studies, and PV. Process 2-III is the final commercial process to support commercial supply at the proposed commercial manufacturing site.

FP comparability studies were performed to compare material of process 2-II to material from process 2-III. Of note, Process 2-II lots include all lots used in the pivotal TROIKA-1 and TROIKA trials, while process 2-III is the intended commercial process for the 150 mg presentation. The comparability exercise included in-process testing, batch release tests results, stability data and extended characterisation. Comparability assessments were conducted to verify the process performance and to ensure the changes did not affect the CQAs. Relevant in-process testing data were compared to verify the process performance and to ensure that each manufacturing process was under adequate control. In addition to the in-process testing results, end-product test results from real-time release tests and stability tests were evaluated on the quality attributes that could potentially be impacted by process changes. Moreover, extended characterisation was conducted to ensure that any attributes not adequately addressed in the release tests, but which could potentially influence the safety and efficacy of HD201 FP, were evaluated. Investigation of the N-glycosylation profile was also included to ensure consistency in glycosylation profiles of FP manufactured using different AS manufacturing processes. Comparability study was performed to ensure that material from final commercial manufacturing process (process 2-III) are comparable to lots used in clinical studies. In general, the design of the comparability approach is in line with the regulatory expectations. However, it should be noted that several FP batches were manufactured using different AS batch processes within the same FP process. A sub-analysis of Process 2-II and Process 2-III FP material processed from AS generated with Process D has been performed to demonstrate comparability between the FP processes. This comparability exercise evaluated data from in-process tests, batch release tests, and extended characterisation. Results were considered acceptable and minor differences observed are not expected to have any significant adverse impact on safety or efficacy of the FP.

Process 2-IV is developed for the process validation of HD201 420 mg FP. To bridge between the intended commercial and the clinical material, lots from process 2-IV (420 mg) were compared to clinical lots from process 2-II. Although this is not the material to be finally commercialized, process 2-II material was used in the clinical studies and seems sufficiently comparable to process 2-III material. Comparability of 150 mg and 420 mg HD201 FP presentations were assessed by in-process testing (IPT), release and stability testing, and extended characterisation. Overall, the 150 mg and 420 mg HD201 FP quality can be considered comparable.

Container closure system

The primary packaging material are borosilicate type I glass vials (Ph. Eur. compliant) with a nominal capacity of 20 mL for the 150 mg presentation and 50 mL for the 420 mg presentation. The vials are sealed with rubber stoppers which comply with the Ph. Eur. requirements for rubber closures for containers. The rubber stopper is secured with a sealed aluminium cap and a polypropylene flip-off cap. HD201 FP is manufactured under aseptic conditions since terminal sterilization of the FP is not possible. To ensure the FP remains sterile, the material is sterile filtered which has been validated in the filtration process. After filling, the vials are sealed with rubber stoppers which, in turn, are covered

with an aluminium seal and a polypropylene flip-off cap. To ensure the sterility of the container closure system, primary packaging materials are sterilised.

Compatibility

To assess the compatibility of the finished product with the reconstitution diluent and excipients, HD201 FP lots manufactured for early development as well as one lot manufactured with the intended commercial manufacturing process were evaluated for their reconstitution stability by subjecting them to in-use stability tests upon reconstitution with WFI and stored at 5 ± 3 °C. Samples were collected at various time points for up to 48 hours (the maximum time described in the SmPC) and subsequently tested with a range of tests which included appearance, identity, purity, content, pH and osmolality. All results were within the respective acceptance criteria, thereby validating the stability of the reconstituted HD201 FP with WFI for at least 48 hours at 5 ± 3 °C.

HD201 FP lots were mixed with infusion saline (0.9% NaCl) in the infusion bag and stored at 30 °C for 24 hours. Results indicated compliance with the respective acceptance criteria, thereby indicating appropriate infusion stability.

2.4.3.2. Manufacture of the product and process controls

Commercial manufacture of HD201 finished product (FP) is performed by a contract manufacturing organisation (CMO) located in Spain and performs all FP manufacturing operations including in-process control tests, excipients testing and release, packaging, and European Union Qualified Person (EU QP) release. Release testing and stability studies are performed by designated sites. Proof of GMP compliance is provided.

HD201 FP manufacturing process consists of thawing of the AS, preparation and filtration of the buffer solutions, compounding, followed by sterile filtration, collection of the solution, vial filling and pre-stoppering, lyophilisation, sealing and capping.

A risk assessment was performed examining all parameters involved in the manufacturing process to derive the proposed routine IPCs. A scoring system defining risk levels is provided. A list of IPCs has been proposed for routine control together with a justification in order to ensure that the manufacturing process is under control. The proposed process control strategy is considered adequate.

Process validation

Process validation batches were manufactured for the 150 mg presentation. Based on all the in-process testing results, the lyophilisation process was considered as validated and no additional study or batch production is required.

For validation of the HD201 420 mg FP manufacturing process three successful PV batches were manufactured. All values fell within the defined acceptance criteria. For the filling unit operation sufficient process capability has been demonstrated.

Validation of the pharmaceutical process filter is performed to ensure that contact with the filter under the worst-case conditions do not alter the composition or efficacy of the pharmaceutical product. Hold times were validated for AS thawing and holding prior filtration. In support of the proposed IPCs, results from IPCs of the PV batches are provided. There are no intermediates in the finished product manufacturing process. The manufacture of HD201 FP has no intermediate products or defined holding between manufacturing steps as the manufacturing process is performed continuously. However, the maximum time for each manufacturing process has been defined in grouped processes until the end of the lyophilisation cycle. The maximum times for the grouped processes have been determined with available hold time studies described.

Transport validation included visual inspection and temperature monitoring. It is noted that for the 150 mg FP in 20 mL Type I borosilicate glass vials, a transport validation study was conducted in a UKAS accredited testing laboratory. No vial damage was observed prior to, or on completion of testing and no vial leakage was observed during vial integrity testing. Hence, the quality of the product is maintained if transported according to the defined conditions. For the 420 mg FP in 50 mL Type I borosilicate glass vial a transport validation study was performed for air and motor freight.

2.4.3.3. Product specification

The specifications for release testing of HD201 finished product (FP) are defined in accordance with ICH Guideline Q6B. The finished product specifications address relevant quality attributes including appearance, identity, purity, content, potency, polysorbate 20 content, safety and general quality attributes.

The specifications for the 420 mg presentation are the same as for the 150 mg presentation, except for the acceptance criteria for content and endotoxin.

A risk assessment was performed in accordance with ICH Q3D guidelines regarding potential elemental impurities resulting from the manufacturing process. The HD201 finished product complies with the requirements established in the ICH Q3D guideline. The levels of elemental impurities are below their permitted daily exposure (PDE). Further the risk of inclusion of elemental impurities was assessed to be low in all the processes involved in the manufacturing of the HD201 FP which is agreed.

A risk assessment for potential nitrosamine impurities resulting from the manufacturing process was conducted and no risk of presence of nitrosamines was identified. No nitrite or other nitrosating agent is used in the manufacturing process of the HD201 AS and FP.

Analytical methods

The analytical methods used for in release and stability testing of HD201 FP are mainly the same methods used for HD201 AS testing. HD201 FP specific tests are described in sufficient detailed. Two sites perform release testing and stability testing. Differences between test methods used at the two sites are described and addressed during method validation. To qualify the methods for release testing employed, standard parameters were evaluated. In addition to the standard parameters for method qualification, the results for each test were also subjected to inter-laboratory comparability to confirm that acceptable and identical results were obtained between the 2 sites.

Reference materials

The same reference standard is used for testing the active substance and finished product.

Batch analysis

For the 150 mg presentation, batch analysis data of process 1, process 2-I, process 2-II (clinical) and process 2-III (intended commercial process) has been provided. For the 420 mg presentation, batch analysis data of process 2-IV (intended commercial process) has been provided. Results comply with the specifications and confirm consistency of the manufacturing process.

Container closure

The HD201 FP is filled into pre-sterilised borosilicate type I glass vials, which are partially stoppered with pre-sterilised rubber stoppers prior to lyophilisation and finally fully stoppered and sealed using aluminium flip-off caps. 20R vials are used for the 150 mg FP and 50R vials are used for the 420 mg FP.

The primary packaging materials comply with Ph. Eur. Guidelines and frequently used. Compatibility of the primary packaging components and HD201 FP was sufficiently demonstrated. The in-use stability study confirms product stability for the claimed in-use shelf-life duration of 48 hours. The extractable testing done on the rubber stopper as part of the QC testing did not give rise to any concerns and in view of the short contact time of the reconstituted material with the container closure system the likelihood of significant leachables appearing in the reconstituted solution after 48 hours is considered minimal.

2.4.3.4. Stability of the product

Based on long-term stability results obtained for batches manufacturing using the intended commercial process, the proposed shelf-life for HD201 FP is 48 months when stored at 5 ± 3 °C.

Stability studies have been conducted using thirteen batches of HD201 150 mg FP manufactured throughout the development of HD201 in long-term storage conditions (5 ± 3 °C) for 48 months using several batches manufactured using Process 1, Process 2-II, Process 2-II, and using the proposed commercial Process 2-III and the intended commercial container closure. In addition, data is available from storage at accelerated storage conditions (25 ± 2 °C / 60 ± 5% RH) for 6 months, and at stress storage conditions (40 ± 3 °C / 75 ± 5% RH) for 2 months

Long-term and accelerated stability studies have been completed and results for all batches were within specifications or were accepted with justifications. For batches stored under stress conditions all parameters apart from purity passed the acceptance criteria. The results suggest that purity may be indicative of product degradation for HD201 150 mg FP.

Stability studies have been conducted using three batches of HD201 420 mg FP manufactured for process validation using the proposed commercial Process 2-IV in long-term storage conditions (5 ± 3 °C) for 48 months and accelerated storage conditions (25 ± 2 °C / 60 ± 5% RH) for 6 months.

Long-term and accelerated stability studies have been completed for the 420 mg presentation. Results for all batches complied with the acceptance criteria.

Photostability studies were conducted for the 150 mg presentation at 25 ± 2 °C with exposure to visible light (NLT 1.2 million lux hours) and UV light (NLT 200-watt hours/m2). Results of the studies small changes in the identity of HD201 150 mg FP.

In-use stability was assessed at 0- and 48-hour time points while stored at 5 ± 3 °C after reconstituting HD201 FP vials with WFI. Thereafter, stability of HD201 FP was assessed for the two dosing regimens (2 mg/kg and 8 mg/kg) for an average 75 kg patient (150 mg and 600 mg) by diluting the reconstituted vials in 0.9% NaCl infusion saline (polypropylene bags). The diluted samples were assessed after holding for 24 hours at 25 ± 2 °C. The studies include one batch tested at the end of shelf life.

In conclusion, proposed shelf life of 48 months when stored at 5 ± 3 °C is supported by real-time/real condition stability data of representative batches. In-use stability data support that HD201 FP may be held for up to 48 hours after reconstituting with WFI, and up to 24 hours after dilution in 0.9% NaCl infusion saline. This is reflected in the SmPC.

2.4.3.5. Adventitious agents

TSE Safety

Cells are grown in suspension culture using defined media with no animal or human derived components. A list of BSE/TSE free materials is presented Certificates of Origin/TSE statements are provided for all raw materials and consumables. Based on the information provided, it is agreed that the risk with regard to BSE/TSE is minimal.

Virus safety

The fermentation process is using a serum-free medium. The CHO cells used for production have been screened sufficiently for viruses according to Guideline ICH Q5A. No viral contaminant has been detected in the MCB with the exception of retrovirus like particles which are well known to be present in CHO cell lines. This is acceptable and in line with ICH Q5A since the virus reduction capacity for this type of viral particles has been demonstrated to exceed widely the particle load in cell culture fluid.

The virus clearance capacity of the manufacturing process has been assessed in virus clearance studies using small-scale models of the respective large-scale manufacturing steps. The design of the studies appears to be in line with the guidance documents ICH Q5A and CPMP/BWP/268/95. The information provided on qualification of the downscaled models is sufficient. Respective data are provided to demonstrate validity of the small-scale models. Robust inactivation/removal of enveloped viruses has been demonstrated by the viral clearance studies.

2.4.3.6. Post approval change management protocol

The PACMP provided is considered acceptable. Validation and comparability strategy are considered to be adequate to support the proposed changes. Stability data of representative lots will be submitted at the time of variation submission and will include complete stress stability study and available accelerated stability and long-term stability study results. A potential shelf life claim will depend on the data.

2.4.3.7. Biosimilarity

A 3-way pairwise analytical biosimilarity exercise was performed comparing HD201 FP lots to EU-Herceptin, HD201 FP to US-Herceptin, and EU-Herceptin to US-Herceptin. The quality attributes were determined based on the quality target product profile (QTPP).

All analytical methods used for the similarity assessment have been validated. Overall, the descriptions and validation data that have been provided for the analytical methods used for the analytical comparability exercise are considered sufficient and indicate that the methods are suitable for the intended purpose.

Each quality attribute was evaluated for criticality using a risk ranking approach, which assessed the possible impact of the attribute on clinical safety and efficacy. The classification and assignment of QA under the proposed tiers 1-3 are acceptable. The quality attributes were stratified into three statistical tiers. For tier 1 quality attributes, equivalence testing was selected as an approach to evaluate the biosimilarity of HD201 and Herceptin. Tier 2 QAs were assessed by a quality range approach. For Tier 3 quality attributes evaluation was performed using descriptive raw data and/or graphical comparison. The overall approach is accepted.

The biosimilarity assessment included HD201 FP (150 mg presentation and 420 mg presentation) and EU-Herceptin. This includes HD201 and Herceptin lots included in the pivotal clinical studies.

Table 1: Analytical similarity overview

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Primary structure	Primary sequence	LC-TUV-MS/MS Peptide mapping	Identical primary sequence
	N- and C-terminal sequence	LC-TUV-MS/MS Peptide mapping	Identical N- and C-terminal sequence
	N-terminal sequence	Edman degradation sequencing	Identical heavy and light chain N-terminal sequence
	Total mass	LC-TUV-MS	Highly similar total mass
	Extinction coefficient	UV spectroscopy	Highly similar
General	Protein content	UV spectroscopy	Highly similar
Higher order structure	Secondary structure	Far UV circular dichroism (CD)	Highly similar spectra and secondary structure
	Secondary structure	Fourier transform infrared spectroscopy (FT-IR)	Highly similar spectra and secondary structure
	Tertiary structure	Fluorescence	Similar
	Thermodynamic stability	Differential scanning calorimetry (DSC)	Highly similar transition temperatures
	Free thiol	Ellman test	Highly similar free thiol content
	Disulfide bond	LC-TUV-MS/MS Peptide mapping	Identical disulfide bridging patterns
Glycosylation	Site specific N-glycosylation	LC-TUV-MS/MS Peptide mapping	Identical glycosylation site (Asn-300)
	High mannose	LC-FLR-MS	Highly similar
	Afucosylated glycan + high mannose	LC-FLR-MS	Similar
	Afucosylated glycan	LC-FLR-MS	Similar with marginal differences. No impact on FcγRIIIa binding and ADCC activity observed
	Galactosylated glycan	LC-FLR-MS	Highly similar
	Sialylation	LC-FLR	Lower total sialylation, Neu5Ac, and Neu5Gc content in HD201
	Non-glycosylated heavy chain	Capillary electrophoresis sodium dodecyl sulfate (CE-SDS; reduced)	Highly similar
Purity	Intact IgG	CE-SDS (non-reduced)	Similar with justifiable differences

Molecular parameter	Attribute	Methods for control and characterization	Key findings
	Sum of LC and HC	CE-SDS (reduced)	Highly similar
	Sum of fragment	CE-SDS (non-reduced)	Similar with justifiable differences
	Monomer	Size exclusion high-performance liquid chromatography (SE-HPLC)	Similar. Higher purity in HD201 compared to EU-Herceptin
	HMW	SE-HPLC	Similar. Lower aggregates in HD201 compared to EU-Herceptin
	Dynamic light scattering (DLS)	DLS	Highly similar
Charge variants	Charge variant profile	Cation exchange high performance liquid chromatography (CEX-HPLC)	Similar percentage of main, acidic and basic species observed in HD201 compared to EU-Herceptin
		Capillary isoelectric focusing (cIEF)	Highly similar main peak pI and similar percentage of main, acidic and basic species observed between HD201 and EU-Herceptin
Modifications	Total isomerisation	Isomerisation kit	Similar
	Isomerisation	LC-TUV-MS/MS	Similar
	Deamidation	Peptide mapping	Similar
	Oxidation	Peptide mapping	Similar
Biological activity	Anti-proliferation assay	Cell-based assay	Equivalent antiproliferative activity
	ADCC activity	Reporter assay	Equivalent ADCC activity
	ADCC activity	Primary PBMCs	Equivalent ADCC PBMC activity
	ADCP activity	Reporter assay	Equivalent ADCP activity
	CDC assay	Cell-based assay	Similarly lack of CDC activity
Binding affinity	HER2 binding	Bio-layer interferometry (BLI)	Equivalent binding affinity to HER2
	FcγRIIa binding (R and H variants)	BLI	Highly similar
	FcγRIIb binding	BLI	Highly similar
	FcγRIIIa binding (V and F variants)	BLI	Highly similar
	FcγRIIIb binding	BLI	Highly similar

Molecular parameter	Attribute	Methods for control and characterization	Key findings
	FcγRI binding	BLI	Highly similar
	FcRn binding	BLI	Highly similar
	Inhibition of VEGF secretion	ELISA	Similar inhibition of VEGF secretion
	C1q binding	ELISA	Highly similar
Degradation profile	High pH stress Thermal stress Oxidative stress Photo stress	SE-HPLC, CE-SDS, CEX-HPLC, Peptide mapping, Extinction coefficient, Antiproliferation assay, HER2 binding, Fcγ receptor binding by BLI	Similar degradation profile

Regarding the tier1 QAs, HER 2 binding and antiproliferative activity are comparable between HD201 and the reference product. The ADCC activity for both V and F Variant, were assessed using ADCC reporter bioassays, which quantify biological activity on nuclear factor of activated T-cells (NFAT) response element (RE) pathway activation. SKBR3 cell line over expressing HER2 were used as target cells for both the assays. The effector cells used for ADCC-V and ADCC-F reporter bioassays were genetically engineered Jurkat T cells that express FcγRIIIa V or F respectively, and a luciferase reporter gene driven by NFAT-RE. ADCC activity (FcγRIIIa V) seems slightly lower for HD201 but this is due to the inclusion of process B derived material. The intentional change from Process B to Process C in order to match quality profile of Herceptin can be considered successful as relative potency derived for ADCC-V activity is more aligned to results for Herceptin after introduction of Process C. Despite this, the equivalence margin was met. The ADCC activity for F Variant of FcγRIIIa is comparable. This is not unexpected and confirmed by structure-function relationship analysis. The ADCC activity using PBMC was also determined and overall the data indicate that HD201 has similar *in vivo* ADCC activity as Herceptin under these more physiological conditions compared to the NK cell assay. Despite the more physiological conditions the intended differences seen between the batches form the three different manufacturing processes B, C, and D is retained indicating that the assay is sufficiently sensitive. ADCP activity of HD201 and Herceptin samples were determined using FcγRIIa-H ADCP reporter bioassay kit. HER2-overexpressing SKBR3 breast cancer cell lines were used as target cells. The effector cells used were genetically engineered Jurkat T cell expressing FcγRIIa-H receptor (G988A) and a luciferase reporter gene driven by NFAT-RE. The ADCP activity is considered comparable. Peptide Mapping and a N- and C-terminal sequencing via peptide mapping confirmed the amino acid sequence similarity between the HD201 and the reference materials. Sequence identification was investigated using LC-TUV-MS and was shown to cover 100% of the light and heavy chain sequence of Trastuzumab.

For tier 2 QAs, binding affinity of HD201, EU- and US-Herceptin to Fcγ receptors were determined. The intended process change (B to C) in order to align the critical quality attributes seem to be reflected in the binding affinity towards the high affinity FcγRIIIa (V variant) as process B derived HD201 material shows slightly lower binding affinities which are more aligned with the reference material after the process change. The effect cannot be observed for binding toward FcγRIIIa (F variant). With regard to FcγRIIIb binding slightly lower binding affinities observed for HD201 are driven by process B material. Protein concentration was determined by UV-Vis Spectroscopy. The extinction coefficient was compared experimentally and found nearly comparable. In the biosimilarity exercise, the extinction coefficient used for protein concentration measurement was experimentally determined for each lot individually. The current extinction coefficient is employed for UV protein quantification to align with

Herceptin and what is used for HD201 release. N-glycan profiling was conducted. Lower values (min-max) of afucosylation+high mannose/afucosylation are observed for process B derived HD201 material clearly outside of the quality range of Herceptin. The difference is diminished after the intended process change to process C. No significant differences were observed for galactosylation, sialylation, Neu5Ac and Neu5Gc levels (present at very low levels). Total mass analysis was measured by UPLC/LC-MS and is qualified as a Tier 2 CQA, therefore a quality range test was performed to evaluate comparability. The total mass of the two main glycoforms G0F(2) and G0F(1)/G1F(1) were within quality range of EU- and US-Herceptin. Regarding purity under non-reduced conditions, the purity min-max ranges were similar for HD201 and EU-Herceptin lots. It is concluded that HD201 and Herceptin are highly comparable in terms of their purity. The profile of charged variants displays some variability for both HD201 and the reference product. During development the profiles were aligned and can be considered sufficiently comparable. With regard to other modifications such as isomerisation, deamidation, and oxidation no significant differences are observed although the degree of variability seems higher for HD201. With FT-IR, secondary structures including α-helix, β-sheet, β-turns and random coils were analysed.

Regarding Tier 3 QAs, C1q binding of HD201 and Herceptin indicates no significant binding activity and the difference observed is not meaningful. Accordingly, CDC activity is not observed and is not part of the mechanism of action of trastzumab.

Structure-function analysis was performed and the known correlation between %afucosylation, FcγRIIIa binding and ADCC activity was confirmed. This further supports the process change from B to C to increase afucosylation levels.

A forced degradation study was included in the biosimilarity exercise between HD201 and Herceptin. The study included thermal forced degradation at 40°C, high pH forced degradation, photo-induced forced degradation, and oxidative forced degradation. Samples were analysed by SEC-HPLC, CE-SDS, CEX-HPLC, peptide mapping, extinction coefficient, HER2 binding and Fcγ-receptor binding. HD201 showed a similar degradation profile than EU- and US-Herceptin in the thermal stress study. No significant differences were observed between HD201 and Herceptin lots in the high pH forced degradation study. Similar degradation profiles were detected between HD201, EU- and US-Herceptin in the photostability study. A minor difference was observed for FcRn binding. However, this observed difference does not preclude biosimilarity. Oxidative stress study was performed on HD201, EU- and US-Herceptin. No significant differences were observed in degradation profiles of HD201, EU- and US-Herceptin. When exposed to different stress conditions, when certain QA are affected, similar trends, degradation patterns, modifications, and binding affinities were observed for HD201 and Herceptin. Thus, forced degradation study results support biosimilarity.

In conclusion, the applicant has addressed the analytical similarity between HD201 and the reference product EU-Herceptin in an extensive comparability study.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

HD201 has been developed as biosimilar to Herceptin. The active substance trastuzumab is manufactured using a typical manufacturing process for monoclonal antibodies. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

An analytical biosimilarity exercise was performed comparing HD201 FP lots to EU sourced Herceptin. The QAs were determined based on the QTPP. Each quality attribute was evaluated for criticality using

a risk ranking approach, which assessed the possible impact of the attribute on clinical safety and efficacy. Structure-function analysis was performed and the known correlation between %afucosylation, FcγRIIIa binding and ADCC activity was confirmed. Overall, the provided data set accumulated to support biosimilarity of HD201 with the reference product is considered comprehensive. The material generated with Process D, which is intended to be the commercial material, is considered highly similar to the EU reference product Herceptin.

During the initial evaluation a major objection was raised since AS material used in pivotal clinical studies, mostly derived from process B and C, could not be considered comparable to the material produced by the proposed commercial manufacturing process, process D. In response, the Applicant provided further justifications, an overview of previously submitted data, as well as data from re-analysis of samples and newly generated data. Overall, the data provided indicate that the differences seen between material from the different processes are not clinically meaningful and the major objection was considered adequately resolved.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

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

Non-clinical evidence to support the demonstration of biosimilarity between HD201 and EU-authorised Herceptin is based on extensive in-vitro comparability studies conducted under non-GLP conditions. These in-vitro functional and binding assays performed as part of the analytical biosimilarity exercise, focused on attributes that are reflective of the modes of action of trastuzumab and of high clinical relevance. No additional nonclinical studies are included in this MAA.

2.5.2. Pharmacology

HD201 (trastuzumab) has been developed as a similar biological medicinal product to the reference medicinal product, Herceptin (Roche Registration Limited). The pharmacology program for HD201 focused on primary pharmacodynamics studies. A battery of in vitro studies was performed as part of the analytical similarity assessment to assess biological and functional similarity of HD201 and Herceptin. Clinical and batches representative of the proposed commercial process were compared to both EU-authorised Herceptin (EU-Herceptin) and US-authorised Herceptin (US-Herceptin) lots in head-to-head-comparisons.

2.5.2.1. Primary pharmacodynamic studies

A number of *in vitro* functional and binding assays reflective of the modes of action of trastuzumab was performed to demonstrate the biosimilarity of HD201 to EU-Herceptin (as part of the analytical biosimilarity exercise).

To derive a robust analytical similarity assessment, in-depth structural and functional characterisation has been executed using fit-for-purpose, sensitive and orthogonal analytical methods.

Evaluation of mode of action (MOA)-related and non-MOA biological activities studies were performed to comprehensively compare the activity of HD201 and Herceptin in functions known to be of high clinical relevance and important to the MOA of trastuzumab.

The biosimilarity assessment was performed to compare HD201 DP (150 mg presentation and 420 mg presentation), EU-Herceptin, and US-Herceptin. HD201 and Herceptin lots included in the pivotal clinical studies (i.e., Phase 1 PK similarity study, and Phase 3 confirmatory study) were included in the biosimilarity exercise.

Overall, HD201 was highly similar to Herceptin in terms of its HER2 binding affinity, anti-proliferation activity, ADCC and ADCP activities. Consistent with highly similar ADCC and ADCP activities, the binding affinities to FcγRIIIa (V and F variants) and FcγRIIa (R and H variants) were also comparable between HD201 and Herceptin. These provided further evidence to support the comparability in ADCC and ADCP activities, thereby demonstrating similarity in MOA-related biological activity of HD201 and Herceptin. As part of non-MOA related antitumour efficacy, comparable suppression of VEGF activity was also demonstrated. Other non-MOA related biological activity (i.e., CDC activity, C1q binding, FcγRI, and FcRn) was highly similar between HD201 and Herceptin.

2.5.3. Ecotoxicity/environmental risk assessment

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

2.5.4. Discussion on non-clinical aspects

Pharmacology
A panel of in vitro functional and binding assays was submitted as part of the quality biosimilarity exercise as described in section 2.4.2.2. *Manufacturing process development* in order to demonstrate

comparability to the originator EU-Herceptin. These studies comprise HER2 binding, a cell-based proliferation-inhibition assay in cancer cells, ADCC and ADCP activity, FcγRIIa binding (R and H variants), FcγRIIb binding, FcγRIIIa binding (V and F variants), FcγRIIIb binding, FcRn binding, inhibition of VEGF secretion, C1q binding, CDC assay as well as FcγRI binding.

As part of its MOA, Herceptin exhibits its anti-tumorigenic effects through HER2 binding, inhibition of downstream signalling leading to the inhibition of proliferation as well as other effector functions including ADCC and ADCP activities. HD201 was found to be highly equivalent to Herceptin in terms of its HER2 binding affinity, antiproliferation activity, ADCC and ADCP activities. Besides HER2 binding, the activities of ADCC and ADCP were initiated through the engagement of Fc receptors on effector cells which impact the overall efficacy of HD201. For instance, Herceptin Fc region binding to FcγRIIIa on the effector cells promotes the induction of ADCC activity while the binding to FcγRIIa participates in phagocytosis and activation of immune cells involved in the induction of ADCP activity. Highly similar PBMC ADCC activity of HD201 confirmed the results of ADCC reporter assays in a physiologically relevant condition and there are no clinically meaningful differences observed between HD201 and Herceptin.

The binding affinities to FcγRIIIa (V and F variants) and FcγRIIa (R and H variants) were also highly similar between HD201 and Herceptin. These provided further evidence to support the comparability in ADCC and ADCP activities, thereby justifying the comparable MOA related biological activity and efficacy between HD201 and Herceptin. Apart from proliferation, inhibition of HER2 by trastuzumab was also shown to inhibit the secretion of VEGF as part of its non-MOA related antitumor efficacy. A high degree of similarity in the assay was noted between HD201 and Herceptin. Although trastuzumab is not capable to induce CDC, it is capable of binding to C1q complement. This was similarly demonstrated in HD201 where comparable C1q binding affinities were observed to Herceptin with little or no CDC activity detected. Other non-MOA related biological activity included FcγRI and FcRn binding, which were also highly similar between HD201 and Herceptin. Unlike other Fc receptors that is associated with efficacy, binding to FcRn receptors prolong the antibody half-life by preventing antibodies from lysosomal degradation (Suzuki et al., 2010). Hence, a similar FcRn binding affinity would indicate comparability in PK profiles exhibited by HD201 and Herceptin.

These data bridged the equivalence of HD201 and Herceptin in all MOA-related biological activities, and HD201 and Herceptin can be expected to mediate the same therapeutic effect in-vivo.

As *in-vitro* assays are considered more specific and sensitive than *in vivo* studies to detect potential differences between the proposed biosimilar and the reference product, *in vivo* studies that were conducted during early development of HD201 were not submitted in support of the primary pharmacology of HD20, which is considered acceptable for a biosimilar application.

Secondary pharmacodynamics studies were not submitted but are not considered necessary for the evaluation of a biosimilar medicinal product. Due to the nature of the product and the type of application, pharmacodynamic drug interactions are also not considered necessary for the evaluation as per the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1).

Overall, non-clinical data submitted do allow a thorough comparison of characteristics relevant for trastuzumab, i.e. binding and effector functions, between test and reference product based on an extensive in-vitro comparability studies conducted under non-GLP conditions.

Pharmacokinetics

PK drug interactions studies are not considered necessary in the evaluation of biosimilars as the established safety profile of the reference product is considered as more relevant, and in accordance with the Guideline on similar biological medicinal products containing monoclonal antibodies, non-

clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

Toxicology

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

No additional non-clinical studies are included in this MAA, which is considered acceptable.

In line with the current Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1), and the Guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998), non-clinical studies such as safety pharmacology, pharmacodynamic drug interactions, distribution, metabolism, excretion, pharmacokinetic drug interactions, single-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity were not conducted for HD201.

2.5.5. Conclusion on the non-clinical aspects

The assessment of the non-clinical data indicated similar activity between HD201 and the reference product Herceptin.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Type of study	Protocol number (Country)	Objective(s) of the study	Study design	Test product(s); dosage regimen; route of administration	Total number of subjects	Healthy subjects or diagnosis of patients	Duration
Pivotal PK similarity	TROIKA-1 (Australia)	Primary: To demonstrate the PK similarity of HD201 to EU-Herceptin and US-Herceptin. Secondary: To evaluate the safety, tolerability, and immunogenicity of HD201 and EU-Herceptin and US-Herceptin and to further evaluate the PK similarity between EU-Herceptin and US-Herceptin	Phase 1, randomised, double-blind, single-dose, 3-arm, parallel group study	Test product: HD201 6 mg/kg as a single 90-minute infusion Reference products: EU-Herceptin 6 mg/kg as a single 90-minute infusion; US-Herceptin 6 mg/kg as a single 90-minute infusion	Randomised: 105 HD201: 35 EU-Herceptin: 35 US-Herceptin: 35 Treated: 105 HD201: 35 EU-Herceptin: 35 US-Herceptin: 35 Completed: 98 HD201: 33 EU-Herceptin: 33 US-Herceptin: 32	Healthy male subjects	Single dose with 54 days of follow-up

Pivotal confirmatory efficacy and safety similarity	TROIKA (70 centres, 5 Belarus, 1 Bulgaria, 1 Estonia, 1 France, 9 Georgia, 9 Italy, 2 Poland, 3 Spain, 7 Malaysia, 3 Thailand, 21 Russia, 8 Ukraine)	Primary: To show equivalence of tpCR in patients treated with HD201 plus chemotherapy to that in patients treated with EU-Herceptin plus chemotherapy assessed at the time of surgery after 8 cycles of neoadjuvant treatment completion Secondary: To evaluate the efficacy of HD201 compared to EU-Herceptin (bpCR at time of surgery, ORR at time of surgery, EFS two years after end of treatment, and OS two years after end of treatment), to compare immunogenicity, safety and tolerability, and PK trough values of HD201 and EU-Herceptin	Phase 3, randomised, multicentre, double-blind, active controlled, 2-arm parallel group study	**Neoadjuvant** Test product: HD201 8 mg/kg loading dose (Cycle 1), then 6 mg/kg every 3 weeks (Cycle 2 to 8) Reference product: EU-Herceptin 8 mg/kg loading dose (Cycle 1), then 6 mg/kg every 3 weeks (Cycle 2 to 8) Chemotherapy: 75 mg/m^2 docetaxel IV every 3 weeks for 4 cycles followed by 75 mg/m^2 epirubicin and 500 mg/m^2 cyclophosphamide IV every 3 weeks for 4 cycles **Adjuvant** Test product: HD201 8 mg/kg loading dose (Cycle 9), then 6 mg/kg every 3 weeks (Cycle 10 to 18) Reference product: EU-Herceptin 8 mg/kg loading dose (Cycle 9), then 6 mg/kg every 3 weeks (Cycle 10 to 18)	Randomised: 503 HD201: 251 EU-Herceptin: 252 Treated: 502 HD201: 250 EU-Herceptin: 252 Completed neoadjuvant: 488 HD201: 244 EU-Herceptin: 244 Completed adjuvant: 450 HD201: 222 EU-Herceptin: 228 Completed post-treatment follow-up: 414 HD201: 198 EU-Herceptin: 216	HER2-positive early breast cancer	54 weeks of active treatment and 2 years follow-up

bpCR: breast pathological complete response; CSR: Clinical study report; EFS: Event-free survival; EU: European Union; HER-2: Human epidermal growth factor receptor-2; IV: Intravenous; ORR: Overall response rate; OS: Overall survival; PK: Pharmacokinetic; ROA: Route of administration; tpCR: Total pathological complete response; US: United State

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The results described in this section were obtained from two pivotal clinical studies included in this Marketing Authorisation Application (MAA) for HD201, a similar biological medicinal product to the reference medicinal product, Herceptin (Roche Registration Limited).

To support the demonstration of biosimilarity of HD201 to EU-authorised Herceptin (hereinafter referred to as EU-Herceptin), data from one completed Phase 1 study in healthy male volunteers (TROIKA-1) and one completed Phase 3 study in patients with Human epidermal growth factor receptor-2 (HER2)-positive early breast cancer (TROIKA) were provided. PK similarity was demonstrated in the Phase 1 PK similarity study, TROIKA-1, and the Phase 3 study, TROIKA, confirmed PK similarity after repeated dose administration of HD201, and EU-Herceptin.

Bioanalytical methods

Bioanalytical methods were used for analysis of HD201/Herceptin pharmacokinetic (PK), anti-HD201/anti-Herceptin antibodies (ADA) and neutralising antibodies (NAb) for the pivotal Phase 1 PK equivalence study (TROIKA-1) and Phase 3 confirmatory efficacy and safety study (TROIKA). During the initial stages of clinical development, a Phase 1 PK similarity study in healthy male volunteers (EAGLE-I-12) was performed with early development batches (i.e., Process A). Subsequent batches produced from later phases of development (mainly processes B and C) were used to perform the TROIKA-1 study in healthy male volunteers and the TROIKA study in HER2+ early breast cancer patients. Bioanalytical methods developed and validated for EAGLE-I-12 study, were transferred, partially validated and used for the TROIKA-1 and TROIKA studies.

An overview and summary of all the bioanalytical studies that were carried out across the various phases are listed below.

Table 1 - Bioanalytical studies

Sl #	Analytical Lab	Project number / Code / Job number	Study type	Bioanalytical method/report	Studies involved
1	ICON	2548/003a (500701)	PK method validation	Validation for the determination of HD201 or trastuzumab in human serum by quantitative ELISA	EAGLE-I-12[a]
2	ICON	2548/003d (500705)	NAb method validation	Validation for the detection of neutralising anti-HD201 or anti-trastuzumab antibodies in human serum by a cell based ADCC assay	EAGLE-I-12[a]
3	AGILEX	VAL322	PK-method transfer validation	Validation of a method transfer for the detection of trastuzumab in human serum	TROIKA and TROIKA-1
4	AGILEX	VAL322	Report Addendum 01	Validation of a method transfer for the detection of trastuzumab in human serum	TROIKA and TROIKA-1
5	AGILEX	VAL322	Report Addendum 02	Validation of a method transfer for the detection of trastuzumab in human serum	TROIKA and TROIKA-1
6	AGILEX	VAL323[b]	ADA method validation	Validation of an electrochemiluminescent method for the detection of anti-Herceptin antibodies in human serum	TROIKA and TROIKA-1
7	AGILEX	VAL323[b]	Report Addendum 01	Validation of an electrochemiluminescent method for the detection of anti-Herceptin antibodies in human serum	TROIKA and TROIKA-1
8	AGILEX	VAL425	ADA method re-validation	Validation of an electrochemiluminescent method for the detection of anti-trastuzumab antibodies in human serum	TROIKA and TROIKA-1
9	AGILEX	GAY	Bioanalytical report (PK and ADA)	Sample analysis report for detection of trastuzumab (HD201/Herceptin) and for determination of anti-HD201/anti-Herceptin antibodies in human serum	TROIKA
10	AGILEX	GAY	Report Amendment 01	Sample analysis report for detection of trastuzumab (HD201/Herceptin) and for detection of anti-HD201/anti-Herceptin antibodies in human serum	TROIKA
11	AGILEX	GCC	Bioanalytical report (PK and ADA)	Sample analysis report for detection of trastuzumab (HD201/Herceptin) and for detection of anti-HD201/anti-Herceptin antibodies in human serum	TROIKA-1
12	AGILEX	GCC	Report Amendment 01	Sample analysis report for detection of trastuzumab (HD201/Herceptin) and for detection of anti-HD201/anti-Herceptin antibodies in human serum	TROIKA-1
13	PBP-ARC (Previously known as CAI)	GLP19001[b]	NAb partial method validation	Method validation-Detection of neutralising anti-trastuzumab antibodies in human serum by a cell based ADCC assay	TROIKA and TROIKA-1
14	PBP-ARC	GLP20005	NAb partial method validation	Method Validation - Detection of neutralising anti-trastuzumab antibodies in human serum by a cell based ADCC assay following sample pre-treatment for drug removal	TROIKA and TROIKA-1

ADA: anti-drug antibody; ADCC: antibody-dependent cellular cytotoxicity; CAI: Cell Assay Innovations; ELISA: enzyme-linked immunosorbent assay; FU: Follow up; NAb: neutralising antibodies; PBR-ARC: Prestige Biopharma Advanced Research Centre; PK: pharmacokinetics.

a EAGLE-I-12 study is a Phase 1 PK similarity study conducted as part of early development of HD201. Bioanalytical methods developed and validated for EAGLE-I-12 that were transferred, partially validated and used for TROIKA-1 and TROIKA

b VAL323 is a validation study for the previous method of ADA analysis (ALM323), which was subsequently re-validated in VAL425 after additional changes had been incorporated.

c GLP19001 is a partial validation study for the original method developed by ICON for NAb analysis, which was subsequently updated and partially validated in GLP20005 with sample pre-treatment for drug removal.

Determination of HD201 or Herceptin in human serum by quantitative ELISA (500701)

An ELISA immunoassay method was validated to quantify HD201 or Herceptin in human serum. The parameters assessed in this study include calibration curve performance, inter-run precision and accuracy, intra-run precision and accuracy, limits of quantitation, matrix effects and selectivity, specificity/interference, dilution integrity, stability (benchtop, freeze/thaw, short-term stability and long-term stability, whole blood).

HD201 or Herceptin concentrations were determined on a standard curve obtained by plotting optical density (OD) versus concentration using a four-parameter logistics curve-fitting programme.

The quantitative ELISA method for determination of HD201 or Herceptin in human serum has been validated for the concentration range of 2.00 µg/mL to 70.0 µg/mL in 100% human serum.

Method transfer for the detection of HD201 or Herceptin in human serum by quantitative ELISA (VAL322)

The objective of this study was to partially validate a method transfer for the determination of HD201 or Herceptin in human serum. The method initially developed and validated by ICON was transferred to and validated by Agilex Biolabs. The parameters that were assessed in this validation study include calibration curve performance, inter-run precision and accuracy, intra-run precision and accuracy, selectivity and specificity. HD201 or Herceptin concentrations were determined on a standard curve obtained by plotting OD versus concentration using a four-parameter logistics curve-fitting programme.

The method was partially validated over the calibration range 1.00 to 100 µg/mL (LLOQ: 2.00 µg/mL; ULOQ: 70.00 µg/mL). Precision and accuracy for all parameters passed the tested set criteria successfully.

Studies

TROIKA-1 study

The pivotal PK similarity study, TROIKA-1, was a randomised, double-blind, three-arm, parallel group, single-dose, active comparator study to demonstrate PK equivalence between HD201 to EU-Herceptin and US-Herceptin in healthy male subjects aged 18 to 55 years. The primary objective of the study was to demonstrate equivalent PK properties of HD201, EU-Herceptin, and US-Herceptin when administered intravenously as a single dose of 6 mg/kg over 90-minute in healthy male subjects. Thirty-five subjects were to be included per treatment group.

Thirteen blood samples were to be drawn from each subject for PK analysis from study start (prior to drug administration) to Day 54.

The primary PK parameter was AUC0-inf. Secondary PK parameters were AUC0-t, Cmax, Tmax, T1/2el, CL, Vd, Kel and Residual area.

The overall Phase 1 clinical study design is considered acceptable for demonstrating comparative pharmacokinetics between HD201 and EU-Herceptin.

In the TROIKA-1 study baseline had been defined in the protocol as "the last available, non-missing assessment prior to study drug administration". Later, after study conduct this definition was changed to "the last available scheduled, non-missing assessment prior to study drug administration". The Applicant clarified during the assessmentthat only seven subjects were affected by the revised definition with similar numbers per arm. It was agreed that the impact on the study results is negligible.

PK analysis methods

The TROIKA-1 study was intended to demonstrate PK similarity between HD201 and EU-Herceptin based on the usual bioequivalence limits and criteria for AUC0-inf. The method for calculating sample size based on inter-subject coefficient of variation from literature and sponsor data is considered essentially sound. In order to demonstrate biosimilarity, comparison of other PK parameters, related to disposition, namely Vd, Cl and half-life is also a valuable supportive element.

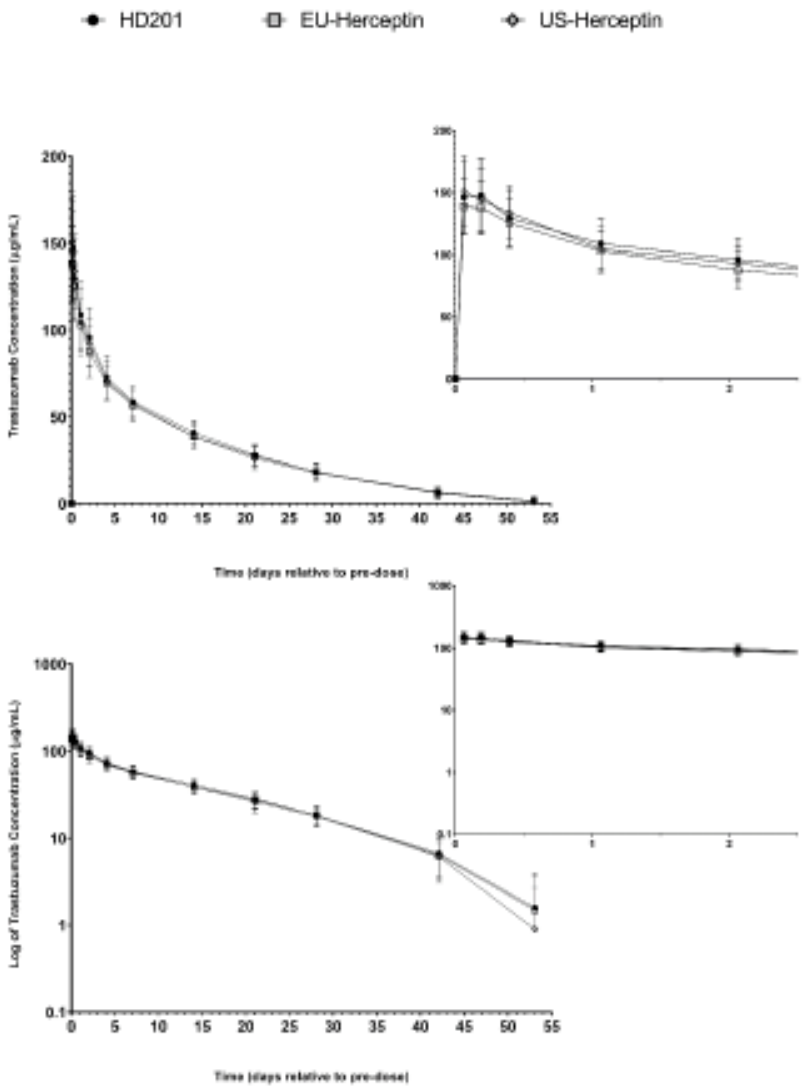
Statistical methods

The definition of the analysis sets had been slightly changed after unblinding. However, since the analysis sets finally used in the assessment of the PK equivalence (including the modified PK parameter (PKP) population set which was analysed) are considered acceptable, these discrepancies are not further pursued. While the protocol states that the assessment of the PK equivalence between

HD201 and EU-Herceptin was to be conducted excluding the data on US-Herceptin, the assessment was finally performed using a model based on the HD201, EU-Herceptin and US-Herceptin data as instructed in the SAP. During the assessment, the Applicant provided the analyses as prespecified in the protocol and in accordance with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), i.e. by excluding the data on US-Herceptin. As expected, the revised analyses give the same point estimates but slightly larger confidence intervals. As the revised confidence intervals still lie well within the bioequivalence acceptance range, this is considered acceptable. Besides, the statistical methods used in TROIKA-1 essentially follow the procedures used in assessing bioequivalence for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} in each pairwise comparison. The acceptance limits are the standard 80.00% to 125.00%. This is acceptable.

PK Results (TROIKA-1)

Mean (±SD) trastuzumab serum concentration-time profiles by treatment group are presented in Figure 1 below.



Mean (±SD) trastuzumab concentrations over time are shown for all three groups on a linear scale (upper panel) and a semi-logarithmic scale (lower panel). Insets show zoom of the first 48 hours after end of infusion. Number

Figure 1: Trastuzumab serum concentration-time profiles (PKC population) from TROIKA-1

Following a 90-minute IV infusion of both HD201 and Herceptin, serum trastuzumab concentrations decreased, on average, by less than 11% across the first 8.5 h after the end of the dose infusion. For

both treatments, the post-dose serum concentrations declined in a biphasic manner, with the terminal decline starting between nominal 48 and 336 h post-infusion start. The serum concentrations of trastuzumab were, on average, very similar across all time points for both treatments.

Table 2: Summary of the PK Parameters for Trastuzumab (PKP Population)

Parameter	HD201	EU-Herceptin	US-Herceptin
$AUC_{0\text{-}inf}$ (h*µg/mL)			
Geometric mean	38350.2	37432.7	37298.5
Geometric CV (%)	16.0	16.7	15.5
$AUC_{0\text{-}last}$ (h*µg/mL)			
Geometric mean	36587.5	35337.1	35619.9
Geometric CV (%)	17.6	17.0	15.3
C_{max} (µg/mL)			
Geometric mean	148.86	142.28	151.10
Geometric CV (%)	19.5	15.5	16.6
T_{max} (h)			
Median	1.725	3.150	1.567
Mean	2.930	3.634	3.337
SD	1.528	2.613	2.759
$T_{1/2el}$ (h)			
Mean	234.205	243.138	238.455
SD	26.308	36.466	34.917
CV (%)	11.2	15.0	14.6
K_{el} (1/h)			
Mean	0.002995	0.002907	0.002964
SD	0.000327	0.000393	0.000405
CV (%)	10.9	13.5	13.7
CL (mL/h)			
Mean	12.48330	12.60262	12.10834
SD	2.25591	2.13641	2.30354
CV (%)	18.1	17.0	19.0
V_d (mL)			
Mean	4194.073	4395.327	4122.044
SD	749.998	902.223	730.135
CV (%)	17.9	20.5	17.7

$AUC_{0\text{-}inf}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}last}$ = area under the concentration-time curve from time 0 to the last quantifiable data point; C_{max} = maximum observed concentration; T_{max} = time of maximum observed concentration; $T_{1/2el}$ = terminal half-life; K_{el} = terminal elimination rate constant; CL = systemic clearance; V_d = volume of distribution; Geo. Mean = geometric mean; Geo. CV (%) = geometric coefficient of variation; CV (%) = coefficient of variation; SD = standard deviation.

These results from TROIKA-1 showed the following:

1. After administration of HD201, EU-Herceptin, or US-Herceptin, the percentage of the $AUC_{0\text{-}inf}$ due to extrapolation (residual area) was 4.6%, 5.5%, and 4.5% of $AUC_{0\text{-}inf}$. Therefore, all summarized PK parameters were considered to be reliably estimated.
2. The inter-subject variability based on AUC0-inf and AUC0-last, was characterized by a geometric CV ranging from 15.3% to 17.6%. For Cmax the inter-subject variability of EU-Herceptin and US-Herceptin were similar (15.5% and 16.6% respectively) and was slightly higher for HD201 (19.5%).
3. Across treatments, the T1/2el was similar. Clearance and volume of distribution of trastuzumab were consistent across treatments.

Therefore, the measured PK parameters are a valid contribution towards demonstration of biosimilarity. Statistical comparison, applying the same procedures, for half-life, clearance and volume of distribution has not been performed. Similarity of the values across treatments is a valuable element in assessing biosimilarity.

Table 3: TROIKA-1: Statistical analysis of PK parameters of HD201, EU-Herceptin, and US-Herceptin (PKP population)

Parameters	Geometric mean [95% CI]	Ratio (%) [90% CI]
HD201 vs. EU-Herceptin		
$AUC_{0\text{-}inf}$ (h*µg/mL)		
HD201 (N = 32)	38350.2 [36251.9; 40570.0]	
EU-Herceptin (N = 34)	37432.7 [35444.1; 39532.9]	
HD201/EU-Herceptin		102.45 [95.95; 109.40]
$AUC_{0\text{-}last}$ (h*µg/mL)		
HD201 (N = 32)	36587.5 [34521.4; 38777.2]	
EU-Herceptin (N = 34)	35337.1 [33399.5; 37387.0]	
HD201/EU-Herceptin		103.54 [96.76; 110.80]
C_{max} (µg/mL)		
HD201 (N = 32)	148.86 [140.19; 158.06]	
EU-Herceptin (N = 34)	142.28 [134.24; 150.81]	
HD201/EU-Herceptin		104.62 [97.55; 112.20]
EU-Herceptin vs. US-Herceptin		
$AUC_{0\text{-}inf}$ (h*µg/mL)		
EU-Herceptin (N = 34)	37432.7 [35444.1; 39532.9]	
US-Herceptin (N = 31)	37298.5 [35226.0; 39492.9]	
EU-/US-Herceptin		100.36 [93.94; 107.22]
$AUC_{0\text{-}last}$ (h*µg/mL)		
EU-Herceptin (N = 34)	35337.1 [33399.5; 37387.0]	
US-Herceptin (N = 31)	35619.9 [33577.2; 37786.8]	
EU-/US-Herceptin		99.21 [92.65; 106.22]
C_{max} (µg/mL)		
EU-Herceptin (N = 34)	142.28 [134.24; 150.81]	
US-Herceptin (N = 31)	151.10 [142.16; 160.60]	
EU-/US-Herceptin		94.17 [87.75; 101.05]
HD201 vs. US-Herceptin		
$AUC_{0\text{-}inf}$ (h*µg/mL)		
HD201 (N = 32)	38350.2 [36251.9; 40570.0]	
US-Herceptin (N = 31)	37298.5 [35226.0; 39492.9]	
HD201/US-Herceptin		102.82 [96.15; 109.96]
$AUC_{0\text{-}last}$ (h*µg/mL)		
HD201 (N = 32)	36587.5 [34521.4; 38777.2]	
US-Herceptin (N = 31)	35619.9 [33577.2; 37786.8]	
HD201/US-Herceptin		102.72 [95.84; 110.09]
C_{max} (µg/mL)		
HD201 (N = 32)	148.86 [140.19; 158.06]	
US-Herceptin (N = 31)	151.10 [142.16; 160.60]	
HD201/US-Herceptin		98.52 [91.71; 105.82]

$AUC_{0\text{-}inf}$: area under the concentration-time curve from 0 extrapolated to infinity; $AUC_{0\text{-}last}$: area under the concentration-time curve from 0 to last quantifiable analyte concentration; C_{max}: maximum observed concentration; Mean: least squares mean; CI: confidence interval; N: number of subjects with the PK parameter.

Statistical comparison, applying the standard procedures used in assessing bioequivalence for AUC0-inf, AUC0-last, and Cmax, demonstrated bioequivalence in each pairwise comparison: HD201 vs EU-

Herceptin; EU-Herceptin vs US-Herceptin and HD201 vs US-Herceptin. For half-life, clearance and volume of distribution has not been performed. However, similarity of the values across treatments is a valuable element in assessing biosimilarity.

A total of 105 subjects were randomised. The safety population consisted of all subjects who received at least one dose of the study medication. The Intention-to-Treat (ITT) Population consisted of all randomised subjects based on the randomised treatment, regardless of the actual treatment received. All subjects were included in the ITT population and in the safety population. Evaluation of immunogenicity was based on the safety population. Evaluation of PK concentration was based on the PK concentration (PKC) population (i.e. all subjects who received a complete dose of the study drug, had at least one quantifiable PK concentration and did not have major protocol deviations that could significantly affect the PK assessment), and statistical analysis of PK parameters was based on the PK parameter (PKP) population (all subjects of the PKC population who received a complete dose of study drug within the maximum prescribed time limits and for whom the PK profile was adequately characterised) and the modified PKP population.

Four subjects (1 subject from the HD201 group and 3 subjects from the US-Herceptin group) were excluded from the PKC population due to incomplete administration of the study drug. Additionally, four subjects of the PKC Population were excluded from the PKP population as the PK profile could not be adequately characterised due to 2 or more consecutive samples missing at the end of the PK profile (2 subjects from the HD201 group, 1 subject from the EU-Herceptin and 1 subject from the US-Herceptin treatment group).Three subjects excluded from the PKP population due to lack of 2 or more consecutive PK samples (2 subjects from the HD201 arm and one subject from the EU-Herceptin arm) were included in the analysis to enable a more complete and consistent evaluation of PK. PK parameters were therefore recalculated in an additional study population including the three subjects (defined as the modified PKP population) to confirm bioequivalence between the test and reference drugs.

The modified PKP population – which is identical to the PKC population for the treatment groups HD201 and EU-Herceptin – is regarded as the relevant population for the PK evaluation. Further, the relevant comparison is the one between HD201 and EU-Herceptin; thus, the results of the US-Herceptin group are not discussed in detail.

Table 4: Number of subjects for each analysis population

Population	HD201	EU-Herceptin	US-Herceptin	Overall
ITT	35	35	35	105
Safety	35	35	35	105
PKC population	34	35	32	101
PKP population	32	34	31	97
modified PKP population	34	35	31	100

ITT: Intention-to-treat population; PKC: Pharmacokinetic concentration; PKP: Pharmacokinetic parameter

Protocol deviations were reported for all subjects. Most of the deviations were minor. Major protocol deviations were reported for 14 subjects, 10 had a major deviation related to the absence of safety evaluations (4, 4 and 2 in the HD201, EU-Herceptin and US-Herceptin group, respectively) and 4 subjects had a major deviation due to administration of an incomplete dose of study drug (1 in the HD201 group and 3 in the US-Herceptin group). It was concluded that the protocol deviations had no material impact on the study and neither affected the safety of the subjects nor the integrity of the study data. The exclusion of one subject in the HD201 group from the modified PKP population is agreed upon.

Overall, systemic exposure based on AUC0-inf, AUC0-last, and Cmax after administration of HD201, EU-Herceptin or US-Herceptin, was similar in the PKP population as well as in the modified PKP population. Similar results between groups were also observed for T1/2el, Kel, CL and Vd.

Differences are noted in the data for the secondary PK parameter Tmax (h) as shown in the following table.

Table 5: Tmax values in the PKP and Modified PKP Population

PKP population			
	HD201 N=32	EU-Herceptin N=34	US-Herceptin N=31
Median	1.725	3.150	1.567
Mean	2.930	3.634	3.337
SD	1.528	2.613	2.759
Modified PKP population			
	HD201 N=34	EU-Herceptin N=35	US-Herceptin N=31
Median	1.767	4.500	1.567
Mean	2.940	3.660	3.337
SD	1.523	2.578	2.759

Distinctly longer Tmax values were observed in the EU-Herceptin group as compared to the HD201 group (as well as the US-Herceptin group) for both, the PKP population and the modified PKP population. The Applicant discussed these differences and provided plots of the patient-wise concentration curves, as requested during assessment. Upon review of the data, it is acknowledged that the majority of subjects across both groups had Tmax close to the end of infusion and 3 hours post-infusion and that the observed differences in mean Tmax are negligible.

The following results were obtained for the ratio of the geometric mean of the primary PK parameter AUC0-inf:

- HD201 vs. EU-Herceptin, PKP population 102.45, with 90% CI [95.95%; 109.40%]
- HD201 vs. EU-Herceptin, modified PKP population 103.76, with 90% CI [97.19% to 110.78%].

The 90% CI of the ratio of geometric means of AUC0-inf was contained within the predefined acceptance range [80.00% to 125.00%].

Additionally, the 90% CI of the ratio of geometric means for the secondary PK parameters, AUC0-last and Cmax, of HD201 vs. EU-Herceptin were both contained within the predefined acceptance interval [80.00% to 125.00%] in both, the PKP and the modified PKP populations.

TROIKA study

PK results (TROIKA)

The primary objective of the TROIKA study was to show equivalence in terms of total pathological complete response (tpCR) assessed at the time of surgery in patients treated with HD201 to that in patients treated with EU-Herceptin after the completion of 8 cycles of neoadjuvant treatment in combination with chemotherapy. Comparison of PK trough (C_{trough}) values of HD201 and EU-Herceptin was one of the secondary endpoints of TROIKA study.

Descriptive statistics of the Ctrough levels for samples taken within 19-23 days after last study drug administration are provided in Table 6 and Table 7 for the PPS and mFAS populations, respectively, for before cycles 5, 8, 10 and 14.

Table 6: PK Ctrough levels (µg/mL) at Before Cycle 5, Cycle 8, Cycle 10, and Cycle 14 (samples)

Statistics	Before Cycle 5		Before Cycle 8		Before Cycle 10		Before Cycle 14	
	HD201 N=238	Herceptin N=236	HD201 N=238	Herceptin N=236	HD201 N=238	Herceptin N=236	HD201 N=238	Herceptin N=236
n	224	222	209	205	25	24	119	122
Mean (SD)	42.85 (20.20)	43.96 (27.47)	54.87 (21.39)	53.12 (18.85)	43.78 (21.83)	34.39 (12.96)	57.96 (25.97)	52.21 (21.70)
Median	41.30	39.25	53.10	51.20	34.80	30.45	57.30	46.85
Min; Max	1.0; 249.0	10.6; 268.0	1.0; 219.0	1.0; 139.0	23.5; 121.0	8.2; 69.9	1.0; 201.0	1.0; 160.0
C_{trough} < 20 µg/mL n'/n (%)	13/224 (5.8%)	12/222 (5.4%)	4/209 (1.9%)	5/205 (2.4%)	0/25 (0.0%)	2/24 (8.3%)	5/119 (4.2%)	2/122 (1.6%)
Mean difference (HD201-Herceptin) % [90% CI]	-2.5% [-11.1%; 6.1%]		3.3% [-2.9%; 9.5%]		27.3% [2.1%; 52.4%]		11.0% [1.3%; 20.8%]	
Geometric mean (HD201/Herceptin) ratio [90% CI]	97.2% [89.7%; 105.4%]		102.8% [95.5%; 110.6%]		124.8% [101.9%; 152.8%]		106.8% [94.3%; 121.0%]	

N: Number of patients within the group; n: Number of patients with an available assessment; n': Number of patients within the category; CI: Confidence interval; PPS: Per protocol set; SD: Standard deviation.

Table 7: PK Ctrough levels (µg/mL) at Before Cycle 5, Cycle 8, Cycle 10, and Cycle 14 (samples

Statistics	Before Cycle 5		Before Cycle 8		Before Cycle 10		Before Cycle 14	
	HD201 N=250	Herceptin N=252	HD201 N=250	Herceptin N=252	HD201 N=250	Herceptin N=252	HD201 N=252	Herceptin N=252
n	230	231	215	213	27	26	122	126
Mean (SD)	42.45 (20.14)	43.77 (27.04)	54.85 (21.36)	53.42 (18.82)	41.65 (22.34)	34.24 (12.44)	57.45 (26.73)	51.96 (21.47)
Median	41.15	39.10	53.10	51.50	34.40	31.05	56.50	46.85
Min; Max	1.0; 249.0	10.6, 268.0	1.0; 219.0	1.0; 139.0	12.2; 121.0	8.2; 69.9	1.0; 201.0	1.0; 160.0
C_{trough} < 20 µg/mL n'/n (%)	15/230 (6.5%)	12/231 (5.2%)	4/215 (1.9%)	5/213 (2.3%)	2/27 (7.4%)	2/26 (7.7%)	7/122 (5.7%)	2/126 (1.6%)
Mean difference (HD201-Herceptin) % [90% CI]	-3.0% [-11.4%; 5.3%]		2.7% [-3.3%; 8.7%]		21.7% [-2.8%; 46.1%]		10.6 [0.8; 20.3%]	
Geometric mean (HD201/Herceptin) ratio [90% CI]	96.4% [89.1%; 104.3%]		102.1% [95.0%; 109.7%]		115.8% [94.2%; 142.5%]		103.1% [90.2%; 117.9%]	

N: Number of patients within the group; n: Number of patients with an available assessment; n': Number of patients within the category; CI: Confidence interval; mFAS: modified full analysis set; SD: Standard deviation.

For the TROIKA clinical study, 1742 samples were analysed in 82 analytical runs. Precision and accuracy for QC samples were met. Incurred sample re-analysis was performed on 140 serum samples and 99.3 % of samples met the acceptance criteria.

C_{trough} was determined in samples drawn at pre-dose of cycles 5, 8, 10 and 14. The analysis of C_{trough} was performed based on the modified full analysis set (mFAS; consisting of all patients who received at least one dose of study treatment) and the per protocol set (PPS; consisting of all patients of the mFAS who received the study treatment according to the protocol, without any major protocol deviation impacting the primary efficacy assessment, and who had surgery after completion of neoadjuvant treatment or did not undergo surgery due to lack of efficacy).

For before Cycle 10, the ratio of the geometric means between the two treatment groups was 124.8% [101.9%; 152.8%] at before Cycle 10 in the PPS population and 115.4% [93.8%; 142.0%] in the mFAS population. The 90% CI on the ratio of geometric means were wide and not within the equivalence margin of 80.00% to 125.00%.

For TROIKA, in all patients of the mFAS (modified Full Analysis set), the mean ratio (90% CI) between the treatment groups was 99.3% [91.2%; 108.2%] before Cycle 5, 100.8% [94.0%; 108.0%] before Cycle 8, and 102.7% [90.1%; 117.0%] before Cycle 14. At each of the before cycles 5, 8, and 14, the 90% confidence interval on the ratio of geometric means of the Ctrough level of the two treatments is contained within the defined equivalence interval [80.00%; 125.00%], implying that bioequivalence of HD201 to Herceptin® for steady-state trough level can be accepted.

2.6.2.2. Pharmacodynamics

HD201 has been developed as a biosimilar product to the reference drug Herceptin (Trastuzumab). HD201 is a humanized IgG1 monoclonal antibody directed against the human epidermal growth factor receptor-2 (HER2).

The Applicant provided an adequate justification for the absence of clinical PD studies, stating that PD studies were not performed for HD201 as no PD markers have been validated for prediction of clinical efficacy of trastuzumab.

2.6.1. Discussion on clinical pharmacology

Two studies TROIKA-1 and TROIKA were performed. The first one is a standard phase I bioequivalence study. The second one contained an assessment of bioequivalence based on the C_{trough} value before each treatment cycle. These studies are used as the main justification to support the MAA.

From TROIKA-1, overall exposure to trastuzumab, assessed by AUC0-inf and AUC0-last, and peak systemic exposure to trastuzumab assessed by Cmax, were shown to be equivalent in each pairwise comparison between HD201 and EU-Herceptin, HD201 and US-Herceptin and EU-Herceptin and US-Herceptin in both the PKP and modified PKP population. For all comparisons, the 90% CIs for the ratio of the geometric mean of AUC0-inf, AUC0-t, and Cmax, were all contained within the acceptance interval of 80.00% to 125.00%.

Based on these results, pharmacological equivalence of HD201 with EU-Herceptin has been demonstrated in both, the PKP and the modified PKP populations in the primary PK parameter AUC0-inf as well as in the secondary PK parameters AUC0-t and Cmax. Furthermore, equivalence of HD201 with US-Herceptin and of EU-Herceptin and US-Herceptin has been demonstrated.

TROIKA was a Phase III study with a PK component, consisting of the analysis of the Ctrough values before each treatment cycle. The comparison of C_{trough} values before Cycle 5 and before Cycle 8 as well

as pre-dose of Cycle 10 and Cycle 14 can be considered an adequate PK end point for study TROIKA, as well as the corresponding method. The method for calculating sample size is essentially sound.

The statistical methods used for C_{trough} in TROIKA essentially follow the standard procedures used in assessing bioequivalence. The acceptance limits were: 90% CIs completely within the acceptance interval of -20% to 20%. This is adequate for the purpose.

At each of the before cycles 5, 8, and 14, the 90% confidence interval on the ratio of geometric means of the Ctrough level of the two treatments is contained within the defined equivalence interval [80.00%; 125.00%], implying that bioequivalence of HD201 to Herceptin for steady-state trough level can be accepted.

At before Cycle 10, only 57 samples were available for analysis and the mean ratio (90% CI) between the treatment groups (115.4% [93.8%; 142.0%] was not contained within the 80% - 125% equivalence margin possibly due to the small sample size. The applicant provided a thorough explanation for the low number of samples at before Cycle 10, which occurred due to a change in the protocol upon regulatory request. At the time of implementation, most patients had already completed Cycle 10 and it would be impossible to revert the situation. This is considered an acceptable explanation and the Ctrough evaluation in Cycles 5, 8 and 14 showed compliance with the bioequivalence criteria, lowering the impact of this finding in the context of a global assessment of this particular subject.

2.6.2. Conclusions on clinical pharmacology

In conclusion, PK results support demonstration of biosimilarity between HD201 and Herceptin.

2.7. Clinical efficacy

2.7.1. Dose response study(ies)

No dose response study was conducted.

2.7.2. Main study

Troika

A randomised, double-blind, parallel group, equivalence, multicentre phase III trial to compare the efficacy, safety, and pharmacokinetics of HD201 to Herceptin in patients with HER2+ early breast cancer.

The clinical development program to compare efficacy, safety, PK and immunogenicity between HD201 and EU-Herceptin is based on a single randomised, double-blind, parallel group, equivalence, multicentre, international Phase III study (TROIKA, 2016-0004019-11). Patients who had histologically confirmed, newly diagnosed clinical Stage II-III (as classified according to the AJCC, Breast Cancer Staging, 8th edition), operable, HER2-positive adenocarcinoma of the breast were eligible for the study.

The study was initiated 19 February 2018 and data cutoff for the primary analysis was 19 April 2019. Subjects were screened between 19 February and 21 September 2018.

The study is completed (LVLP 13 January 2022).

Methods

Study participants

Patients were recruited from 19 February 2018 (date of first informed consent) through 21 September 2018 (date of last informed consent) in 70 centres across 12 countries. Last patient completed the adjuvant treatment period (i.e., completing the EOT visit) on 21 January 2020, and the last patient completed the last follow-up visit on 13 January 2022.

Study population selected for the TROIKA study included women with histologically confirmed and newly diagnosed clinical stage II-III (as classified according to the American Joint Committee on Cancer, Breast Cancer Staging Manual 8th edition), operable, HER2-positive EBC. Patients with EBC are a more homogenous and sensitive population with fewer confounding characteristics (i.e., multiple prior treatments, comorbidities) and were therefore chosen for the study.

Inclusion criteria

Patients had to meet all the following criteria to be eligible for the study:

1. Able and willing to give written informed consent
2. Female aged ≥ 18 years old
3. Eastern Cooperative Oncology Group (ECOG) performance status < 2.
4. Known hormone receptor (oestrogen and progesterone receptors) status.
5. HER2 overexpressed as assessed by:
    - Immunohistochemistry (IHC) or
    - Fluorescent in situ hybridization (FISH); FISH positive is defined as FISH amplification ratio ≥ 2/number of HER2 gene copies per cell > 2; or
    - Chromogenic in situ hybridization (CISH) positive
    - Inform HER2 Dual ISH (DISH positive)
    - Patients with IHC score 3+ or positive FISH/CISH/DISH test
    - Patients with IHC score 2+ must have positive FISH/CISH/DISH test.
6. Left ventricular ejection fraction (LVEF) ≥ 50% or within the normal level of the institution, as assessed by echocardiography or multiple gated acquisition (MUGA) scan.
7. Life expectancy > 12 weeks.
8. Adequate bone marrow function as evidenced by the following (maximum 5% deviation):
    - Absolute neutrophils count ≥ 1,500/μL
    - Haemoglobin ≥ 9 g/dL
    - Platelet count ≥ 100,000/μL.

9. Adequate hepatic and renal function as evidenced by the following

(maximum 10% deviation is acceptable):

- Creatinine clearance ≥ 60 mL/min
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- AST (SGOT) and (SGPT) ≤ 2.5 x ULN.

10. Ability to comply with the study protocol.

11. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to first dose of study treatment and agree to use effective contraception (intrauterine device, diaphragm, diaphragm with spermicide or a reliable barrier method, e.g. condom, or condom with spermicide) throughout the study period and 7 months after discontinuation of study drug.

12. Non- metastatic, unilateral newly diagnosed, operable early breast cancer (EBC) of clinical stage II to III including inflammatory breast cancer. Histologically confirmed primary invasive carcinoma of the breast.

Exclusion criteria

Patients meeting any of the following criteria were not eligible for the study:

1. Metastatic (Stage IV) with exception of supraclavicular nodes.

2. Bilateral breast cancer.

3. Multicentric breast cancer.

4. History of any prior invasive breast carcinoma, except for patients with a history of ductal carcinoma in situ (DCIS) treated with surgery.

5. 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 neoplasms occurring more than 5 years prior to randomisation were permitted if curatively treated with surgery only).

6. Previous history of radiation therapy, anti-neoplastic immunotherapy, chemotherapy, or anti-neoplastic biotherapy (including prior HER2 directed therapy).

7. Major surgery within 2 weeks prior to randomization.

8. Serious cardiac illness that would preclude use of trastuzumab such as:

- History of documented congestive heart failure (CHF) (New York Heart Association, NYHA, class III, or greater heart disease)
- LVEF < 50% by echocardiography or MUGA scan
- Angina pectoris requiring anti-anginal medication
- Evidence of transmural infarction on electrocardiogram (ECG)
- Uncontrolled hypertension (systolic >180 mmHg and/or diastolic >100 mmHg)
- Clinically significant valvular heart disease

- High risk uncontrolled arrhythmias.

9. Serious pulmonary illness enough to cause dyspnoea at rest or requiring supplementary oxygen therapy.

10. Known history of active hepatitis B and hepatitis C virus infections.

11. Known HIV infection by patient declaration.

12. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgement of the investigator would make the patient inappropriate for entry into this study.

13. Known hypersensitivity to the investigational medicinal product (IMP), non-IMPs or any of the ingredients or excipients of the IMP or non-IMP.

14. Known hypersensitivity to murine proteins.

15. Pre-existing peripheral sensory or motor neuropathy ≥ grade 2, as defined by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

16. Lactating or pregnant 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 contraceptive methods during the study and for 7 months after the last dose of IMP.

17. Participation in any clinical study or having taken any investigational therapy during the 1-month period immediately preceding administration of the first dose.

18. Patients unwilling to follow the study requirements.

Treatments

Neoadjuvant Period

Investigational product (H201 or Herceptin)

- Cycle 1: 8 mg/kg IV loading dose over 90 min
- Cycle 2: 6 mg/kg over 60 min
- Cycles 3-8: 6 mg/kg over 30 min

Chemotherapy was to be administered in both groups as follows:

- Cycles 1-4: Docetaxel 75 mg/m² on day 1 of each cycle via a 1h IV infusion
- Cycles 5-8: EC on day 1 of each cycle:
    - Epirubicin 75 mg/m² administered between 3-30 min via IV infusion
    - Cyclophosphamide 500 mg/m² administered between 3-30 minutes via IV infusion

Adjuvant Period (after surgery)

Investigational product (H201 or Herceptin)

- Cycle 9: 8 mg/kg IV loading dose over 90 min
- Cycles 10-18: 6 mg/kg over 30 min

Objectives

Primary objective

- The primary objective of this study is to compare the total pathological complete response rate (tpCR) in patients treated with HD201 plus chemotherapy to that in patients treated with Herceptin plus chemotherapy in HER2+ early breast cancer.

Secondary objectives

- To evaluate the efficacy of HD201 compared to Herceptin by total breast pathological complete response rate (bpCR), overall response rate (ORR), event-free survival (EFS) and overall survival (OS).

To compare immunogenicity, safety and tolerability and PK between HD201 and Herceptin.

Outcomes/endpoints

Primary endpoint

Total pathological complete response (tpCR), defined as complete absence of cancer cells in the breast and in axillary lymph nodes (ypT0/is, ypN0) at the time of surgery, after eight cycles of neoadjuvant treatment completion. tpCR was to be assessed both at the study site (local reading) and by a central institution (central reading).

The analysis of the primary efficacy variable is an equivalence analysis based on an exact 95% CI on the difference in tpCR rate at the time of surgery. Equivalence will be concluded if the 95% CI on the difference of the two proportions is completely contained within the interval ±15%.

Secondary efficacy endpoints

- Breast pathological complete response (bpCR) is defined as complete disappearance of cancer cells in the breast (ypT0/is) at the time of surgery.
- Overall response rate (ORR) is defined as proportion of patients whose best overall response is either complete response (CR) or partial response (PR) as assessed by ultrasound, mammography and clinical examination prior to surgery.
- Event free survival (EFS) is defined as the time from randomisation until progression of disease or death from any cause two years after end of treatment.
- Overall survival (OS) is defined as the time from randomisation until death from any cause two years after end of treatment.

The breast tumour should be assessed before and after neoadjuvant treatment by mammography, ultrasound, and clinical assessment.

Safety and Tolerability

- Adverse events
- Clinical laboratory parameters
- Cardiac dysfunction monitored by 12-lead ECG
- LVEF measured by electrocardiography or MUGA scan
- Vital signs
- Physical examination

Immunogenicity

- Incidence of human trastuzumab antibodies at baseline, before Cycle 5 (this sample was only to be tested if pre-surgery sample is (ADA) positive), before surgery, post-surgery (before Cycle 10), before Cycle 14, at end of treatment and one year after completion of trastuzumab therapy.

Pharmacokinetics

C_{trough} at Cycle 5 (Week 12), Cycle 8 (Week 21), Cycle 10 and Cycle 14.

Sample size

The sample size calculation was based on results from randomised trials with data for tpCR. The assumptions used were that the response rate with both treatments would be 40% and that equivalence was to be shown based on a 95% CI on the difference between the 2 groups, using an equivalence margin of 15%.

To have 80% power of showing equivalence data should be available for 224 patients per treatment group. Considering approximately 10% dropouts or non-evaluable patients a total of 500 patients were to be randomised.

To demonstrate equivalence of the two treatment groups based on PK C_{trough} values before Cycle 5 and before Cycle 8, data were to be available in a total of 300 of the randomised patients (150 per treatment group). This number was calculated to have 90% power to show equivalence, when testing the difference between the two treatment groups at the 5% level of significance using a 20% margin of equivalence. To ensure values would be available for 150 patients in each treatment group, blood samples for PK were to be analysed for a total of 320 randomised patients.

Randomisation and blinding (masking)

Patients were randomised by IWRS in a 1:1 ratio to HD201 or reference Herceptin®. A list containing the randomization numbers and corresponding treatments was kept with the IWRS vendor.

Patients were stratified by:

- Geographical region (Asia, Eastern Europe, Central Europe, Western Europe).
- Clinical stage: Stage II vs. III
- Oestrogen and progesterone receptor status (positive vs. negative).

The TROIKA study was double-blind study.

Statistical methods

The primary efficacy analysis aimed to show the equivalence in terms of the tpCR rate between HD201 and Herceptin within pre-defined equivalence margins, which was set to [−15% ; 15%] in this study.

In accordance with the published EMA position, equivalence was declared if the 95% CI of the difference in the tpCR rate between treatments was entirely contained within the equivalence margin.

The two-sided 95% CI of the difference in the tpCR was estimated for the Per protocol Set (PPS) as primary analysis and for the modified Full Analysis Set (mFAS) as supportive analysis.

The secondary efficacy analysis aimed to demonstrate similarity in terms of bpCR, ORR, EFS, and OS between HD201 and Herceptin. All statistical comparisons were made using two sided tests at the α=0.05 significance level. Time to event endpoints (OS, EFS) were analyzed using the Kaplan-Meier approach for survival data and Cox regression.

AEs were summarized by the number and percentage of patients experiencing events by MedDRA system organ class, preferred term, relationship with study drug and chemotherapy, and severity.

The incidence of ADAs was summarized by treatment group and time-point. Confirmed ADA positive samples were further analysed to assess the neutralizing potential.

Population selection:

The following analysis sets were defined for this study:

Total Set: All patients who consented to participate in the study.

Full Analysis Set (FAS): All randomised patients.

modified FAS (mFAS): All patients of the FAS who received at least one dose of study medication (HD201 or Herceptin).

Per Protocol Set (PPS): All patients of the mFAS who received the study treatment according to the protocol, without any major protocol deviation impacting the primary efficacy assessment, and who had surgery after completion of neoadjuvant treatment or did not undergo surgery due to lack of efficacy. Protocol deviations were assessed during a pre-analysis review meeting that was held before database lock.

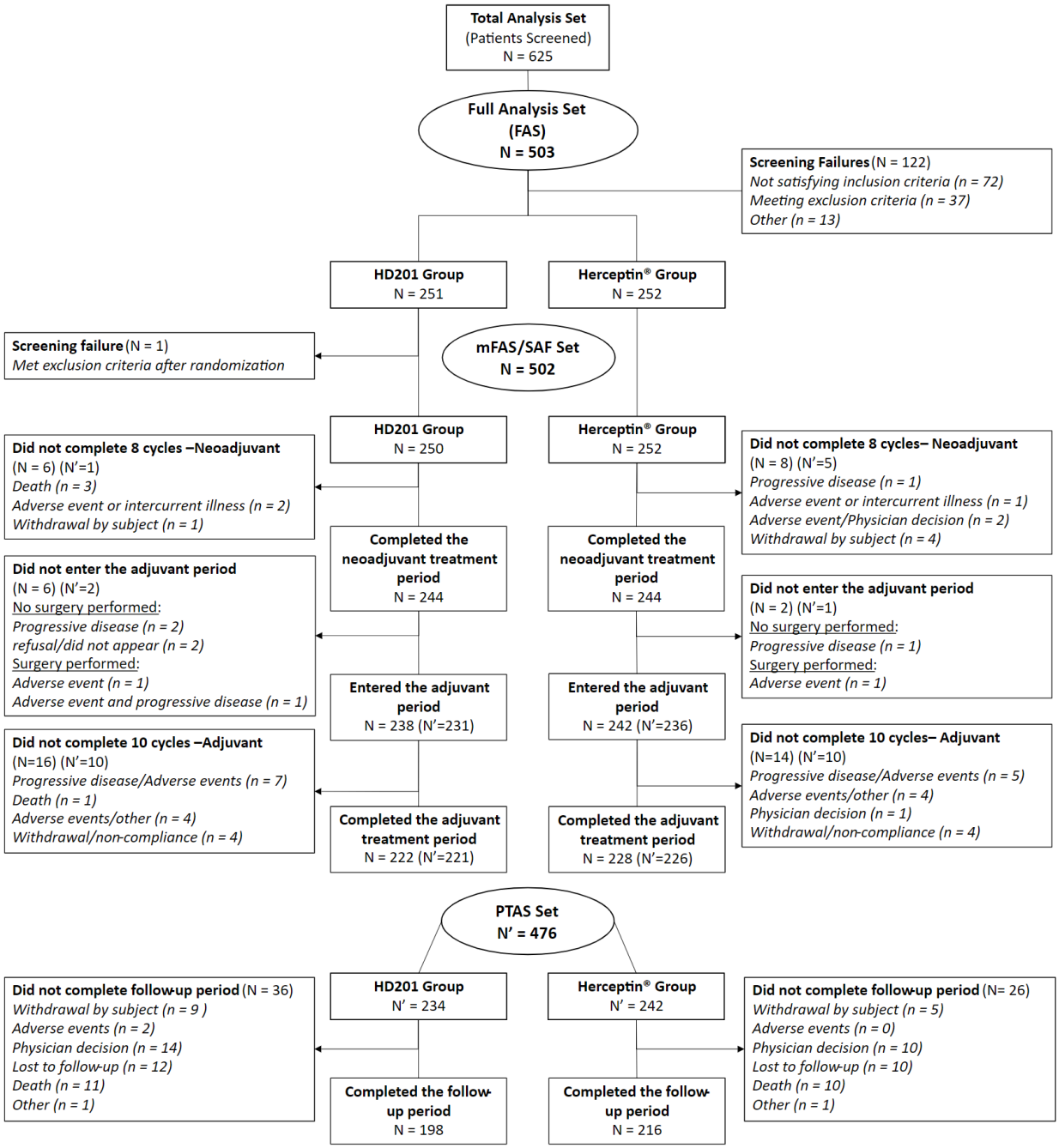
restricted PPS (rPPS): All patients of the PPS excluding:

- Patients with sentinel node biopsy procedure and positive nodes at screening.
- Patients without residual breast tumour, without axillary clearance, and without sentinel node biopsy performed at screening.

Safety Set (SAF): All patients of the FAS who received at least one dose of study medication (HD201 or Herceptin).

Results

Participant flow



Recruitment

Patients were recruited from 19 February 2018 (date of first informed consent) through 21 September 2018 (date of last informed consent) in 70 centres across 12 countries.

Last patient completed the adjuvant treatment period (i.e. completing the EOT visit) on 21 January 2020, and the last patient completed the last follow-up visit on 13 January 2022.

Conduct of the study

The original study protocol (version 2.1) is dated 08 November 2017.

The protocol version 2.1 was amended to version 2.2 on 19 April 2018 (to add Dual ISH (DISH) test to the inclusion criteria to assess overexpression of HER2+, to update section on blinding to indicate that the pharmacists were only partially blinded, not blinded and to add details on dosing regimen, period (neoadjuvant, surgery, adjuvant), treatment cycle and treatment duration.), Version 3.0 were introduced in 01 October 2018 -to change the planned completion of recruitment changed from Q2 2018 to Q3 2018, planned end of study from Q4 2021 to Q1 2022, and analysis of primary endpoint from Q4 2018 to Q1 2019; to add timepoints for the collection of immunogenicity samples to include Cycle 5; top add NAb testing, in which only ADA-positive samples were to be tested for Nab; to update Section on PK analysis with a change in the number of patients required for PK analysis; to add IHC2+/DISH+ to define HER2 positive tumours; and to alter timing of central reading of tpCR to "to be performed at a later stage".

A local protocol amendment version 2.2 dated 26 April 2018 based on protocol version 2.2 was locally approved in France (N = 2) which included additional eligibility criteria based on local regulatory requirement (to add the following exclusion criteria (EC 19 to 22): patients with stage 1 breast cancer, patients with acute urinary tract infection or pre-existing haemorrhagic cystitis, patients who have received live attenuated vaccines, patients who have received prohibited drugs).

Protocol amendment version 3.0 was approved in Belarus, Georgia, Malaysia, Russia, Spain, Thailand, and Ukraine (N = 477).

GCP Inspection

Pre-approval GCP inspections of the sponsor and two of the sites in Russia and Thailand were conducted (EudraCTnr: 2016-004019-11).

The first GCP inspection for the phase III TROIKA study (EudraCTnr: 2016-004019-11) revealed critical GCP non-compliance that affected the credibility of the data. The sponsor was re-inspected, involving one CRO and one clinical site in Spain.

The second inspection in 2021 was conducted at a clinical site in Spain), the CRO in Spain, and Sponsor Prestige Biopharma.

Baseline data

Table 8: Demographic data (SAF and PPS)

	SAF			PPS		
	HD201	**Herceptin®**	**Total**	**HD201**	**Herceptin®**	**Total**
	N=250	**N=252**	**N=502**	**N=238**	**N=236**	**N=474**
Age (years)	n' = 250	n' = 252	n' = 502	n' = 238	n' = 236	n' = 474
Mean (SD)	53.58 (11.52)	53.13 (11.41)	53.35 (11.45)	53.40 (11.67)	52.67 (11.13)	53.03 (11.40)
Median	53.69	54.21	54.05	53.69	53.56	53.61
Min ; Max	26.3 ; 79.4	28.0 ; 82.1	26.3 ; 82.1	26.3 ; 79.4	28.0 ; 77.9	26.3 ; 79.4
Race n (%)	n' = 250	n' = 252	n' = 502	n' = 238	n' = 236	n' = 474
Asian	24 (9.6%)	24 (9.5%)	48 (9.6%)	22 (9.2%)	21 (8.9%)	43 (9.1%)
White/ Caucasian	226 (90.4%)	228 (90.5%)	454 (90.4%)	216 (90.8%)	215 (91.1%)	431 (90.9%)
Region n (%)	n' = 250	n' = 252	n' = 502	n' = 238	n' = 236	n' = 474
Asia	20 (8.0%)	19 (7.5%)	39 (7.8%)	19 (8.0%)	17 (7.2%)	36 (7.6%)
Western Europe	13 (5.2%)	12 (4.8%)	25 (5.0%)	9 (3.8%)	6 (2.5%)	15 (3.2%)
Central Europe	1 (0.4%)	2 (0.8%)	3 (0.6%)	1 (0.4%)	2 (0.8%)	3 (0.6%)
Eastern Europe	216 (86.4%)	219 (86.9%)	435 (86.7%)	209 (87.8%)	211 (89.4%)	420 (88.6%)
Childbearing Potential Status n (%)	n' = 250	n' = 252	n' = 502	n' = 238	n' = 236	n' = 474
Childbearing potential	94 (37.6%)	100 (39.7%)	194 (38.6%)	91 (38.2%)	97 (41.1%)	188 (39.7%)
Surgical sterilization	6 (2.4%)	11 (4.4%)	17 (3.4%)	6 (2.5%)	10 (4.2%)	16 (3.4%)
Peri-menopausal	6 (2.4%)	10 (4.0%)	16 (3.2%)	6 (2.5%)	10 (4.2%)	16 (3.4%)
Post-menopausal for ≥ 2 years	144 (57.6%)	131 (52.0%)	275 (54.8%)	135 (56.7%)	119 (50.4%)	254 (53.6%)

N = number of patients in the analysis set; n' = number of patients with assessments; n = number of patients in the category; SD = standard deviation; Min = minimum; Max = maximum.
Percentages were based on the number of patients with assessments.

Table 9: Demographic data (SAF)

	HD201	Herceptin®	Total
	N=250	N=252	N=502
Age (years)	n' = 250	n' = 252	n' = 502
Mean (SD)	53.57 (11.52)	53.13 (11.41)	53.35 (11.46)
Median	53.69	54.21	54.01
Min ; Max	26.3 ; 79.4	28.0 ; 82.1	26.3 ; 82.1
Race n (%)	n' = 250	n' = 252	n' = 502
Asian	24 (9.6%)	24 (9.5%)	48 (9.6%)
White/Caucasian	226 (90.4%)	228 (90.5%)	454 (90.4%)
Childbearing Potential Status n (%)	n' = 250	n' = 252	n' = 502
Childbearing potential	95 (38.0%)	97 (38.5%)	192 (38.2%)
Surgical sterilization	5 (2.0%)	10 (4.0%)	15 (3.0%)
Peri-menopausal	5 (2.0%)	11 (4.4%)	16 (3.2%)
Post-menopausal for ≥ 2 years	145 (58.0%)	134 (53.2%)	279 (55.6%)

N = number of subjects in the SAF; n' = number of subjects with assessments; n = number of subjects in the category; SD = standard deviation; Min = minimum; Max = maximum. Percentages were based on the number of subjects with assessments.

Table 10: Physical status and cardiac function (SAF)

	HD201	Herceptin®	Total
	N=250	N=252	N=502
Weight (kg)	n' = 250	n' = 252	n' = 502
Mean (SD)	71.2 (15.1)	72.8 (15.2)	72.0 (15.1)
Median	69.1	71.0	70.0
Min ; Max	43 ; 125	45 ; 122	43 ; 125
BMI (kg/m²)	n' = 250	n' = 252	n' = 502
Mean (SD)	27.22 (5.74)	27.86 (5.66)	27.54 (5.70)
Median	25.98	27.37	26.69
Min ; Max	17.1 ; 47.0	16.9 ; 44.9	16.9 ; 47.0
ECOG Performance Status n (%)	n' = 250	n' = 252	n' = 502
0	204 (81.6%)	190 (75.4%)	394 (78.5%)
1	46 (18.4%)	62 (24.6%)	108 (21.5%)
Left Ventricular Ejection Fraction (%)	n' = 250	n' = 252	n' = 502
Mean (SD)	65.1 (5.5)	65.8 (5.7)	65.5 (5.6)
Median	66.0	66.0	66.0
Min ; Max	52 ; 78	52 ; 80	52 ; 80
ECG Result n (%)	n' = 250	n' = 252	n' = 502
Normal	155 (62.0%)	145 (57.5%)	300 (59.8%)
Abnormal, not clinically significant	93 (37.2%)	107 (42.5%)	200 (39.8%)
Abnormal, clinically significant	2 (0.8%)	0 (0.0%)	2 (0.4%)

Table 11: Breast cancer history

	HD201	Herceptin®	Total
	N=250	N=252	N=502
Time Since Initial Diagnosis (months)	n' = 250	n' = 252	n' = 502
Mean (SD)	0.73 (1.61)	0.84 (1.96)	0.79 (1.79)
Median	0.46	0.53	0.51
Min ; Max	-0.5 ; 24.2	-0.7 ; 24.2	-0.7 ; 24.2
Clinical Stage n (%)	n' = 250	n' = 252	n' = 502
I B	0 (0.0%)	1 (0.4%)	1 (0.2%)
II A	65 (26.0%)	69 (27.4%)	134 (26.7%)
II B	80 (32.0%)	74 (29.4%)	154 (30.7%)
III A	38 (15.2%)	31 (12.3%)	69 (13.7%)
III B	47 (18.8%)	51 (20.2%)	98 (19.5%)
III C	20 (8.0%)	26 (10.3%)	46 (9.2%)
Hormone Receptor Status n (%)	n' = 250	n' = 252	n' = 502
ER+ or PR+	155 (62.0%)	153 (60.7%)	308 (61.4%)
ER+ / PR+	106 (42.4%)	98 (38.9%)	204 (40.6%)
ER+ / PR-	45 (18.0%)	46 (18.3%)	91 (18.1%)
ER- / PR+	4 (1.6%)	9 (3.6%)	13 (2.6%)
ER- / PR -	95 (38.0%)	99 (39.3%)	194 (38.6%)
Histological Grade n (%)	n' = 180	n' = 192	n' = 372
I	7 (3.9%)	6 (3.1%)	13 (3.5%)
II	108 (60.0%)	103 (53.6%)	211 (56.7%)
III	65 (36.1%)	83 (43.2%)	148 (39.8%)
Operable at Screening n (%)	n' = 248	n' = 248	n' = 496
Yes	181 (73.0%)	175 (70.6%)	356 (71.8%)
No	67 (27.0%)	73 (29.4%)	140 (28.2%)
Breast Cancer Symptoms n (%)	n' = 250	n' = 252	n' = 502
Presence of Any Symptom	89 (35.6%)	106 (42.1%)	195 (38.8%)
Inflammatory Breast	32 (12.8%)	37 (14.7%)	69 (13.7%)
Breast Pain	21 (8.4%)	25 (9.9%)	46 (9.2%)
Oedema arm(s)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Pain in arm(s)	2 (0.8%)	2 (0.8%)	4 (0.8%)
Subfebrile Status	2 (0.8%)	0 (0.0%)	2 (0.4%)
Other	42 (16.8%)	57 (22.6%)	99 (19.7%)

ER: Oestrogen receptor; PR: Progesterone receptor.
N = number of subjects in the SAF; n' = number of subjects with assessments; n = number of subjects in the category; SD = standard deviation; Min = minimum; Max = maximum. Percentages were based on the number of subjects with assessments.

HER2 results (2+ or 3+), medical and surgical history were similar between the two treatment groups and also diameters of tumour lesions at baseline were balanced between the two treatment groups.

Baseline disease characteristics

Table 12: Breast Cancer History (SAF and PPS)

	SAF			PPS		
	HD201 N=250	Herceptin® N=252	Total N=502	HD201 N=238	Herceptin® N=236	Total N=474
Time Since Initial Diagnosis (months)	n' = 250	n' = 252	n' = 502	n' = 238	n' = 236	n' = 474
Mean (SD)	0.64 (0.61)	0.84 (1.96)	0.74 (1.45)	0.64 (0.61)	0.83 (2.01)	0.73 (1.48)
Median	0.46	0.53	0.49	0.46	0.53	0.49
Min ; Max	-0.5 ; 4.0	-0.7 ; 24.2	-0.7 ; 24.2	-0.5 ; 4.0	-0.7 ; 24.2	-0.7 ; 24.2
Clinical Stage n (%)	n' = 250	n' = 252	n' = 502	n' = 238	n' = 236	n' = 474
I B	0 (0.0%)	1 (0.4%)	1 (0.2%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
II A	64 (25.6%)	70 (27.8%)	134 (26.7%)	61 (25.6%)	65 (27.5%)	126 (26.6%)
II B	80 (32.0%)	74 (29.4%)	154 (30.7%)	76 (31.9%)	68 (28.8%)	144 (30.4%)
III A	37 (14.8%)	29 (11.5%)	66 (13.1%)	34 (14.3%)	27 (11.4%)	61 (12.9%)
III B	50 (20.0%)	53 (21.0%)	103 (20.5%)	48 (20.2%)	51 (21.6%)	99 (20.9%)
III C	19 (7.6%)	25 (9.9%)	44 (8.8%)	19 (8.0%)	24 (10.2%)	43 (9.1%)
Hormone Receptor Status n (%)	n' = 250	n' = 252	n' = 502	n' = 238	n' = 236	n' = 474
ER+ or PR+	155 (62.0%)	152 (60.3%)	307 (61.2%)	152 (63.9%)	144 (61.0%)	296 (62.4%)
ER+ / PR+	106 (42.4%)	97 (38.5%)	203 (40.4%)	103 (43.3%)	93 (39.4%)	196 (41.4%)
ER+ / PR-	45 (18.0%)	48 (19.1%)	93 (18.5%)	45 (18.9%)	45 (19.1%)	90 (19.0%)
ER- / PR+	4 (1.6%)	7 (2.8%)	11 (2.2%)	4 (1.7%)	6 (2.5%)	10 (2.1%)
ER- / PR -	95 (38.0%)	100 (39.7%)	195 (38.8%)	86 (36.1%)	92 (39.0%)	178 (37.6%)
Histological Grade n (%)	n' = 180	n' = 192	n' = 372	n' = 169	n' = 179	n' = 348
I	6 (3.3%)	6 (3.1%)	12 (3.2%)	6 (3.6%)	6 (3.4%)	12 (3.4%)
II	109 (60.6%)	105 (54.7%)	214 (57.5%)	101 (59.8%)	99 (55.3%)	200 (57.5%)
III	65 (36.1%)	81 (42.2%)	146 (39.2%)	62 (36.7%)	74 (41.3%)	136 (39.1%)
Operable at Screening n (%)	n' = 248	n' = 248	n' = 496	n' = 236	n' = 232	n' = 468
Yes	183 (73.8%)	175 (70.6%)	358 (72.2%)	177 (75.0%)	166 (71.6%)	343 (73.3%)
No	65 (26.2%)	73 (29.4%)	138 (27.8%)	59 (25.0%)	66 (28.4%)	125 (26.7%)
Breast Cancer Symptoms n (%)	n' = 250	n' = 252	n' = 502	n' = 238	n' = 236	n' = 474
Presence of Any Symptom	92 (36.8%)	113 (44.8%)	205 (40.8%)	90 (37.8%)	109 (46.2%)	199 (42.0%)
Inflammatory Breast	32 (12.8%)	38 (15.1%)	70 (13.9%)	30 (12.6%)	36 (15.3%)	66 (13.9%)
Breast Pain	19 (7.6%)	24 (9.5%)	43 (8.6%)	18 (7.6%)	23 (9.7%)	41 (8.6%)
Oedema arm(s)	0 (0.0%)	1 (0.4%)	1 (0.2%)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Pain in arm(s)	3 (1.2%)	4 (1.6%)	7 (1.4%)	2 (0.8%)	4 (1.7%)	6 (1.3%)
Subfebrile Status	2 (0.8%)	0 (0.0%)	2 (0.4%)	2 (0.8%)	0 (0.0%)	2 (0.4%)
Other	48 (19.2%)	67 (26.6%)	115 (22.9%)	48 (20.2%)	66 (28.0%)	114 (24.1%)

ER = Oestrogen receptor; PR = Progesterone receptor; N = number of patients in the analysis set; n' = number of patients with assessments; n = number of patients in the category; SD = standard deviation; Min = minimum; Max = maximum.
Percentages were based on the number of patients with assessments.

Table 13: Data sets analysed for efficacy (TROIKA Study)

Analysis population	HD201 n	EU-Herceptin n	Total n
Modified full analysis set (mFAS and SAF)	250	252	502
PPS	238	236	474
Reason for exclusion			
Not administered all 8 cycles of neoadjuvant study drug	6	7	13
Not known whether 8 cycles were received	1	0	1
No surgery performed	2	3	5
Pathological findings not yet available	2	2	4
One of the vials used in Cycle 7 contained EU-Herceptin	1	0	1
Chemotherapy not administered as scheduled	0	4	4
rPPS	230	233	463
PPS excluding Italian sites	230	233	463
PPS without patients with inflammatory breast cancer	208	200	408
PPS w/o one site in the Russian Federation	215	215	430
PPS w/o one site in Thailand	234	230	464

PPS w/o one site in the Russian Federation and one site in Thailand	211	209	420
PPS w/o sites monitored by the CRO in Spain	228	228	456

PPS – per protocol set; mFAS – modified full analysis set; rPPS – restricted per protocol set; SAF – safety set; w/o – without.

The modified Full Analysis Set (mFAS) consist of the 502 subjects randomised subjects, who received at least one dose of study treatment. PPS is the primary analysis population.

Table 14: Data sets analysed for efficacy

	HD201	Herceptin®	Total
Modified Full Analysis Set (mFAS)	250	252	502
Per Protocol Set (PPS)	238	236	474
Subjects of the mFAS excluded from the PPS	12	16	
Major protocol deviation			
Study drug	2	0	
Chemotherapy	0	1	
Study drug not administered on all cycles due to:			
Death of subject	3	0	
Adverse events	2	2	
Subject withdrew	1	4	
Physician's decision	0	1	
Insufficient chemotherapy due to an AE	0	3	
Surgery not performed because:			
Subject refused surgery or did not appear	2	0	
Adverse events	0	1	
Surgery not documented upon database lock	0	2	
No pathological findings upon surgery	2	2	
Restricted Per Protocol Set (rPPS)	230	233	463
PPS without subjects from Italy	230	233	463

Outcomes and estimation

Primary efficacy results

- **Total pathological complete response (tpCR)**

The analysis of the primary efficacy variable is based on a 95% CI on the difference in tpCR rate between the two treatment groups for the PPS, tpCR was locally assessed.

Table 15: Total pathological complete response

	HD201	Herceptin®	Difference (HD201- Herceptin®)
PPS			
Responders n (%)	111 (46.6%)	109 (46.2%)	0.5%
95% CI	[40.2% ; 53.2%]	[39.7% ; 52.8%]	[-8.6% ; 9.6%]
N, n'	238, 238	236, 236	
mFAS			
Responders n (%)	112 (46.5%)	109 (45.0%)	1.4%
95% CI	[40.0% ; 53.0%]	[38.7% ; 51.5%]	[-7.7% ; 10.4%]
N, n'	250, 241	252, 242	
rPPS			
Responders n (%)	111 (48.3%)	109 (46.8%)	1.5%
95% CI	[41.6% ; 54.9%]	[40.2% ; 53.4%]	[-7.8% ; 10.6%]
N, n'	230, 230	233, 233	
PPS w/o Italian Sites			
Responders n (%)	109 (47.4%)	109 (46.8%)	0.6%
95% CI	[40.8% ; 54.1%]	[40.2% ; 53.4%]	[-8.6% ; 9.8%]
N, n'	230, 230	233, 233	

tpCR = total pathological complete response; CI = confidence interval; N = number of subjects in the analysis set; n' = number of subjects with available assessment results; n = number of subjects with a positive assessment; PPS = per protocol set; mFAS = modified full analysis set; rPPS = restricted PPS. Percentages were based on n' and are rounded to the nearest tenth of a percent.

The ratio [95% CI] of tpCR between the groups in the PPS was 1.01 [0.832; 1.225].

Table 16: Effect of Stratification Factors on tpCR Response

Analysis Set	HD201		Herceptin®		p-value
Stratification Factor	n'	n (%)	n'	n (%)	
PPS	N = 238		N = 236		
Region					
Eastern Europe	209	103 (49.3%)	211	103 (48.8%)	
Western Europe	10	2 (20.0%)	8	1 (12.5%)	0.033
Asia	19	6 (31.6%)	17	5 (29.4%)	0.027
Stage					
II	138	65 (47.1%)	133	70 (52.6%)	
III	100	46 (46.0%)	103	39 (37.9%)	0.027
Receptor Status					
Negative	86	46 (53.5%)	90	51 (56.7%)	
Positive	152	65 (42.8%)	146	58 (39.7%)	0.004
mFAS	N = 250		N = 252		
Region					
Eastern Europe	212	104 (49.1%)	213	103 (48.4%)	
Western Europe	10	2 (20.0%)	11	1 (9.1%)	0.011
Asia	19	6 (31.6%)	18	5 (27.8%)	0.022
Stage					
II	141	66 (46.8%)	137	70 (51.1%)	
III	100	46 (46.0%)	105	39 (37.1%)	0.034
Receptor Status					
Negative	87	47 (54.0%)	94	51 (54.3%)	
Positive	154	65 (42.2%)	148	58 (39.2%)	0.004
rPPS	N = 230		N = 233		
Region					
Eastern Europe	207	103 (49.8%)	209	103 (49.3%)	
Western Europe	5	2 (40.0%)	7	1 (14.3%)	0.221
Asia	18	6 (33.3%)	17	5 (29.4%)	0.032
Stage					
II	132	65 (49.2%)	131	70 (53.4%)	
III	98	46 (46.9%)	102	39 (38.2%)	0.024
Receptor Status					
Negative	85	46 (54.1%)	89	51 (57.3%)	
Positive	145	65 (44.8%)	144	58 (40.3%)	0.004
PPS (w/o Italian sites)	N = 230		N = 233		
Region					
Eastern Europe	209	103 (49.3%)	211	103 (48.8%)	
Western Europe	2	0 (0.0%)	5	1 (20.0%)	0.180
Asia	19	6 (31.6%)	17	5 (29.4%)	0.027
Stage					
II	133	64 (48.1%)	130	70 (53.8%)	
III	97	45 (46.4%)	103	39 (37.9%)	0.021
Receptor Status					
Negative	86	46 (53.5%)	90	51 (56.7%)	
Positive	144	63 (43.8%)	143	58 (40.6%)	0.004

tpCR = total pathological complete response; N = number of subjects in the analysis set; n' = number of subjects with available assessment results; n = number of subjects with a positive assessment; PPS = per protocol set; mFAS = modified full analysis set; receptor status = positive if either oestrogen or progesterone status is positive.

Percentages were based on the number of subjects in the stratification with available assessment results.

Secondary efficacy results

- **Breast pathological complete response (bpCR) and total pathological complete response after re-monitoring (tpCR).**

As a part of corrective and preventive action (CAPA) plan for the preapproval GCP inspection, a 100% re-monitoring of neoadjuvant data was performed. Analysis of tpCR and bpCR from the initial database lock of 19 April 2019 and database lock after re-monitoring (September 2020), was conducted. Although, minor changes for these parameters were noted for both treatment groups as presented in the table below, there was apparently no impact on the response outcome.

Table 17: Total and Breast Pathological Complete Response (tpCR and bpCR) Before and After Re-monitoring - PPS

Efficacy parameter	HD201	Herceptin	Difference (HD201- Herceptin)
Total pathological complete response			
Before re-monitoring			
Responders n (%)	111 (46.6%)	109 (46.2%)	0.5% [-8.6%; 9.6%]
95% CI	[40.2%; 53.2%]	[39.7%; 52.8%]	
N, n'	238, 238	236, 236	
After re-monitoring			
Responders n (%)	107 (45.0%)	115 (48.7%)	-3.8% [-12.8%; 5.4%]
95% CI	[38.5%; 51.5%]	[42.2%; 55.3%]	
N, n'	238, 238	236, 236	
Breast pathological complete response			
Before re-monitoring			
Responders n (%)	131 (55.0%)	126 (53.4%)	1.7% [-7.5%; 10.7%]
95% CI	[48.5%; 61.5%]	[46.8%; 59.9%]	
N, n'	238, 238	236, 236	
After re-monitoring			
Responders n (%)	126 (52.9%)	127 (53.8%)	-0.9% [-10.0%; 8.2%]
95% CI	[46.4%; 59.4%]	[47.2%; 60.3%]	
N, n'	238, 238	236, 236	

CI = confidence interval; N = number of subjects in the analysis set; n' = number of subjects with available assessment results; n = number of subjects with a positive assessment; PPS = per protocol set. Percentages were based on n' and are rounded to the nearest tenth of a percent.

The 95% CI for both tpCR and bpCR after re-monitoring are contained within the predefined equivalence margin of ±15%.

The ratio [95% CI] of bpCR between the groups (HD201/Herceptin) was 1.031 [0.874; 1.217] in the PPS (based on the results presented initially, before re-monitoring). Similar ratio was found in the mFAS.

Table 18: Effect of stratification factors on bpCR response

Analysis Set	HD201		Herceptin®		p-value
Stratification Factor	n'	n (%)	n'	n (%)	
PPS	N = 238		N = 236		
Region					
Eastern Europe	209	118 (56.5%)	211	118 (55.9%)	
Western Europe	10	5 (50.0%)	8	3 (37.5%)	0.563
Asia	19	8 (42.1%)	17	5 (29.4%)	0.017
Stage					
II	138	75 (54.3%)	133	78 (58.6%)	
III	100	56 (56.0%)	103	48 (46.6%)	0.115
Receptor Status					
Negative	86	52 (60.5%)	90	57 (63.3%)	
Positive	152	79 (52.0%)	146	69 (47.3%)	0.006
mFAS	N = 250		N = 252		
Region					
Eastern Europe	212	119 (56.1%)	213	119 (55.9%)	
Western Europe	10	5 (50.0%)	11	3 (27.3%)	0.205
Asia	19	8 (42.1%)	18	5 (27.8%)	0.012
Stage					
II	141	76 (53.9%)	137	79 (57.7%)	
III	100	56 (56.0%)	105	48 (45.7%)	0.127
Receptor Status					
Negative	87	53 (60.9%)	94	58 (61.7%)	
Positive	154	79 (51.3%)	148	69 (46.6%)	0.006

bpCR = breast pathological complete response; N = number of subjects in the analysis set; n' = number of subjects with available assessment results; n = number of subjects with a positive assessment; PPS = per protocol set; mFAS = modified full analysis set; receptor status = positive if either oestrogen or progesterone status is positive.
Percentages were based on the number of subjects in the stratification with available assessment results.

- **Overall response at the end of neoadjuvant treatment**

Table 19: Overall response at the end of neoadjuvant treatment

	PPS		mFAS	
	HD201	**Herceptin®**	**HD201**	**Herceptin®**
	N = 238, n' = 238	N = 236, n' = 236	N = 250, n' = 243	N = 252, n' = 245
	n (%)	n (%)	n (%)	n (%)
CR	81 (34.0%)	67 (28.5%)	82 (33.7%)	70 (28.6%)
PR	135 (56.7%)	144 (61.3%)	137 (56.4%)	149 (60.8%)
SD	20 (8.4%)	22 (9.4%)	22 (9.1%)	23 (9.4%)
PD	2 (0.8%)	2 (0.8%)	2 (0.8%)	2 (0.8%)
NE	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.4%)
Response	216 (90.8%)	211 (89.4%)	219 (87.6%)	219 (86.9%)
	Difference (HD201- Herceptin®)			
Difference	1.3%		0.7%	
95% CI	[-7.5% ; 10.5%]		[-8.1% ; 9.3%]	
	Ratio (HD201:Herceptin®)			
Ratio	1.015		1.008	
95% CI	[0.956 ; 1.078]		[0.943 ; 1.078]	

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; CI = confidence interval; N = number of subjects in the analysis set; n' = number of subjects with available assessment results; n = number of subjects with a positive assessment, PPS = per protocol set; mFAS = modified full analysis set.
Percentages are calculated based on n' for CR, PR, SD, PD, and NE and based on N for response.

Table 20: Overall response analysis adjusted for stratification factors

Analysis Set	HD201		Herceptin®		p-value
Stratification Factor	n'	n (%)	n'	n (%)	
PPS	N = 238		N = 236		
Region					
Eastern Europe	209	193 (92.3%)	211	191 (90.5%)	
Western Europe	10	9 (90.0%)	8	7 (87.5%)	0.753
Asia	19	14 (73.7%)	17	13 (76.5%)	0.002
Stage					
II	138	122 (88.4%)	133	126 (94.7%)	
III	100	94 (94.0%)	103	85 (82.5%)	0.180
Receptor Status					
Negative	86	79 (91.9%)	90	81 (90.0%)	
Positive	152	137 (90.1%)	146	130 (89.0%)	0.488
mFAS	N = 250		N = 252		
Region					
Eastern Europe	216	196 (90.7%)	219	194 (88.6%)	
Western Europe	14	9 (64.3%)	14	11 (78.6%)	0.004
Asia	20	14 (70.0%)	19	14 (73.7%)	0.002
Stage					
II	145	124 (85.5%)	144	131 (91.0%)	
III	105	95 (90.5%)	108	88 (81.5%)	0.399
Receptor Status					
Negative	95	80 (84.2%)	99	86 (86.9%)	
Positive	155	139 (89.7%)	153	133 (86.9%)	0.367

N = number of subjects in the analysis set; n' = number of subjects with available assessment results; n = number of subjects with a positive assessment; PPS = per protocol set; mFAS = modified full analysis set; receptor status = positive if either oestrogen or progesterone status is positive. Percentages were based on the number of subjects in the stratification with available assessment results.

Ancillary analyses

Supportive analyses were performed on the mFAS, restricted PPS (rPPS), and PPS excluding Italian sites, PPS excluding one site in the Russian Federation, PPS excluding one site in Thailand, PPS excluding one site in the Russian Federation and one site in Thailand, and PPS excluding sites monitored by the CRO in Spain.

Table 21: Summary of % locally assessed tpCR by treatment, excluding subjects from concerned sites - PPS

Statistic / Parameter	HD201 N=201	EU-Herceptin N=201	Difference (HD201 – EU-Herceptin) [95% CI]	Ratio (HD201 / EU-Herceptin) [95% CI]
% tpCR [95% CI]	46.8 [39.7; 53.9]	47.8 [40.7; 54.9]	-1.0 [-11.0; 9.0]	0.979 [0.796; 1.204]

CI: confidence interval; tpCR: total complete pathological response.
Based on exact Clopper-Pearson 95% CI for % tpCR, exact Santner-Snell 95% CI for the difference and normally approximated Wald 95% confidence intervals for the ratio.

Table 22 - Summary of % locally assessed tpCR by treatment based on MAR multiple

Statistic / Parameter	HD201 N=208	EU-Herceptin N=211
Number of subjects with tpCR assessment missing	4	6
Summary of statistics for %tpCR		
Number of imputed datasets	1000	1000
Pooled estimate %tpCR [95% CI]	46.6 [39.7; 53.4]	47.4 [40.5; 54.2]
Pooled estimate for difference in %tpCR [95% CI]	-0.8 [-10.5; 8.9]	
Pooled estimate for ratio in %tpCR [95% CI]	0.983 [0.777; 1.189]	

Summary of main efficacy results

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 23: Summary of Efficacy for trial TROIKA - locally assessed tpCR

	HD201	EU-Herceptin	Difference, % (HD201-Herceptin) [95% CI]
PPS			
N, n'	238, 238	236, 236	-3.8% [-12.8%; 5.4%]
Responders, n (%)	107 (45.0)	115 (48.7)	
95% CI	[38.5; 51.5]	[42.2; 55.3]	
mFAS			
N, n'	250, 242	252, 245	-2.7% [-11.7%; 6.2%]
Responders, n (%)	108 (44.6)	116 (47.3)	
95% CI	[38.3; 51.1]	[41.0; 53.8]	
rPPS			
N, n'	230, 230	233, 233	-2.8% [-12.0%; 6.4%]
Responders, n (%)	107 (46.5)	115 (49.4)	
95% CI	[39.9; 53.2]	[42.8; 56.0]	
PPS w/o Italian sites			
N, n'	230, 230	233, 233	-3.7% [-12.9%; 5.5%]
Responders, n (%)	105 (45.7)	115 (49.4)	
95% CI	[39.1; 52.3]	[42.8; 56.0]	
PPS w/o one site in the Russian Federation			
N, n'	215, 215	215, 215	-1.9% [-11.5%; 7.8%]
Responders, n (%)	96 (44.7)	100 (46.5)	
95% CI	[37.9; 51.6]	[39.7; 53.4]	
PPS w/o one sitein Thailand			
N, n'	234, 234	230, 230	-3.0%
Responders, n (%)	107 (45.7)	112 (48.7)	

95% CI	[39.2; 52.3]	[42.1; 55.4]	[-12.1%; 6.3%]
PPS w/o one site in the Russian Federation and one site in Thailand			
N, n'	211, 211	209, 209	-0.9% [-10.5%; 8.8%]
Responders, n (%)	96 (45.5)	97 (46.4)	
95% CI	[38.6; 52.5]	[39.5; 53.4]	
PPS w/o sites monitored by the CRO in Spain			
N, n'	228, 228	228, 228	-3.9% [-13.3%; 5.4%]
Responders, n (%)	105 (46.1)	114 (50.0)	
95% CI	[39.5; 52.8]	[43.3; 56.7]	

Secondary Efficacy Results

Table 24 - Locally assessed bpCR

	HD201	EU-Herceptin	Difference, % (HD201-Herceptin) [95% CI]	Ratio (HD201:Herceptin) [95% CI]
PPS				
N, n'	238, 238	236, 236	-0.9% [-10.0%; 8.2%]	0.984 [0.831; 1.164]
Responders, n (%)	126 (52.9)	127 (53.8)		
95% CI	[46.4; 59.4]	[47.2; 60.3]		
mFAS				
N, n'	250, 242	252, 245	0.2% [-8.7%; 9.2%]	1.004 [0.848; 1.190]
Responders, n (%)	127 (52.5)	128 (52.2)		
95% CI	[46.0; 58.9]	[45.8; 58.6]		
rPPS				
N, n'	230, 230	233, 233	-0.6% [-9.8%; 8.6%]	0.989 [0.834; 1.172]
Responders, n (%)	122 (53.0)	125 (53.6)		
95% CI	[46.4; 59.6]	[47.0; 60.2]		
PPS w/o Italian sites				
N, n'	230, 230	233, 233	-1.5% [-10.6%; 7.8%]	0.973 [0.820; 1.154]
Responders, n (%)	121 (52.6)	126 (54.1)		
95% CI	[45.9; 59.2]	[47.4; 60.6]		

Table 25 - ORR at the end of the neoadjuvant treatment period

	HD201 n (%)	EU-Herceptin n (%)	Difference [95% CI]	Ratio [95% CI]
PPS				
N, n'	238, 238	236, 236	2.2% [-6.7%; 11.3%]	1.025 [0.965; 1.088]
Assessment				
Complete response	83 (34.9)	69 (29.2)		
Partial response	134 (56.3)	141 (59.7)		
Stable disease	19 (8.0)	23 (9.7)		
Progressive disease	2 (0.8)	2 (0.8)		
Not evaluable	0	1 (0.4)		
Response	217 (91.2)	210 (89.0)		
mFAS				

N, n'	250, 244	252, 245	1.5% [-7.3%; 10.1%]	1.017 [0.951; 1.088]
Assessment				
Complete response	84 (34.4)	72 (29.4)		
Partial response	136 (55.7)	146 (59.6)		
Stable disease	22 (9.0)	24 (9.8)		
Progressive disease	2 (0.8)	2 (0.8)		
Not evaluable	0 (0.0)	1 (0.4)		
Response	220 (88.0)	218 (86.5)		
PPS w/o Italian sites				
N, n'	230, 230	233, 233	1.6% [-7.5%; 10.8%]	1.018 [0.958; 1.081]
Assessment				
Complete response	81 (35.2)	67 (28.8)		
Partial response	128 (55.7)	141 (60.5)		
Stable disease	19 (8.3)	23 (9.9)		
Progressive disease	2 (0.9)	2 (0.9)		
Not evaluable	0	0		
Response	209 (90.9)	208 (89.3)		
PPS w/o patients with inflammatory breast cancer				
N, n'	208, 208	200, 200	3.3% [-6.5%; 13.0%];	1.037 [0.974; 1.104]
Assessment				
Complete response	74 (35.6)	53 (26.5)		
Partial response	118 (56.7)	125 (62.5)		
Stable disease	15 (7.2)	19 (9.5)		
Progressive disease	1 (0.5)	2 (1.0)		
Not evaluable	0	1 (0.5)		
Response	192 (92.3)	178 (89.0)		

Table 26 - Event free survival

Patients presenting an event	**PPS**				**mFAS**			
	HD201		**Herceptin**		**HD201**		**EU-Herceptin**	
	N = 238		**N = 236**		**N = 250**		**N = 252**	
	n'	**n (%)**	**n'**	**n (%)**	**n'**	**n (%)**	**n'**	**n (%)**
All Patients	238	34 (14.3%)	236	35 (14.8%)	250	38 (15.2%)	252	38 (15.1%)
Region								
Eastern Europe	209	30 (14.4%)	211	33 (15.6%)	216	32 (14.8%)	219	34 (15.5%)
Western Europe	10	0 (0%)	8	1 (12.5%)	14	2 (14.3%)	14	2 (14.3%)
Asia	19	4 (21.1%)	17	1 (5.9%)	20	4 (20.0%)	19	2 (10.5%)
Stage								
II	137	12 (8.8%)	134	12 (9.0%)	144	14 (9.7%)	145	13 (9.0%)
III	101	22 (21.8%)	102	23 (22.5%)	106	24 (22.6%)	107	25 (23.4%)
Receptor Status								
Negative	86	19 (22.1%)	92	16 (17.4%)	95	23 (24.2%)	100	19 (19.0%)
Positive	152	15 (9.9%)	144	19 (13.2%)	155	15 (9.7%)	152	19 (12.5%)

Type of the first event within a patient								
Death	34	1 (2.9%)	35	5 (14.3%)	38	4 (10.5%)	38	5 (13.2%)
Progressive disease	34	32 (94.1%)	35	29 (82.9%)	38	33 (86.8%)	38	32 (84.2%)
Second primary cancer	34	1 (2.9%)	35	1 (2.9%)	38	1 (2.6%)	38	1 (2.6%)
Any Covid-Related Protocol Deviation								
No	153	24 (15.7%)	141	27 (19.1%)	161	27 (16.8%)	152	29 (19.1%)
Yes	85	10 (11.8%)	95	8 (8.4%)	89	11 (12.4)	100	9 (9.0%)
Exposure to Covid								
No	21	12 (57.1%)	10	5 (50.0%)	28	15 (53.6%)	15	5 (33.3%)
Yes	217	22 (10.1%)	226	30 (13.3%)	222	23 (10.4%)	237	33 (13.9%)

Table 27 - Cox Proportional Hazards Regression adjusted for stratification factors, and Presence of any Covid-Related Protocol Deviation

Analysis Set	PPS		mFAS		
	HR [95%CI]	p-value	HR	95% CI	p-value
Treatment					
HD201	0.81 [0.50; 1.32]	0.402	0.87 [0.55; 1.38]		0.557
Herceptin	Reference		Reference		
Region					
Eastern Europe	Reference		Reference		
Western Europe*	0.54 [0.07; 3.96]	0.546	1.44 [0.52; 4.02]		0.481
Asia	1.10 [0.44; 2.76]	0.835	1.21[0.52; 2.82]		0.652
Stage					
II**	Reference		Reference		
III	2.03 [1.21; 3.41]	0.008	1.97 [1.21; 3.22]		0.007
Receptor Status					
Negative	Reference		Reference		
Positive	0.64 [0.40; 1.05]	0.075	0.53 [0.33; 0.84]		0.007
Presence of any Covid-Related Protocol Deviation					
No	Reference		Reference		
Yes	0.80 [0.45; 1.42]	0.441	0.81 [0.47; 1.41]		0.460
Covid Exposure					
No	Reference		Reference		
Yes	0.05 [0.02; 0.10]	<0.001	0.04 [0.02; 0.09]		<0.001

Table 28 - Overall survival

	PPS				mFAS			
	HD201		Herceptin		HD201		EU-Herceptin	
	N = 238		N = 236		N = 250		N = 252	
	n'	n (%)	n'	n (%)	n'	n (%)	n'	n (%)
All Patients	238	12 (5%)	236	10 (4.2%)	250	16 (6.4%)	252	10 (4.0%)
Region								
Eastern Europe	209	10 (4.8%)	211	10 (4.7%)	216	12 (5.6%)	219	10 (4.6%)
Western Europe	10	0 (0%)	8	0 (0%)	14	2 (14.3%)	14	0 (0%)
Asia	19	2 (10.5%)	17	0 (0%)	20	2 (10.0%)	19	0 (0%)
Stage								
II	137	4 (2.9%)	134	3 (2.2%)	144	6 (4.2%)	145	3 (2.1%)
III	101	8 (7.9%)	102	7 (6.9%)	106	10 (9.4%)	107	7 (6.5%)
Receptor Status								
Negative	86	9 (10.5%)	92	7 (7.6%)	95	13 (13.7%)	100	7 (7.0%)
Positive	152	3 (2.0%)	144	3 (2.1%)	155	3 (1.9%)	152	3 (2.0%)

Clinical studies in special populations

No specific studies considering children, elderly patients, patients with renal or hepatic impairment were conducted.

In vitro biomarker test for patient selection for efficacy

Data on HER2 status and the methods used for its determination were described for the SAF and PPS population in Table 29.

HER2 was positive for all patients of the SAF and the PPS population.

In the SAF, among the patients for whom the HER2 status was determined using IHC, in the HD201 treatment group the result was 2+ for 11 patients (4.6%) and 3+ for 229 patients (95.4%). In the EU-Herceptin treatment group the result was 2+ for 14 patients (5.8%) and 3+ for 228 patients (94.2%). All patients with IHC 2+ had a positive FISH or CISH or DISH result.

No notable differences were observed between the SAF, and the PPS population.

Table 29: HER2 status for the SAF and PPS population (study TROIKA)

	SAF population			PPS population		
	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)	Total N=502 n (%)	HD201 N=238 n (%)	EU-Herceptin N=236 n (%)	Total N=474 n (%)
HER2 status	n'= 250	n'=252	n'=502	n'=238	n'=236	n'=474
Positive	250 (100)	252 (100)	502 (100)	238 (100)	236 (100)	474 (100)
Negative	0	0	0	0	0	0
Use of each type of method for HER2 determination						
IHC	240 (96.0)	242 (96.0)	482 (96.0)	228 (95.8)	228 (96.6)	456 (96.2)
FISH	17 (6.8)	24 (9.5)	41 (8.2)	17 (7.1)	19 (8.1)	36 (7.6)
CISH	5 (2.0)	2 (0.8)	7 (1.4)	4 (1.7)	2 (0.8)	6 (1.3)
Use of combination of methods for HER2 determination						
IHC only	228 (91.2)	226 (89.7)	454 (90.4)	217 (91.2)	215 (91.1)	432 (91.1)
FISH only	8 (3.2)	8 (3.2)	16 (3.2)	8 (3.4)	6 (2.5)	14 (3.0)
CISH only	2 (0.8)	2 (0.8)	4 (0.8)	2 (0.8)	2 (0.8)	4 (0.8)
IHC and FISH	9 (3.6)	16 (6.3)	25 (5.0)	9 (3.8)	13 (5.5)	22 (4.6)
IHC and CISH	3 (1.2)	0	3 (0.6)	2 (0.8)	0	2 (0.4)
IHC result	n'=240	n'=242	n'=482	n'=228	n'=228	n'=456
2+	11 (4.6)	14 (5.8)	25 (5.2)	10 (4.4)	13 (5.7)	23 (5.0)
3+	229 (95.4)	228 (94.2)	457 (94.8)	218 (95.6)	215 (94.3)	433 (95.0)

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

Not applicable.

Supportive study(ies)

TROIKA-1 investigated the PK profile of HD201 in health volunteers and the findings are presented in the Clinical Pharmacology section above.

2.7.3. Discussion on clinical efficacy

HD201 is proposed as a biosimilar to Herceptin. Herceptin is authorised in metastatic and early breast cancer settings as well as in gastric cancer. The applicant is applying for the same indications as Herceptin, even though from an efficacy point of view, the clinical development has been carried out on metastatic breast cancer. The Applicant has provided a sufficient rationale as to why data from the TROIKA trail supports the indication in gastric metastatic cancer which is recommended in the "Guideline on similar biological medicinal products" (CHMP/437/04 Rev 1): as "If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification."

Design and conduct of clinical studies

The clinical development program to assess biosimilarity concerning efficacy, immunogenicity and safety between HD201 and EU-Herceptin was based on one phase III study (TROIKA) in women with HER2-positive early breast cancer. The overall study design (double blind, randomised, parallel group) as well as study population and primary endpoint has been accepted by the CHMP in the Scientific Advice (EMEA/H/SA/2212/1/FU/1/2017/II). The clinical model is considered sufficiently sensitive to detect potential differences between the biosimilar and the originator. The primary efficacy endpoint tpCR (ypT0/is ypN0) at the time of surgery is a reasonable surrogate marker for clinical efficacy widely used and is consistent with EMA's Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/703715/2012).The primary efficacy endpoint was assessed after neoadjuvant treatment. In an appropriately designed study, HD201 was administered in line with the approved posology for the reference product. A standard chemotherapy regimen was administered in the neoadjuvant setting and it was also in line with other trastuzumab biosimilar studies.

HD201 / Herceptin dosing and administration was according to the SmPC of Herceptin for treatment of ECB. Upon request, the Applicant clarified how missed doses by >1 week were handled. The overall proportion of patients displaying dose delays > 1 week and the total number of dose delays > 1 week was approximately double in the EU-Herceptin group (13.5% and 43 doses) in comparison to the HD201 group (7.6% and 25 doses). Noted imbalances occurred especially in the neoadjuvant treatment period, while frequencies for the adjuvant treatment period appear balanced between treatment groups. The cumulative dose (mean (SD) 49.46 (5.78) mg/kg HD201, 49.58 (5.64) mg/kg EU-Herceptin) and relative dose intensity (RDI) (mean (SD) [min; max] 99.12 (4.87) [88.2; 129.6] % HD201, 99.01 (4.84) [86.1 ; 129.6] % EU-Herceptin) was comparable between treatment groups in the neoadjuvant setting. In the majority of patients, the dose delays were due to adverse events (AE), many of which were assessed as related to concurrent chemotherapy. A sensitivity analysis performed on the PPS excluding these patients revealed that the difference [95% CI] of -3.7% [-13.0%; 5.7%] between the two groups in local tpCR rates were well contained within the equivalence margin [-15% ; 15%] and thus confirms the conclusion of the primary analysis.

The definition of the primary endpoint, tpCR (ypT0/is ypN0 i.e. absence of any residual invasive tumour cells, except ductal carcinoma in situ, in the resected breast specimen and lymph nodes) is in line with current EMA guidance (Appendix 4 to the GL on the evaluation of anticancer medicinal products in man: EMA/CHMP/703715/2012 Rev. 2) and is accepted as a surrogate marker for clinical efficacy. Notably, no clinical justification concerning the chosen equivalence margin for the difference in response rates between study arms ([-15 %, 15 %]) has been provided. Of note, a previous trastuzumab biosimilar had been approved based on an efficacy study with comparable design demonstrating a treatment difference (95% CI) for pathological complete response of -0.036 (-0.124, 0.052) in the per-protocol set and of -0.036 (-0.120, 0.048) in the ITT set. As results are comparable, no concern is raised.

The primary analysis was based on an exact 95% CI for the difference in response rates between study arms. As secondary analyses, this difference was estimated in a multivariable model adjusting for the stratification variables region, stage, and E2/P4 receptor status using binomial regression with either an identity link if rate difference were estimated or a log link if rate ratios were estimated. As it had been specified in the protocol that logistic regression was to be used for multivariable modelling, the Applicant was requested to provide an unconditional estimate of the difference in local tpCR rates estimated from logistic regression using the standardized estimator described in *Jon Arni Steingrimsson, Daniel F. Hanley, Michael Rosenblum [Improving precision by adjusting for prognostic baseline variables in randomized trials with binary outcomes, without regression model assumptions. Contemporary Clinical Trials, Volume 54, 2017, Pages 18-24]*. The resulting 95% CIs ([-11.6%, 5.6%]

in the PPS and [-10.8%; 6.0%] in the mFAS based on multiple imputation) were lying well within the acceptance range of (-15%, 15%), thus the issue was considered resolved. The primary set for the analysis of the primary endpoint was considered to be the PP population, but all efficacy endpoints including the primary endpoint were analysed both on the PP population and the mFAS, which is supported. It should be noted that the mFAS (all randomised and treated patients) was only smaller by one patient compared to the FAS (all randomised patients). However, other than specified in the protocol, the analyses on the mFAS were only based on patients with 'available' assessment results (97.0% of patients in the mFAS). Additional analyses were provided using the full mFAS either based on multiple imputation assuming missingness at random or exploring a worst case scenario, where subjects with missing values are imputed as non-responders in the HD201 arm and as responders in the Herceptin arm. The approach based on multiple imputation resulted in a 95% CI of (-11.7%, 6.0%) and the approach exploring the worst case scenario gave a 95% CI of (-14.4%, 3.2%). As both CIs lie within the acceptance range of (-15%, 15%) the issue is considered resolved.

The study was conducted in four geographic regions (Asia, Eastern Europe, Central Europe and Western Europe) encompassing 70 study sites and the majority of patients was enrolled in non-EU countries, predominantly in Russia. The efficacy measures including the primary endpoint tpCR were assessed locally. An independent central review of primary efficacy data is generally preferred, which was also stated in the Scientific Advice (EMEA/H/SA/2212/1/FU/1/2017/II). However, central review for tpCR was planned as supportive analysis, which is acceptable.

Notably, only DS from process D reflects material intended for commercial purpose, whereas the majority of used batches contained drug substance material from process B or C, which are considered sufficiently similar to the proposed commercial manufacturing process D material and similar to the RMP Herceptin. The results of the submitted pivotal phase 3 study TROIKA are considered valid for the assessment of comparative efficacy between Tuznue and Herceptin.

While overall protocol deviations in the mFAS were balanced between the treatment groups (92.4% in the HD201 arm and 92.9% in the Herceptin arm), major protocol deviations occurred more frequently in the Herceptin group (10 patients, 4.0%) with respect to the HD201 group (3 patients, 1.2%). Most major protocol deviations in the Herceptin arm concerned eligibility criteria (7 patients).

There were 2 protocol amendments with the final version (version 3.0) being adopted on 01. October 2018, after the first patient was screened (19. February 2018). The neoadjuvant period was concluded for the last patient on 24. April 2019. A comparative list of changes among protocol versions has been provided. However, the dossier mentions three versions of statistical analysis plans for the TROIKA study which are all dated after the third version of the clinical study report, i.e. clearly written in retrospective. The statistical analysis plan dated 19 April 2019 included the prespecified analyses of the primary endpoint. Logistic issues were reported for Italian study sites where neoadjuvant efficacy data were not entirely entered and monitored upon interim analysis database lock. Hence, a sensitivity analysis on the PPS excluding affected patients (6 of the PPS in the HD201 arm, 2 of the PPS in Herceptin arm) was conducted.

Additional sensitivity analyses excluding all data for which credibility concerns had been raised were provided. As these analyses resulted in 95% CI ([-11.0%, 9.0%] in the PPS and [-10.5%; 8.9%] in the mFAS) which were lying well within the acceptance range of (-15%, 15%), the issue was considered resolved. Submitted efficacy results for the screening, neoadjuvant and surgery period are based on re-monitored data, which were presented in the CSR Version 3.0 (01. February 2021) along with data for the adjuvant treatment period. The CSR was additionally updated twice: upon final analysis of the 2-year post-treatment follow-up (database lock 02. February 2022), as well as to include requested sensitivity analyses due to above mentioned GCP compliance concerns (CSR Version

4.0, 21. March 2022) and a final update on safety, outcomes and concomitant medication from the treatment period (CSR Version 4.0_amended, 24. July 2023).

Efficacy data and additional analyses

In a study design based on scientific advice, the pivotal TROIKA study met its primary and secondary endpoints indicating equivalence in terms of efficacy between the proposed biosimilar (HD201) and the reference product in the EBC indication. Apart from ECOG status, demographic and baseline characteristics were generally well-balanced between the two treatment groups. The study population appears to reflect the intended target populations.

A similar number of patients from the mFAS completed the neoadjuvant treatment phase, including surgery, and entered the adjuvant treatment phase (238 out of 250 patients in the HD201 group and 242 out of 252 patients in the Herceptin group).

The primary analysis was based on local tpCR assessment of resected breast and lymph node specimens after neoadjuvant treatment. It was noted that information concerning procedures and management of local pathological response assessment is lacking in the provided protocol (Version 3.0, 01.10.2023). Summaries on surgical subtypes and performed lymph node dissection per treatment arm and per country with more than 10 patients were provided during the assessment. Divergences in surgical approaches from the overall pattern were apparent in some countries, which may indeed reflect local differences in surgical tumour management subject to the surgeon's discretion, while a standardized approach would have been preferrable. Notably, the group sizes for the majority of countries were rather small. Hence, while differences in surgical management may have affected post-surgery outcome measures, trade-offs due to a small sample size in most countries impede deducing a meaningful conclusion. Noted deviations from the overall pattern or between treatment arms may therefore as well be due to chance. The issue is thus considered resolved.

Based on local reading from the PPS, 107 (45.0%) patients in the HD201 group and 115 (48.7%) patients in the Herceptin group achieved tpCR. A similar response rate was reported in another trastuzumab phase III biosimilar study with a comparable study design. The difference in response rates [95% CI] for HD201 versus Herceptin was -3.8% [-12.8%; 5.4%]. As the 95% CI was entirely contained in the pre-defined bioequivalence margin of ±15%, the primary endpoint of the study was met. The same trend was seen in supportive analyses performed on all analysis sets, upon adjustment for stratification factors (geographic regions, clinical breast cancer stage and hormone receptor status)d. Concerning the effect of stratification factors, a roughly 10% higher tpCR for breast cancer stage II and hormone receptor (HR)-negative patients in the Herceptin treatment group when compared to the HD201 arm in the local assessment was noted. In addition to local tpCR assessment, a supportive analysis of centrally reviewed tpCR was planned. This is considered crucial to re-assure integrity of locally assessed primary efficacy endpoints Central tpCR readings supported in principle the primary analysis result. The 95% CI of the difference was within the pre-defined ±15% margin (-2.1 [-11.6%, 7.5%]) and agreement between local and central tpCR readings was overall 84.8% (95 % CI [81.0%; 88.1%]). Concordance between local and central readings per treatment groups was comparable (85.9% for the HD201, 83.9 % for Herceptin). Notably, central reading of tpCR was performed for 429 out of 502 patients from the mFAS (85.5 %). Hence, 14.5% of patients lacked a central assessment due to "missing or unrepresentative" samples. Moreover, a higher number of samples was seemingly unavailable for central reading in the HD201 arm (33 PPS; 34 mFAS) than in the Herceptin arm (20 PPS; 24 mFAS). Results of secondary endpoints after neoadjuvant treatment (bpCR, ORR) reflected the primary analysis results, as similar outcomes between treatment groups were observed. Data on EFS and OS further revealed in principle comparable event-free and overall survival outcomes when evaluated through the entire treatment and follow-up period (3-years in

total). However, the HD201 arm seemingly displayed more events (i.e. progressive disease, second primary cancer, or death due to any cause) or deaths during the treatment phase with respect to the Herceptin arm. For instance, 7 deaths were reported while neoadjuvant / adjuvant treatment in the HD201 arm and 0 in the Herceptin arm. The number of deaths assigned to respective study periods based on date of death was provided to better assess the temporal relationship of event occurrences. An increased number of events were noted during neoadjuvant treatment in the HD201 group with respect to the EU-Herceptin group, most importantly 3 deaths vs 0 deaths, respectively. However, it is agreed that the number of events were overall small and that the description of reported deaths in the EU-Herceptin group during neoadjuvant treatment do not indicate a concern pertaining to efficacy during neoadjuvant or adjuvant treatment. Further event occurrences were overall balanced between treatment groups, as also reflected by the statistical analysis on event-free survival and overall survival.

HR-negative patients displayed higher pathological and overall response rates than HR-positive patients in both treatment arms after neoadjuvant treatment, which is in line with a meta-analysis of neoadjuvant breast cancer studies (Cortazar et al., 2014). However, this trend was not observed in event-free survival, as more HR-negative patients were reported with an event than HR-positive patients. This observation was more apparent in the HD201 treatment arm than in the Herceptin arm (HD201 group: 22.1 % HR-negative with an event, 9.9 % HR-positive with an event; Herceptin group: 17.4 % HR-negative with an event, 13.2 % HR-positive with an event; PPS). Similarly, more deaths were observed in HR-negative patients in both treatment groups. Upon request, the Applicant investigated the correlation of tpCR with EFS and OS using Cox regression and Kaplan-Meier analyses. Although the conducted analyses are not clearly interpretable since tpCR, which was assessed after baseline, was included in the time-to-event analyses as covariate, it can be agreed that an association between tpCR and EFS as well OS can be observed in the TROIKA study. Similarly, the provided analyses support the observation that HR-negative patients had worse EFS and OS outcomes than ER-positive patients, but tpCR seemed still of prognostic value in both tumour subtypes, which is in line with above-mentioned meta-analysis (Cortazar et al., 2014). In addition, the proportion of patients receiving hormonal and/or radiotherapy was higher in the HR-positive group (70.4 % in the HD201 arm, 76.4 % in the EU-Herceptin arm) than in the HR-negative group (47.7 % in the HD201 arm, 50.0 % in the EU-Herceptin arm), which provides a plausible link to less favourable EFS and OS outcome in ER-negative patient within the timeframe of the TROIKA study. The use of concomitant medication throughout the treatment phase was overall balanced between HD201 and Herceptin arms. Hormonal and/or radiotherapy was permitted during the adjuvant setting as additional anti-cancer treatment. A summary depicting the proportion of patients receiving either or both types of additional anti-cancer treatment has been provided. Further information concerning the type and nature of administered hormonal and/or radiotherapy were provided upon request, which did not raise concerns.

2.7.4. Conclusions on clinical efficacy

The primary efficacy outcome was within the equivalence acceptance margin, suggesting biosimilarity from an efficacy point of view. Further, secondary endpoints and supplementary analyses support results from the primary endpoint.

In conclusion, clinical efficacy between HD201 and Herceptin is considered to be similar.

2.7.5. Clinical safety

Patient exposure

Table 30 - Summary of the safety population by study

Study	Number of subjects in the safety population			
	HD201	EU-Herceptin	US-Herceptin	Total
Healthy subject PK studies				
TROIKA-1				
Safety population	35	35	35	105
Controlled clinical study pertinent to the claimed indication				
TROIKA				
SAF	250	252	n/a	502
aSAF	238	242	n/a	480
PTAS	234	242	n/a	476

Phase III study TROIKA

Table 31: Exposure of patients (TROIKA)

	HD201	EU-Herceptin	Total
Patients randomised, n	251	252	503
SAF, n	250	252	502
Initiated neoadjuvant treatment, n	250	252	502
Completion of neoadjuvant treatment, n (%)	244 (97.6%)	244 (96.8%)	488 (97.2%)
Discontinued neoadjuvant period, n (%)	6 (2.4%)	8 (3.2%)	14 (2.8%)
Initiated adjuvant treatment, n	238	242	480
Completion of adjuvant treatment, n (%)	222 (93.3%)	228 (94.2%)	450 (93.8%)
Discontinued neoadjuvant period, n (%)	16 (6.7%)	14 (5.8%)	30 (6.3%)

SAF: Safety set, or all randomised patients who received at least one dose of the study drug; n: Number of patients within the category

Table 32: Summary of Exposure to Study Drug for the Entire Study – Safety Set (TROIKA)

Variable	HD201 N=250	EU-Herceptin N=252
Exposure duration (weeks)		
Mean (SD)	56.48 (10.38)	56.88 (9.95)
Median	58.86	58.86
Q1, Q3	57.43, 60.14	57.71, 60.00
Min, Max	3.0, 68.9	3.0, 69.9
Exposure duration per week, n (%)		
≤ 12 weeks	5 (2.0)	5 (2.0)
> 12 weeks and ≤ 24 weeks	1 (0.4)	4 (1.6)

> 24 weeks and ≤ 36 weeks	7 (2.8)	3 (1.2)
> 36 weeks and ≤ 48 weeks	9 (3.6)	4 (1.6)
> 48 weeks and ≤ 54 weeks	3 (1.2)	5 (2.0)
> 54 weeks and ≤ 60 weeks	160 (64.0)	176 (69.8)
> 60 weeks and ≤ 66 weeks	60 (24.0)	49 (19.4)
> 66 weeks	5 (2.0)	6 (2.4)
Cumulative dose (mg/kg)		
Mean (SD)	107.40 (19.02)	107.95 (18.40)
Median	112.05	112.25
Q1, Q3	109.90, 114.40	110.15, 114.50
Min, Max	8.0, 122.3	8.0, 120.7
Number of cycles study drug was administered, n (%)		
Cycle 1	3 (1.2)	3 (1.2)
Cycle 2	2 (0.8)	0
Cycle 3	0	2 (0.8)
Cycle 4	0	0
Cycle 5	0	1 (0.4)
Cycle 6	1 (0.4)	2 (0.8)
Cycle 7	0	0
Cycle 8	6 (2.4)	2 (0.8)
Cycle 9	0	2 (0.8)
Cycle 10	1 (0.4)	1 (0.4)
Cycle 11	3 (1.2)	0
Cycle 12	1 (0.4)	3 (1.2)
Cycle 13	2 (0.8)	1 (0.4)
Cycle 14	3 (1.2)	0
Cycle 15	2 (0.8)	4 (1.6)
Cycle 16	2 (0.8)	3 (1.2)
Cycle 17	2 (0.8)	0
Cycle 18	222 (88.8)	228 (90.5)

Min: Minimum, Max: Maximum; N: Number of patients within the treatment group; Q1: 1st quartile; Q3: 3rd quartile; SD: Standard deviation; n: number of patients within the category

Table 33: Summary of exposure to study drug in the neoadjuvant - SAF period (TROIKA)

	HD201 N = 250		EU-Herceptin N = 252	
	Mean (SD)	Min; Max	Mean (SD)	Min; Max
Duration and dosage				
Study treatment duration (weeks)	24.07 (3.00)	3.0; 30.4	24.14 (2.94)	3.0; 31.0
Cumulative dose (mg/kg)	49.46 (5.78)	8.0; 56.5	49.58 (5.64)	8.0; 56.1
Dose intensity (mg/kg/week)	2.065 (0.102)	1.84; 2.70	2.063 (0.101)	1.79; 2.70
Relative Dose Intensity (RDI) (%)	99.12 (4.87)	88.2; 129.6	99.01 (4.84)	86.1; 129.6
Cycle completion				
Number of cycles study drug was administered, n (%)				
1	3 (1.2)		3 (1.2)	
2	2 (0.8)		0	
3	0		2 (0.8)	
4	0		0	
5	0		1 (0.4)	
6	1 (0.4)		2 (0.8)	
7	0		0	
8	244 (97.6)		244 (96.8)	
Dose delays				
Any delay > 2 Days, n (%)	90 (36.4)		91 (36.5)	
Any delay Due to AE > 2 Days, n (%)	60 (24.3)		58 (23.3)	

N: Number of patients in the analysis set; n: Number of patients; SD: Standard deviation; Min: Minimum; Max: Maximum; AE: Adverse Events
Percentages were based on the number of patients in the analysis set.

Table 34: Exposure to study drug in the adjuvant period – aSAF (TROIKA)

	HD201 N = 238		EU-Herceptin N = 242	
	Mean (SD)	Min; Max	Mean (SD)	Min; Max
Duration and dosage				
Study treatment duration (weeks)	29.38 (3.74)	5.9; 34.0	29.46 (3.92)	3.0; 37.4
Cumulative dose (mg/kg)	60.86 (7.60)	14.4; 70.1	60.78 (7.78)	8.0; 68.7
Dose intensity (mg/kg/week)	2.076 (0.083)	1.86; 2.46	2.072 (0.107)	1.66; 2.70
Relative Dose Intensity (RDI) (%)	100.46 (4.01)	90.2; 119.0	100.28 (5.16)	80.5; 130.6
Cycle completion				
Number of cycles study drug was administered, n (%)				
9	0		2 (0.8)	
10	1 (0.4)		1 (0.4)	
11	3 (1.3)		0	
12	1 (0.4)		3 (1.2)	
13	2 (0.8)		1 (0.4)	
14	3 (1.3)		0	
15	2 (0.8)		4 (1.7)	
16	2 (0.8)		3 (1.2)	
17	2 (08)		0	
18	222 (93.3)		228 (94.2)	
Dose delays				
Any delay > 2 Days, n (%)	61 (25.6)		67 (27.9)	
Any delay Due to AE > 2 Days, n (%)	9 (3.8)		19 (7.9)	

N: Number of patients in the analysis set; n: Number of patients; SD: Standard deviation; Min: Minimum; Max: Maximum; AE: Adverse Events
Percentages were based on the number of patients in the analysis set.

Table 35: Summary of exposure to chemotherapy in the neoadjuvant treatment phase – safety set (TROIKA)

	HD201 N=250		EU-Herceptin N=252	
	n (%)	Cumulative (n%)	n (%)	Cumulative (n%)
Number of cycles administered				
Docetaxel				
0	0	0	0	0
1	3 (1.2)	3 (1.2)	3 (1.2)	3 (1.2)
2	2 (0.8)	5 (2.0)	0	3 (1.2)
3	0	5 (2.0)	2 (0.8)	5 (2.0)
4	245 (98.0)	250 (100)	246 (97.6)	251 (99.6)
8	0	250 (100)	1 (0.4)	252 (100)
Epirubicin				
0	5 (2.0)	5 (2.0)	7 (2.8)	7 (2.8)
1	0	5 (2.0)	3 (1.2)	10 (4.0)
2	1 (0.4)	6 (2.4)	2 (0.8)	12 (4.8)
3	0	6 (2.4)	0	12 (4.8)
4	244 (97.6)	250 (100)	240 (95.2)	252 (100)
Cyclophosphamide				
0	5 (2.0)	5 (2.0)	7 (2.8)	7 (2.8)
1	0	5 (2.0)	3 (1.2)	10 (4.0)
2	1 (0.4)	6 (2.4)	2 (0.8)	12 (4.8)
3	0	6 (2.4)	0	12 (4.8)
4	244 (97.6)	250 (100)	240 (95.2)	252 (100)
Patients with 8 cycles with the full dose administered as per package insert and as scheduled in the protocol	218 (87.2)		218 (86.5)	

N: Number of patients within the treatment group; n: number of patients within the category
Percentages were based on the number of patients with an available assessment within the group.

Adverse events

Phase I study TROIKA-1

Table 36: Summary of Treatment-Emergent Adverse Events – Safety Population (TROIKA-1)

Category	HD201 N=35 n (%) nae	EU-Herceptin N=35 n (%) nae	US-Herceptin N=35 n (%) nae	Total N=105 n (%) nae
Any TEAEs	27 (77.1) 62	30 (85.7) 71	29 (82.9) 73	86 (81.9) 206
Study treatment related TEAEs	18 (51.4) 37	23 (65.7) 45	24 (68.6) 42	65 (61.9) 124
Severity of any TEAEs				
Mild	27 (77.1) 61	29 (82.9) 59	28 (80.0) 64	84 (80.0) 184
Moderate	1 (2.9) 1	9 (25.7) 12	6 (17.1) 9	16 (15.2) 22
Severe	0	0	0	0
TEAEs of special interest	7 (20.0) 10	12 (34.3) 12	11 (31.4) 11	30 (28.6) 33
Any serious TEAEs	0	1 (2.9) 1	0	1 (1.0) 1
Study treatment related serious TEAEs	0	0	0	0
TEAEs leading to drug interruption/ withdrawal	1 (2.9) 1	0	3 (8.6) 3	4 (3.8) 4
Death	0	0	0	0

N = Number of subjects in the population; n: Number of subjects with an event; nae: number of adverse events TEAE: Treatment-emergent adverse event

Table 37: Incidence of all TEAEs by SOC and PT reported in any treatment arm – safety population (TROIKA-1)

SOC PT (MedDRA V 21.1)	HD201 N=35 n (%) nae	EU-Herceptin N=35 n (%) nae	US-Herceptin N=35 n (%) nae	Total N=105 n (%) nae
Nervous system disorders	11 (31.4) 16	8 (22.9) 8	11 (31.4) 12	30 (28.6) 36
Headache	11 (31.4) 16	8 (22.9) 8	7 (20.0) 7	26 (24.8) 31
Presyncope	0	0	2 (5.7) 2	2 (1.9) 2
Dizziness	0	0	1 (2.9) 1	1 (1.0) 1
Dysgeusia	0	0	1 (2.9) 1	1 (1.0) 1
Somnolence	0	0	1 (2.9) 1	1 (1.0) 1
General disorders and administration site conditions	7 (20.0) 8	8 (22.9) 9	2 (5.7) 3	17 (16.2) 20
Chest pain	2 (5.7) 2	2 (5.7) 2	1 (2.9) 1	5 (4.8) 5
Pyrexia	2 (5.7) 2	3 (8.6) 3	0	5 (4.8) 5
Influenza-like illness	2 (5.7) 3	0	0	2 (1.9) 3
Catheter site pain	0	2 (5.7) 2	0	2 (1.9) 2
Infusion site reaction	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Extravasation	1 (2.9) 1	0	0	1 (1.0) 1
Fatigue	0	1 (2.9) 1	0	1 (1.0) 1
Chills	0	0	1 (2.9) 1	1 (1.0) 1
Infections and infestations	6 (17.1) 6	7 (20.0) 7	12 (34.3) 13	25 (23.8) 26
Viral upper respiratory tract infection	2 (5.7) 2	1 (2.9) 1	0	3 (2.9) 3

SOC PT (MedDRA V 21.1)	HD201 N=35 n (%) nae	EU-Herceptin N=35 n (%) nae	US-Herceptin N=35 n (%) nae	Total N=105 n (%) nae
Pharyngitis	1 (2.9) 1	1 (2.9) 1	0	2 (1.9) 2
Rhinitis	1 (2.9) 1	0	4 (11.4) 5	5 (4.8) 6
Folliculitis	1 (2.9) 1	0	0	1 (1.0) 1
Tooth infection	1 (2.9) 1	0	0	1 (1.0) 1
Upper respiratory tract infection	0	2 (5.7) 2	5 (14.3) 5	7 (6.7) 7
Influenza	0	1 (2.9) 1	2 (5.7) 2	3 (2.9) 3
Nasopharyngitis	0	1 (2.9) 1	0	1 (1.0) 1
Urinary tract infection	0	1 (2.9) 1	0	1 (1.0) 1
Tonsillitis	0	0	1 (2.9) 1	1 (1.0) 1
Respiratory, thoracic and mediastinal disorders	5 (14.3) 7	7 (20.0) 8	4 (11.4) 5	16 (15.2) 20
Oropharyngeal pain	3 (8.6) 3	2 (5.7) 2	0	5 (4.8) 5
Rhinorrhoea	2 (5.7) 2	1 (2.9) 1	1 (2.9) 1	4 (3.8) 4
Cough	1 (2.9) 1	4 (11.4) 4	0	5 (4.8) 5
Nasal congestion	1 (2.9) 1	0	0	1 (1.0) 1
Epistaxis	0	1 (2.9) 1	2 (5.7) 2	3 (2.9) 3
Nasal discomfort	0	0	1 (2.9) 1	1 (1.0) 1
Upper-airway cough syndrome	0	0	1 (2.9% 1	1 (1.0) 1
Musculoskeletal and connective tissue disorders	5 (14.3) 7	3 (8.6) 3	7 (20.0) 7	15 (14.3) 17
Musculoskeletal pain	2 (5.7) 3	0	0	2 (1.9) 3
Arthralgia	1 (2.9) 2	0	1 (2.9) 1	2 (1.9) 3
Back pain	1 (2.9) 1	1 (2.9) 1	3 (8.6) 3	5 (4.8) 5
Myalgia	1 (2.9) 1	1 (2.9) 1	0	2 (1.9) 2
Tendonitis	0	1 (2.9) 1	0	1 (1.0) 1
Muscular weakness	0	0	1 (2.9) 1	1 (1.0) 1
Musculoskeletal chest pain	0	0	1 (2.9) 1	1 (1.0) 1
Spinal pain	0	0	1 (2.9) 1	1 (1.0) 1
Injury, poisoning and procedural complications	5 (14.3) 5	9 (25.7) 11	14 (40.0) 15	28 (26.7) 31
Infusion related reactions	4 (11.4) 4	7 (20.0) 8	11 (31.4)12	22 (21.0) 24
Joint injury	1 (2.9) 1	0	0	1 (1.0) 1
Joint dislocation	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Hand fracture	0	1 (2.9) 1	0	1 (1.0) 1
Ligament sprain	0	1 (2.9) 1	0	1 (1.0) 1
Contusion	0	0	1 (2.9) 1	1 (1.0) 1
Muscle strain	0	0	1 (2.9) 1	1 (1.0) 1
Gastrointestinal disorders	3 (8.6) 4	6 (17.1) 8	2 (5.7) 3	11 (10.5) 15
Nausea	2 (5.7) 3	2 (5.7) 3	1 (2.9) 1	5 (4.8) 7
Vomiting	1 (2.9) 1	0	0	1 (1.0) 1
Diarrhoea	0	2 (5.7) 2	0	2 (1.9) 2
Mouth ulceration	0	1 (2.9) 1	1 (2.9) 2	2 (1.9) 3
Abdominal pain	0	1 (2.9) 1	0	1 (1.0) 1
Haemorrhoids	0	1 (2.9) 1	0	1 (1.0) 1
Skin and subcutaneous tissue disorders	3 (8.6) 3	6 (17.1) 6	4 (11.4) 4	13 (12.4) 13

SOC PT (MedDRA V 21.1)	HD201 N=35 n (%) nae	EU-Herceptin N=35 n (%) nae	US-Herceptin N=35 n (%) nae	Total N=105 n (%) nae
Erythema	1 (2.9) 1	1 (2.9) 1	0	2 (1.9) 2
Skin reaction	1 (2.9) 1	1 (2.9) 1	0	2 (1.9) 2
Acne	1 (2.9) 1	0	0	1 (1.0) 1
Rash	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Dermatitis	0	1 (2.9) 1	0	1 (1.0) 1
Dry skin	0	1 (2.9) 1	0	1 (1.0) 1
Rash maculo-papular	0	1 (2.9) 1	0	1 (1.0) 1
Dermatitis acneiform	0	0	2 (5.7) 2	2 (1.9) 2
Skin exfoliation	0	0	1 (2.9) 1	1 (1.0) 1
Cardiac disorders	2 (5.7) 2	0	0	2 (1.9) 2
Bundle branch block right	1 (2.9) 1	0	0	1 (1.0) 1
Tachycardia	1 (2.9) 1	0	0	1 (1.0) 1
Investigations	1 (2.9) 2	0	2 (5.7) 3	3 (2.9) 5
Alanine aminotransferase increased	1 (2.9) 1	0	0	1 (1.0) 1
Aspartate aminotransferase increased	1 (2.9) 1	0	0	1 (1.0) 1
Blood creatine phosphokinase increased	0	0	1 (2.9) 1	1 (1.0) 1
Haemoglobin decreased	0	0	1 (2.9) 1	1 (1.0) 1
Transaminases increased	0	0	1 (2.9) 1	1 (1.0) 1
Eye disorders	1 (2.9) 1	1 (2.9) 1	2 (5.7) 2	4 (3.8) 4
Visual acuity reduced	1 (2.9) 1	1 (2.9) 1	1 (2.9) 1	3 (2.9) 3
Vision blurred	0	0	1 (2.9) 1	1 (1.0) 1
Metabolism and nutrition disorders	1 (2.9) 1	1 (2.9) 1	1 (2.9) 1	3 (2.9) 3
Dehydration	1 (2.9) 1	0	0	1 (1.0) 1
Hypophosphataemia	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Blood and lymphatic system disorders	0	5 (14.3) 7	1 (2.9) 2	6 (5.7) 9
Lymphopenia	0	4 (11.4) 4	1 (2.9) 1	5 (4.8) 5
Neutrophilia	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Anaemia	0	1 (2.9) 1	0	1 (1.0) 1
Leukocytosis	0	1 (2.9) 1	0	1 (1.0) 1
Psychiatric disorders	0	1 (2.9) 1	2 (5.7) 3	3 (2.9) 4
Agitation	0	1 (2.9) 1	0	1 (1.0) 1
Apathy	0	0	1 (2.9) 1	1 (1.0) 1
Insomnia	0	0	1 (2.9) 1	1 (1.0) 1
Mood altered	0	0	1 (2.9) 1	1 (1.0) 1
Vascular disorders	0	1 (2.9) 1	0	1 (1.0) 1
Hypertension	0	1 (2.9) 1	0	1 (1.0) 1

N: Number of subjects in the population; n: Number of subjects with an event; nae: number of adverse events; PT: Preferred term; SOC: System organ class

A subject experiencing multiple occurrences of an adverse event was counted once per SOC and PT. The numbers of subjects within each column cannot be added because a subject may have had more than one adverse event.

Table 38: Maximal severity of TEAEs by SOC for the safety population (TROIKA-1)

SOC	HD201 N=35 n (%) nae	EU-Herceptin N=35 n (%) nae	US-Herceptin N=35 n (%) nae	Total N=105 n (%) nae
Subjects with mild TEAEs	27 (77.1) 61	29 (82.9) 59	28 (80.0) 64	84 (80.0) 184
Nervous system disorders	11 (31.4) 16	7 (20.0) 7	11 (31.4) 12	29 (27.6) 35
General disorders and administration site conditions	7 (20.0) 8	7 (20.0) 8	2 (5.7) 2	16 (15.2) 18
Infections and infestations	6 (17.1) 6	5 (14.3) 5	11 (31.4) 12	22 (21.0) 23
Respiratory, thoracic and mediastinal disorders	5 (14.3) 7	7 (20.0) 8	4 (11.4) 5	16 (15.2) 20
Musculoskeletal and connective tissue disorders	5 (14.3) 7	2 (5.7) 2	7 (20.0) 7	14 (13.3) 16
Injury, poisoning and procedural complications	5 (14.3) 5	6 (17.1) 6	11 (31.4) 11	22 (21.0) 22
Gastrointestinal disorders	3 (8.6) 4	6 (17.1) 8	2 (5.7) 3	11 (10.5) 15
Skin and subcutaneous tissue disorders	2 (5.7) 2	6 (17.1) 6	4 (11.4) 4	12 (11.4) 12
Cardiac disorders	2 (5.7) 2	0	0	2 (1.9) 2
Eye disorders	1 (2.9) 1	1 (2.9) 1	2 (5.7) 2	4 (3.8) 4
Investigations	1 (2.9) 2	0	1 (2.9) 1	2 (1.9) 3
Metabolism and nutrition disorders	1 (2.9) 1	0	0	1 (1.0) 1
Blood and lymphatic system disorders	0	4 (11.4) 6	1 (2.9) 2	5 (4.8) 8
Psychiatric disorders	0	1 (2.9) 1	2 (5.7) 3	3 (2.9) 4
Vascular disorders	0	1 (2.9) 1	0	1 (1.0) 1
Subjects with moderate TEAEs	1 (2.9) 1	9 (25.7) 12	6 (17.1) 9	16 (15.2) 22
Skin and subcutaneous tissue disorders	1 (2.9) 1	0	0	1 (1.0) 1
Injury, poisoning and procedural complications	0	5 (14.3) 5	4 (11.4) 4	9 (8.6) 9
Infections and infestations	0	2 (5.7) 2	1 (2.9) 1	3 (2.9) 3
Nervous system disorders	0	1 (2.9) 1	0	1 (1.0) 1
General disorders and administration site conditions	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Musculoskeletal and connective tissue disorders	0	1 (2.9) 1	0	1 (1.0) 1
Blood and lymphatic system disorders	0	1 (2.9) 1	0	1 (1.0) 1
Metabolism and nutrition disorders	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Respiratory, thoracic and mediastinal disorders	0	0	0	0
Gastrointestinal disorders	0	0	0	0
Eye disorders	0	0	0	0

SOC	HD201 N=35 n (%) nae	EU-Herceptin N=35 n (%) nae	US-Herceptin N=35 n (%) nae	Total N=105 n (%) nae
Psychiatric disorders	0	0	0	0
Cardiac disorders	0	0	0	0
Investigations	0	0	1 (2.9) 2	1 (1.0) 2
Vascular disorders	0	0	0	0
Subjects with severe TEAEs	0	0	0	0

N: Number of subjects in the population; n: Number of subjects with an event; nae: number of adverse events; TEAE: Treatment-emergent adverse event
A subject experiencing multiple occurrences of an adverse event was counted once per SOC and PT. The numbers of subjects within each column cannot be added because a subject may have had more than one adverse event.

Table 39: Study treatment related TEAEs by SOC and PT for the safety population (TROIKA-1)

SOC PT (MedDRA V 21.1)	HD201 N=35 n (%) nae	EU-Herceptin N=35 n (%) nae	US-Herceptin N=35 n (%) nae	Total N=105 n (%) nae
Any study treatment related TEAEs	18 (51.4) 37	23 (65.7) 45	24 (68.6) 42	65 (61.9) 124
Nervous system disorders	9 (25.7) 12	7 (20.0) 7	10 (28.6) 10	26 (24.8) 29
Headache	9 (25.7) 12	7 (20.0) 7	7 (20.0) 7	23 (21.9) 26
Dizziness	0	0	1 (2.9) 1	1 (1.0) 1
Dysgeusia	0	0	1 (2.9) 1	1 (1.0) 1
Somnolence	0	0	1 (2.9) 1	1 (1.0) 1
General disorders and administration site conditions	5 (14.3) 5	5 (14.3) 5	1 (2.9) 2	11 (10.5) 12
Chest pain	2 (5.7) 2	2 (5.7) 2	1 (2.9) 1	5 (4.8) 5
Pyrexia	2 (5.7) 2	2 (5.7) 2	0	4 (3.8) 4
Fatigue	0	1 (2.9) 1	0	1 (1.0) 1
Influenza like illness	1 (2.9) 1	0	0	1 (1.0) 1
Infusion site reaction	0	0	1 (2.9 1	1 (1.0) 1
Injury, poisoning and procedural complications	4 (11.4) 4	7 (20.0) 8	12 (34.3) 13	23 (21.9) 25
Infusion-related reaction	4 (11.4) 4	7 (20.0) 8	11 (31.4) 12	22 (21.0) 24
Muscle strain	0	0	1 (2.9) 1	1 (1.0) 1
Gastrointestinal disorders	2 (5.7) 3	5 (14.3) 5	1 (2.9) 1	8 (7.6) 9
Nausea	2 (5.7) 3	2 (5.7) 2	1 (2.9) 1	5 (4.8) 6
Diarrhoea	0	2 (5.7) 2	0	2 (1.9) 2

SOC PT (MedDRA V 21.1)	HD201 N=35 n (%) nae	EU-Herceptin N=35 n (%) nae	US-Herceptin N=35 n (%) nae	Total N=105 n (%) nae
Abdominal pain	0	1 (2.9) 1	0	1 (1.0) 1
Skin and subcutaneous tissue disorders	2 (5.7) 2	5 (14.3) 5	4 (11.4) 4	11 (10.5) 11
Acne	1 (2.9) 1	0	0	1 (1.0) 1
Erythema	1 (2.9) 1	0	0	1 (1.0) 1
Rash	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Dermatitis	0	1 (2.9) 1	0	1 (1.0) 1
Dry skin	0	1 (2.9) 1	0	1 (1.0) 1
Rash maculo-papular	0	1 (2.9) 1	0	1 (1.0) 1
Skin reaction	0	1 (2.9) 1	0	1 (1.0) 1
Dermatitis acneiform	0	0	2 (5.7) 2	2 (1.9) 2
Skin exfoliation	0	0	1 (2.9) 1	1 (1.0) 1
Respiratory, thoracic and mediastinal disorders	2 (5.7) 2	4 (11.4) 4	1 (2.9) 1	7 (6.7) 7
Cough	1 (2.9) 1	2 (5.7) 2	0	3 (2.9) 3
Epistaxis	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Nasal congestion	1 (2.9) 1	0	0	1 (1.0) 1
Rhinorrhoea	0	1 (2.9) 1	0	1 (1.0) 1
Infections and infestations	2 (5.7) 2	2 (5.7) 2	3 (8.6) 3	7 (6.7) 7
Folliculitis	1 (2.9) 1	0	0	1 (1.0) 1
Pharyngitis	1 (2.9) 1	0	0	1 (1.0) 1
Upper respiratory tract infection	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Urinary tract infection	0	1 (2.9) 1	0	1 (1.0) 1
Rhinitis	0	0	2 (5.7) 2	2 (1.9) 2
Musculoskeletal and connective tissue disorders	2 (5.7) 2	2 (5.7) 2	1 (2.9) 1	5 (4.8) 5
Myalgia	1 (2.9) 1	1 (2.9) 1	0	2 (1.9) 2
Musculoskeletal pain	1 (2.9) 1	0	0	1 (1.0) 1
Tendonitis	0	1 (2.9) 1	0	1 (1.0) 1
Arthralgia	0	0	1 (2.9) 1	1 (1.0) 1

Investigations	1 (2.9) 2	0	2 (5.7) 3	3 (2.9) 5
Alanine aminotransferase increased	1 (2.9) 1	0	0	1 (1.0) 1
Aspartate aminotransferase increased	1 (2.9) 1	0	0	1 (1.0) 1
Blood creatine phosphokinase increased	0	0	1 (2.9) 1	1 (1.0) 1
Haemoglobin decreased	0	0	1 (2.9) 1	1 (1.0) 1
Transaminases increased	0	0	1 (2.9) 1	1 (1.0) 1
Metabolism and nutrition disorders	1 (2.9) 1	1 (2.9) 1	1 (2.9) 1	3 (2.9) 3
Dehydration	1 (2.9) 1	0	0	1 (1.0) 1
Hypophosphataemia	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Eye disorders	1 (2.9) 1	0	1 (2.9) 1	2 (1.9) 2
Visual acuity reduced	1 (2.9) 1	0	0	1 (1.0) 1
Vision blurred	0	0	1 (2.9) 1	1 (1.0) 1
Cardiac disorders	1 (2.9) 1	0	0	1 (1.0) 1
Tachycardia	1 (2.9) 1	0	0	1 (1.0) 1
Blood and lymphatic system disorders	0	4 (11.4) 6	1 (2.9) 2	5 (4.8) 8
Lymphopenia	0	3 (8.6) 3	1 (2.9) 1	4 (3.8) 4
Neutrophilia	0	1 (2.9) 1	1 (2.9) 1	2 (1.9) 2
Anaemia	0	1 (2.9) 1	0	1 (1.0) 1
Leukocytosis	0	1 (2.9) 1	0	1 (1.0) 1

N: Number of subjects in the population; n: Number of subjects with an event; nae: number of adverse events; TEAE: Treatment-emergent adverse event

A subject experiencing multiple occurrences of an adverse event was counted once per SOC and PT. The numbers of subjects within each column cannot be added because a subject may have had more than 1 adverse event.

Related TEAEs are defined as those assessed as 'definitively related', 'probably related', or 'possibly related' to study treatment

Table 40: TEAEs of special interest by SOC and PT (TROIKA-1)

SOC PT (MedDRA V21.1)	HD201 N=35 n (%) nae	EU-Herceptin N=35 n (%) nae	US-Herceptin N=35 n (%) nae	Total N=105 n (%) nae
Subjects with TEAEs of special interest	**7 (20.0) 10**	**12 (34.3) 12**	**11 (31.4) 11**	**30 (28.6) 33**
General disorders and administration site conditions	**3 (8.6) 4**	**3 (8.6) 3**	**0**	**6 (5.7) 7**
Chest pain	1 (2.9) 1	2 (5.7) 2	0	3 (2.9) 3
Pyrexia	1 (2.9) 1	1 (2.9) 1	0	2 (1.9) 2
Influenza-like illness	1 (2.9) 2	0	0	1 (1.0) 2
Injury, poisoning and procedural complications	**2 (5.7) 2**	**7 (20.0) 7**	**11 (31.4)**	**20 (19.0) 20**
Infusion-related reaction	2 (5.7) 2	7 (20.0) 7	11 (31.4)	20 (19.0) 20
Nervous system disorders	**2 (5.7) 2**	**0**	**0**	**2 (1.9) 2**
Headache	2 (5.7) 2	0	0	2 (1.9) 2
Gastrointestinal disorders	**1 (2.9) 1**	**1 (2.9) 1**	**0**	**2 (1.9)2**
Nausea	1 (2.9) 1	1 (2.9) 1	0	2 (1.9) 2
Cardiac disorders	**1 (2.9) 1**	**0**	**0**	**1 (1.0) 1**
Tachycardia	1 (2.9) 1	0	0	1 (1.0) 1
Vascular disorders	**0**	**1 (2.9) 1**	**0**	**1 (1.0) 1**
Hypertension	0	1 (2.9) 1	0	1 (1.0) 1

N: Number of subjects in the population; n: Number of subjects with an event; nae = number of adverse events; PT: Preferred term; SOC: System organ class; TEAE: Treatment-emergent adverse event

Phase III study TROIKA

Table 41: Summary of treatment-emergent adverse events overall – safety set (study TROIKA)

Category	Neoadjuvant period (SAF)		Adjuvant period (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%) nae [95% CI]	EU-Herceptin N=252 n (%) nae [95% CI]	HD201 N=238 n (%) nae [95% CI]	EU-Herceptin N=242 n (%) nae [95% CI]	HD201 N=250 n (%) nae [95% CI]	EU-Herceptin N=252 n (%) nae [95% CI]
Any TEAEs	246 (98.4) 2191 [96.0; 99.6]	243 (96.4) 2134 [93.3; 98.4]	164 (68.9) 678 [62.6; 74.7]	167 (69.0) 629 [62.8; 74.8]	250 (100) 2862 [98.5; 100.0]	247 (98.0) 2760 [95.4; 99.4]
Study treatment related TEAEs	86 (34.4) 312 [28.5; 40.6]	90 (35.7) 377 [29.8; 42.0]	74 (31.1) 233 [25.3; 37.4]	74 (30.6) 168 [24.8; 36.8]	128 (51.2) 543 [44.8; 57.5]	136 (54.0) 544 [47.6; 60.2]
Chemotherapy treatment related TEAEs	243 (97.2) 1894 [94.3; 98.9]	238 (94.4) 1866 [90.9; 96.9]	-	-	-	-
Grade 3 or higher TEAEs	76 (30.4) 135 [24.8; 36.5]	65 (25.8) 114 [20.5; 31.7]	15 (6.3) 33 [3.6; 10.2]	8 (3.3) 12 [1.4; 6.4]	86 (34.4) 167 [28.5; 40.6]	70 (27.8) 126 [22.3; 33.7]
Any serious TEAEs	16 (6.4) 22 [3.7; 10.2]	12 (4.8) 17 [2.5; 8.2]	8 (3.4) 8 [1.5; 6.5]	6 (2.5) 7 [0.9; 5.3]	24 (9.6) 30 [6.2; 13.9]	17 (6.7) 24 [4.0; 10.6]
Study treatment related serious TEAEs	0	1 (0.4) 2 [0.0; 2.2]	1 (0.4) 1 [0.0; 2.3]	2 (0.8) 2 [0.1; 3.0]	1 (0.4) 1 [0.0; 2.2]	3 (1.2) 4 [0.2; 3.4]
Chemotherapy treatment related serious TEAEs	11 (4.4) 14 [2.2; 7.7]	7 (2.8) 11 [1.1; 5.6]	-	-	-	-
TEAEs leading to discontinuation	6 (2.4) 7 [0.9; 5.2]	3 (1.2) 9 [0.2; 3.4]	11 (4.6) 28 [2.3; 8.1]	9 (3.7) 10 [1.7; 6.9]	16 (6.4) 34 [3.7; 10.2]	12 (4.8) 19 [2.5; 8.2]
TEAEs leading to dose/administration modification or discontinuation	69 (27.6) 123 [22.2; 33.6]	61 (24.2) 118 [19.1; 30.0]	21 (8.8) 50 [5.5; 13.2]	26 (10.7) 42 [7.1; 15.3]	83 (33.2) 172 [27.4; 39.4]	78 (31.0) 160 [25.3; 37.1]
Study treatment related TEAEs leading to dose/administration modification or discontinuation	14 (5.6) 22 [3.1; 9.2]	10 (4.0) 18 [1.9; 7.2]	6 (2.5) 13 [0.9; 5.4]	7 (2.9) 9 [1.2; 5.9]	18 (7.2) 35 [4.3; 11.1]	16 (6.3) 27 [3.7; 10.1]
Serious TEAEs leading to dose/administration modification or discontinuation	4 (1.6) 4 [0.4; 4.0]	5 (2.0) 6 [0.6; 4.6]	3 (1.3) 3 [0.3; 3.6]	3 (1.2) 4 [0.3; 3.6]	7 (2.8) 7 [1.1; 5.7]	7 (2.8) 10 [1.1; 5.6]
TEAEs of special interest	205 (82.0) 903 [76.7; 86.6]	197 (78.2) 835 [72.6; 83.1]	117 (49.2) 270 [42.6; 55.7]	111 (45.9) 236 [39.5; 52.4]	220 (88.0) 1169 [83.3; 91.8]	213 (84.5) 1070 [79.5; 88.8]

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events, TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
Note: Patients may experience one event spanning both treatment periods, thus the number of events reported in each treatment period may not add up to the number of events reported for the entire treatment period.

Table 42: Summary of treatment-emergent adverse events across geographical regions for the overall period – safety set (study TROIKA)

Category	Eastern Europe		Western Europe*		Asia	
	HD201 N = 216 n (%) nae [95% CI]	EU-Herceptin N = 219 n (%) nae [95% CI]	HD201 N = 14 n (%) nae [95% CI]	EU-Herceptin N = 14 n (%) nae [95% CI]	HD201 N = 20 n (%) nae [95% CI]	EU-Herceptin N = 19 n (%) nae [95% CI]
Any TEAEs	212 (98.1) 1844 [95.3; 99.5]	212 (96.8) 1825 [93.5; 98.7]	14 (100) 139 [76.8; 100.0]	14 (100) 149 [76.8; 100.0]	20 (100) 208 [83.2; 100.0]	17 (89.5) 160 [66.9; 98.7]
Study treatment related TEAEs	71 (32.9) 241 [26.6; 39.6]	74 (33.8) 286 [27.6 40.5]	5 (35.7) 27 [12.8; 64.9]	6 (42.9) 29 [17.7; 17.1]	10 (50.0) 44 [27.2; 72.8]	10 (52.6) 62 [28.9; 75.6]
Chemotherapy treatment related TEAEs	211 (97.7) 1639 [94.7; 99.2]	208 (95.0) 1619 [27.6; 40.5]	14 (100) 95 [12.8; 64.9]	14 (100) 113 [76.8; 100.0]	18 (90.0) 160 [68.3; 98.8]	16 (84.2) 134 [60.4; 96.6]
Grade 3 or higher TEAEs	54 (25.0) 94 [19.4; 31.3]	52 (23.7) 89 [18.3; 29.9]	10 (71.4) 21 [41.9; 91.6]	5 (35.7) 11 [12.8; 64.9]	12 (60.0) 20 [36.1; 80.9]	8 (42.1) 14 [20.3; 66.5]
Any serious TEAEs	5 (2.3) 6 [0.8; 5.3]	6 (2.7) 6 [1.0; 5.9]	5 (35.7) 5 [12.8; 64.9]	0	6 (30.0) 11 [11.9; 54.3]	6 (31.6) 11 [12.6; 56.6]
Study treatment related serious TEAEs	0	0	0	0	0	1 (5.3) 2 [0.1; 26.0]
Chemotherapy treatment related serious TEAEs	3 (1.4) 3 [0.3; 4.0]	2 (0.9) 2 [0.1; 3.3]	3 (21.4) 3 [4.7; 50.8]	0	5 (26.3) 8 [9.1; 51.2]	5 (26.3) 9 [91.1; 51.2]
TEAEs leading to discontinuation	3 (1.4) 4 [0.3; 4.0]	1 (0.5) 7 [0.0; 2.5]	2 (14.3) 2 [1.8; 42.8]	1 (7.1) 1 [0.2; 33.9]	1 (5.0) 1 [0.1; 24.9]	1 (5.3) 1 [0.1; 26.0]
TEAEs leading to dose/administration modification or discontinuation	51 (23.6) 89 [18.1; 29.8]	51 (23.3) 97 [17.9; 29.5]	8 (57.1) 13 [28.9; 82.3]	4 (28.6) 11 [8.4; 58.1]	10 (50.0) 21 [27.2; 72.8]	6 (31.6) 10 [12.6; 56.6]
Study treatment related TEAEs leading to dose/administration modification or discontinuation	7 (3.2) 11 [1.3; 6.6]	6 (2.7) 9 [1.0; 5.9]	4 (28.6) 7 [8.4; 58.1]	1 (7.1) 3 [0.2; 33.9]	3 (15.0) 4 [3.2; 37.9]	3 (15.8) 6 [3.4; 39.6]
Serious TEAEs leading to dose/administration modification or discontinuation	1 (0.5) 1 [0.0; 2.6]	4 (1.8) 4 [0.5; 4.6]	2 (14.3) 2 [1.8; 42.8]	0	1 (5.0) 1 [0.1; 24.9]	1 (5.3) 2 [0.1; 26.0]
TEAEs of special interest	173 (80.1) 747 [74.1; 85.2]	168 (76.7) 706 [70.5; 82.1]	13 (92.9) 62 [66.1; 99.8]	14 (100) 59 [76.8; 100.0]	19 (95.0) 94 [75.1; 99.9]	15 (78.9) 70 [54.4; 93.9]

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
*Data from Central European regions (HD201: N=1, EU-Herceptin: N=2) were pooled together with the data from Western European regions.

Table 43: Summary of TEAEs across geographical regions for the adjuvant period – aSAF (TROIKA)

Category	Eastern Europe		Western Europe*		Asia	
	HD201 N = 209 n (%) nae [95% CI]	EU-Herceptin N = 211 n (%) nae [95% CI]	HD201 N = 11 n (%) nae [95% CI]	EU-Herceptin N = 13 n (%) nae [95% CI]	HD201 N = 18 n (%) nae [95% CI]	EU-Herceptin N = 18 n (%) nae [95% CI]
Any TEAEs	141 (67.5) 578 [60.7; 73.8]	146 (69.2) 576 [62.5; 75.4]	8 (72.7) 39 [39.0; 94.0]	10 (76.9) 34 [46.2; 95.0]	15 (83.3) 61 [58.6; 96.4]	11 (61.1) 19 [35.7; 82.7]
Study treatment related TEAEs	65 (31.1) 212 [24.9; 37.9]	69 (32.7) 161 [26.4; 39.5]	5 (45.5) 7 [16.7; 76.6]	2 (15.4) 3 [1.9; 45.4]	4 (22.2) 14 [6.4; 47.6]	3 (16.7) 4 [3.6; 41.4]
Grade 3 or higher TEAEs	13 (6.2) 31 [3.4; 10.4]	7 (3.3) 11 [1.3; 6.7]	1 (9.1) 1 [0.2; 41.3]	0	1 (5.6) 1 [0.1; 27.3]	1 (5.6) 1 [0.1; 27.3]
Any serious TEAEs	7 (3.3) 7 [1.4; 6.8]	6 (2.8) 7 [1.1; 6.1]	0	0	1 (5.6) 1 [0.1; 27.3]	0
Study treatment related serious TEAEs	0	2 (0.9) 2 [0.1; 3.4]	0	0	1 (5.6) 1 [0.1; 27.3]	0
TEAEs leading to discontinuation	10 (4.8) 27 [2.3;8.6]	7 (3.3) 8 [1.3; 6.7]	0	0	1 (5.6) 1 [0.1; 27.3]	2 (11.1) 2 [1.4; 34.7]
TEAEs leading to dose/administration modification or discontinuation	19 (9.1) 48 [5.6; 13.8]	23 (10.9) 39 [7.0; 15.9]	1 (9.1) 1 [0.2; 41.3]	0	1 (5.6) 1 [0.1; 27.3]	3 (16.7) 3 [3.6; 41.4]
Study treatment related TEAEs leading to dose/administration modification or discontinuation	5 (2.4) 12 [0.8; 5.5]	6 (2.8) 8 [1.1; 6.1]	0	0	1 (5.6) 1 [0.1; 27.3]	1 (5.6) 1 [0.1; 27.3]
Serious TEAEs leading to dose/administration modification or discontinuation	2 (1.0) 2 [0.1; 3.4]	3 (1.4) 4 [0.3; 4.1]	0	0	1 (5.6) 1 [0.1; 27.3]	0
TEAEs of special interest	102 (48.8) 236 [41.8; 55.8]	100 (47.4) 220 [40.5; 54.4]	6 (54.5) 14 [23.4; 83.3]	6 (46.2) 10 [19.2; 74.9]	9 (50.0) 20 [26.0; 74.0]	5 (27.8) 6 [9.7; 53.5]

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
*Data from Central European regions (HD201: N=1, EU-Herceptin: N=2) were pooled together with the data from Western European regions.

Table 44: Summary of TEAEs across geographical regions for the entire treatment period – SAF (TROIKA)

Category	Eastern Europe		Western Europe*		Asia	
	HD201 N = 216 n (%) nae [95% CI]	EU-Herceptin N = 219 n (%) nae [95% CI]	HD201 N = 14 n (%) nae [95% CI]	EU-Herceptin N = 14 n (%) nae [95% CI]	HD201 N = 20 n (%) nae [95% CI]	EU-Herceptin N = 19 n (%) nae [95% CI]
Any TEAEs	216 (100) 2415 [98.3; 100.0]	215 (98.2) 2399 [95.4; 99.5]	14 (100) 178 [76.8; 100.0]	14 (100) 182 [76.8; 100.0]	20 (100) 269 [83.2; 100.0]	18 (94.7) 179 [74.0; 99.9]
Study treatment related TEAEs	110 (50.9) 451 [44.1; 57.8]	119 (54.3) 447 [47.5; 61.1]	8 (57.1) 34 [28.9; 82.3]	6 (42.9) 31 [17.7; 71.1]	10 (50.0) 58 [27.2; 72.8]	11 (57.9) 66 [33.5; 79.7]
Grade 3 or higher TEAEs	63 (29.2) 124 [23.2; 35.7]	56 (25.6) 100 [19.9; 31.9]	10 (71.4) 22 [41.9; 91.6]	5 (35.7) 11 [12.8; 64.9]	13 (65.0) 21 [40.8; 84.6]	9 (47.4) 15 [24.4; 71.7]
Any serious TEAEs	12 (5.6) 13 [2.9; 9.5]	11 (5.0) 13 [2.5; 8.8]	5 (35.7) 5 [12.8; 64.9]	0	7 (35.0) 12 [15.4; 59.2]	6 (31.6) 11 [12.6; 56.6]
Study treatment related serious TEAEs	0	2 (0.9) 2 [0.1; 3.3]	0	0	1 (5.0) 1 [0.1; 24.9]	1 (5.3) 2 [0.1; 26.0]
TEAEs leading to discontinuation	12 (5.6) 30 [2.9; 9.5]	8 (3.7) 15 [1.6; 7.1]	2 (14.3) 2 [1.8; 42.8]	1 (7.1) 1 [0.2; 33.9]	2 (10.0) 2 [1.2; 31.7]	3 (15.8) 3 [3.4; 39.6]
TEAEs leading to dose/administration modification or discontinuation	63 (29.2) 136 [23.2; 35.7]	66 (30.1) 136 [24.1; 36.7]	9 (64.3) 14 [35.1; 87.2]	4 (28.6) 11 [8.4; 58.1]	11 (55.0) 22 [31.5; 76.9]	8 (42.1) 13 [20.3; 66.5]
Study treatment related TEAEs leading to dose/administration modification or discontinuation	10 (4.6) 23 [2.2; 8.3]	12 (5.5) 17 [2.9; 9.4]	4 (28.6) 7 [8.4; 58.1]	1 (7.1) 3 [0.2; 33.9]	4 (20.0) 5 [5.7; 43.7]	3 (15.8) 7 [3.4; 39.6]
Serious TEAEs leading to dose/administration modification or discontinuation	3 (1.4) 3 [0.3; 4.0]	6 (2.7) 8 [1.0; 5.9]	2 (14.3) 2 [1.8; 42.8]	0	2 (10.0) 2 [1.2; 31.7]	1 (5.3) 2 [0.1; 26.0]
TEAEs of special interest	188 (87.0) 979 [81.8; 91.2]	183 (83.6) 925 [78.0; 88.2]	13 (92.9) 76 [66.1; 99.8]	14 (100) 69 [76.8; 100.0]	19 (95.0) 114 [75.1; 99.9]	16 (84.2) 76 [60.4; 96.6]

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
*Data from Central European regions (HD201: N=1, EU-Herceptin: N=2) were pooled together with the data from Western European regions.

Table 45: Summary of PTAEs for all regions for the post-treatment follow-up period – PTAS (TROIKA)

Category	HD201 N=234 n (%) nae [95% CI]	EU-Herceptin N=242 n (%) nae [95% CI]
Any PTAEs	64 (27.4) 126 [21.7; 33.5]	72 (29.8) 154 [24.1; 35.9]
Study treatment related PTAEs	21 (9.0) 34 [5.6; 13.4]	23 (9.5) 47 [6.1; 13.9]
Grade 3 or higher PTAEs	7 (3.0) 8 [1.2; 6.1]	13 (5.4) 14 [2.9; 9.0]
Any serious PTAEs	4 (1.7) 4 [0.5; 4.3]	5 (2.1) 5 [0.7; 4.8]
Study treatment related serious PTAEs	0	0
Any PTAEs of special interest	35 (15.0) 50 [10.6; 20.2]	40 (16.5) 56 [12.1; 21.8]

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; PTAEs: Post-treatment adverse events
% calculated based on N for each treatment group

Table 46: Summary of PTAEs across geographical regions for the post-treatment follow-up period – PTAS (TROIKA)

Category	Eastern Europe		Western Europe*		Asia	
	HD201 N = 204 n (%) nae [95% CI]	EU-Herceptin N = 210 n (%) nae [95% CI]	HD201 N = 11 n (%) nae [95% CI]	EU-Herceptin N = 14 n (%) nae [95% CI]	HD201 N = 19 n (%) nae [95% CI]	EU-Herceptin N = 18 n (%) nae [95% CI]
Any PTAEs	56 (27.5) 116 [21.5; 34.1]	66 (31.4) 146 [25.2; 38.2]	4 (36.4) 4 [10.9; 69.2]	4 (28.6) 6 [8.4; 58.1]	4 (21.1) 6 [6.1; 45.6]	2 (11.1) 2 [1.4; 34.7]
Study treatment related PTAEs	21 (10.3) 34 [6.5; 15.3]	22 (10.5) 46 [6.7; 15.4]	0	0	0	1 (5.6) 1 [0.1; 27.3]

Grade 3 or higher PTAEs	4 (2.0) 4 [0.5; 4.9]	12 (5.7) 13 [3.0; 9.8]	2 (18.2) 2 [2.3; 51.8]	1 (7.1) 1 [0.2, 33.9]	1 (5.3) 2 [0.1; 26.0]	0
Any serious PTAEs	2 (1.0) 2 [0.1; 3.5]	5 (2.4) 5 [0.8; 5.5]	1 (9.1) 1 [0.2; 41.3]	0	1 (5.3) 1 [0.1; 26.0]	0
Study treatment related serious PTAEs	0	0	0	0	0	0
Any PTAEs of special interest	31 (15.2) 46 [10.6; 20.9]	38 (18.1) 54 [13.1; 24.0]	1 (9.1) 1 [0.2; 41.3]	1 (7.1) 1 [0.2; 33.9]	3 (15.8) 3 [3.4; 39.6]	1 (5.6) 1 [0.1; 27.3]

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; PTAEs: Post-treatment adverse events
% calculated based on N for each treatment group
*Data from Central European regions (HD201: N=1, EU-Herceptin: N=2) were pooled together with the data from Western European regions.

Table 47: Incidence of TEAEs occurring in ⩾ 5% of patients by SOC and PT reported in any treatment arm for the entire study – safety set (study TROIKA)

SOC PT (MedDRA V21.0)	Neoadjuvant period (SAF)		Adjuvant period (aSAF)		Entire treatment period (SAF)	
	HD201 N=250	EU-Herceptin N=252	HD201 N=238	EU-Herceptin N=242	HD201 N=250	EU-Herceptin N=252
	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae
Any TEAEs	**246 (98.4) 2191**	**243 (96.4) 2134**	**164 (68.9) 678**	**167 (69.0) 629**	**250 (100) 2862**	**247 (98.0) 2760**
Skin and subcutaneous tissue disorders	**211 (84.4) 283**	**210 (83.3) 280**	**16 (6.7) 19**	**13 (5.4) 20**	**214 (85.6) 302**	**210 (83.3) 300**
Alopecia	202 (80.8) 202	200 (79.4) 200	0	0	202 (80.8) 202	200 (79.4) 200
Rash	23 (9.2) 40	13 (5.2) 25	3 (1.3) 3	5 (2.1) 5	26 (10.4) 43	17 (6.7) 30
General disorders and administration site conditions	**139 (55.6) 363**	**135 (53.6) 316**	**36 (15.1) 66**	**40 (16.5) 55**	**148 (59.2) 429**	**153 (60.7) 370**
Asthenia	65 (26.0) 217	59 (23.4) 193	15 (6.3) 18	17 (7.0) 18	68 (27.2) 235	66 (26.2) 210
Fatigue	59 (23.6) 88	60 (23.8) 86	11 (4.6) 29	11 (4.5) 18	62 (24.8) 117	67 (26.6) 104
Oedema peripheral	13 (5.2) 21	6 (2.4) 6	5 (2.1) 5	8 (3.3) 8	17 (6.8) 26	14 (5.6) 14
Pyrexia	13 (5.2) 14	11 (4.4) 12	5 (2.1) 6	3 (1.2) 3	17 (6.8) 20	13 (5.2) 15
Gastrointestinal disorders	**131 (52.4) 411**	**129 (51.2) 396**	**15 (6.3) 25**	**11 (4.5) 16**	**137 (54.8) 436**	**132 (52.4) 412**
Nausea	86 (34.4) 234	93 (36.9) 234	2 (0.8) 4	1 (0.4) 1	86 (34.4) 238	93 (36.9) 235
Diarrhoea	45 (18.0) 68	42 (16.7) 62	5 (2.1) 7	4 (1.7) 4	47 (18.8) 75	45 (17.9) 66
Vomiting	21 (8.4) 32	18 (7.1) 25	1 (0.4) 1	1 (0.4) 1	21 (8.4) 33	18 (7.1) 26
Stomatitis	19 (7.6) 23	14 (5.6) 22	0	0	19 (7.6) 23	14 (5.6) 22
Blood and lymphatic system disorders	**126 (50.4) 304**	**120 (47.6) 288**	**49 (20.6) 108**	**45 (18.6) 88**	**135 (54.0) 410**	**134 (53.2) 375**
Neutropenia	69 (27.6) 120	72 (28.6) 123	15 (6.3) 23	14 (5.8) 15	77 (30.8) 143	78 (31.0) 138
Anaemia	68 (27.2) 93	56 (22.2) 74	19 (8.0) 22	14 (5.8) 17	72 (28.8) 113	61 (24.2) 90
Leukopenia	36 (14.4) 55	38 (15.1) 62	19 (8.0) 27	21 (8.7) 30	44 (17.6) 82	51 (20.2) 92
Hypoglobulinaemia	12 (4.8) 18	13 (5.2) 16	10 (4.2) 18	7 (2.9) 11	14 (5.6) 36	13 (5.2) 27
Thrombocytopenia	6 (2.4) 7	2 (0.8) 2	9 (3.8) 14	9 (3.7) 9	13 (5.2) 21	10 (4.0) 11

SOC PT (MedDRA V21.0)	Neoadjuvant period (SAF)		Adjuvant period (aSAF)		Entire treatment period (SAF)	
	HD201 N=250	EU-Herceptin N=252	HD201 N=238	EU-Herceptin N=242	HD201 N=250	EU-Herceptin N=252
	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae
Investigations	**81 (32.4) 196**	**84 (33.3) 214**	**61 (25.6) 131**	**57 (23.6) 128**	**107 (42.8) 324**	**105 (41.7) 341**
Alanine aminotransferase increased	28 (11.2) 40	34 (13.5) 47	12 (5.0) 12	13 (5.4) 13	35 (14.0) 52	41 (16.3) 60
Aspartate aminotransferase increased	25 (10.0) 31	24 (9.5) 35	19 (8.0) 22	16 (6.6) 19	37 (14.8) 52	31 (12.3) 54
Gamma-glutamyl transferase increased	16 (6.4) 20	23 (9.1) 33	6 (2.5) 6	10 (4.1) 12	19 (7.6) 25	29 (11.5) 45
Neutrophil count decreased	13 (5.2) 20	8 (3.2) 8	3 (1.3) 3	2 (0.8) 4	15 (6.0) 23	8 (3.2) 12
Blood alkaline phosphatase increased	6 (2.4) 7	13 (5.2) 14	11 (4.6) 16	17 (7.0) 24	15 (6.0) 23	24 (9.5) 38
Ejection fraction decreased	11 (4.4) 11	13 (5.2) 13	12 (5.0) 12	9 (3.7) 9	21 (8.4) 22	21 (8.3) 22
Electrocardiogram abnormal	10 (4.0) 10	5 (2.0) 5	10 (4.2) 11	4 (1.7) 4	16 (6.4) 21	9 (3.6) 9
Musculoskeletal and connective tissue disorders	**62 (24.8) 118**	**58 (23.0) 121**	**30 (12.6) 41**	**28 (11.6) 44**	**80 (32.0) 159**	**76 (30.2) 165**
Arthralgia	28 (11.2) 49	23 (9.1) 43	14 (5.9) 16	11 (4.5) 14	40 (16.0) 65	31 (12.3) 57
Bone pain	17 (6.8) 28	13 (5.2) 34	4 (1.7) 8	4 (1.7) 12	19 (7.6) 36	16 (6.3) 46
Myalgia	15 (6.0) 22	18 (7.1) 26	1 (0.4) 1	1 (0.4) 1	16 (6.4) 23	19 (7.5) 27
Nervous system disorders	**58 (23.2) 75**	**57 (22.6) 99**	**31 (13.0) 51**	**19 (7.9) 25**	**78 (31.2) 126**	**73 (29.0) 124**
Peripheral sensory neuropathy	12 (4.8) 12	13 (5.2) 13	0	0	12 (4.8) 12	13 (5.2) 13
Headache	9 (3.6) 11	12 (4.8) 16	19 (8.0) 22	11 (4.5) 14	26 (10.4) 33	22 (8.7) 30
Dysgeusia	7 (2.8) 9	12 (4.8) 24	4 (1.7) 5	1 (0.4) 1	9 (3.6) 14	13 (5.2) 25
Infections and infestations	**47 (18.8) 70**	**47 (18.7) 66**	**22 (9.2) 25**	**27 (11.2) 32**	**61 (24.4) 95**	**64 (25.4) 98**
Cardiac disorders	**44 (17.6) 73**	**48 (19.0) 84**	**33 (13.9) 50**	**41 (16.9) 59**	**61 (24.4) 122**	**69 (27.4) 143**
Sinus tachycardia	15 (6.0) 15	10 (4.0) 10	2 (0.8) 2	7 (2.9) 7	16 (6.4) 17	16 (6.3) 17
Mitral valve incompetence	7 (2.8) 7	7 (2.8) 7	3 (1.3) 3	9 (3.7) 9	10 (4.0) 10	14 (5.6) 16
Metabolism and nutrition disorders	**41 (16.4) 81**	**36 (14.3) 73**	**22 (9.2) 38**	**20 (8.3) 35**	**49 (19.6) 119**	**44 (17.5) 108**
Hypoproteinaemia	19 (7.6) 26	14 (5.6) 24	7 (2.9) 13	7 (2.9) 9	20 (8.0) 39	17 (6.7) 33

SOC PT (MedDRA V21.0)	Neoadjuvant period (SAF)		Adjuvant period (aSAF)		Entire treatment period (SAF)	
	HD201 N=250	EU-Herceptin N=252	HD201 N=238	EU-Herceptin N=242	HD201 N=250	EU-Herceptin N=252
	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae
Decreased appetite	13 (5.2) 18	12 (4.8) 21	1 (0.4) 1	0	13 (5.2) 19	12 (4.8) 21
Hypocalcaemia	6 (2.4) 10	10 (4.0) 13	12 (5.0) 16	9 (3.7) 12	14 (5.6) 26	15 (6.0) 25
Respiratory, thoracic and mediastinal disorders	**33 (13.2) 42**	**25 (9.9) 44**	**20 (8.4) 36**	**16 (6.6) 20**	**45 (18.0) 78**	**39 (15.5) 64**
Injury, poisoning and procedural complications	**34 (13.6) 43**	**35 (13.9) 48**	**26 (10.9) 29**	**37 (15.3) 40**	**55 (22.0) 72**	**67 (26.6) 88**
Procedural pain	31 (12.4) 32	29 (11.5) 33	5 (2.1) 5	16 (6.6) 16	36 (14.4) 37	44 (17.5) 49
Radiation skin injury	0	0	16 (6.7) 16	16 (6.6) 16	16 (6.4) 16	16 (6.3) 16
Vascular disorders	**27 (10.8) 33**	**22 (8.7) 33**	**14 (5.9) 17**	**21 (8.7) 28**	**40 (16.0) 49**	**38 (15.1) 61**
Hypertension	7 (2.8) 7	11 (4.4) 15	5 (2.1) 5	5 (2.1) 6	11 (4.4) 11	16 (6.3) 21
Hepatobiliary disorders	**16 (6.4) 28**	**15 (6.0) 18**	**3 (1.3) 5**	**3 (1.2) 4**	**17 (6.8) 33**	**18 (7.1) 22**
Eye disorders	**13 (5.2) 22**	**10 (4.0) 12**	**5 (2.1) 8**	**3 (1.2) 3**	**16 (6.4) 30**	**13 (5.2) 15**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**11 (4.4) 14**	**7 (2.8) 8**	**7 (2.9) 7**	**7 (2.9) 8**	**18 (7.2) 21**	**14 (5.6) 16**
Reproductive system and breast disorders	**11 (4.4) 13**	**11 (4.4) 12**	**3 (1.3) 4**	**10 (4.1) 14**	**13 (5.2) 17**	**21 (8.3) 26**

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
Note: Patients may experience one event spanning both treatment periods, thus the number of events reported in each treatment period may not add up to the number of events reported for the entire treatment period.

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4%) 3	0	0	0	1 (0.4%) 3	0
Tumour pain	1 (0.4%) 3	0	0	0	1 (0.4%) 3	0

N = Number of patients within the treatment group, n = number of patients with an event, nae = number of adverse events, TEAE = Treatment-Emergent Adverse Event

Table 48: Patients with TEAEs by maximal severity for the entire treatment period – SAF and aSAF (TROIKA)

Category	Neoadjuvant period (SAF)		Adjuvant period (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)	HD201 N=238 n (%)	EU-Herceptin N=242 n (%)	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)
Any TEAEs	246 (98.4)	243 (96.4)	164 (68.9)	167 (69.0)	250 (100)	247 (98.0)
Maximal severity of TEAEs						
Mild (Grade 1)	22 (8.8)	24 (9.5)	89 (37.4)	91 (37.6)	18 (7.2)	25 (9.9)
Moderate (Grade 2)	148 (59.2)	154 (61.1)	60 (25.2)	68 (28.1)	146 (58.4)	152 (60.3)
Severe (Grade 3)	58 (23.2)	55 (21.8)	13 (5.5)	7 (2.9)	66 (26.4)	59 (23.4)
Life-threatening (Grade 4)	14 (5.6)	10 (4.0)	0	1 (0.4)	14 (5.6)	11 (4.4)
Fatal (Grade 5)	4 (1.6)	0	2 (0.8)	0	6 (2.4)	0

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
For incidence of patients, the maximal severity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1) is reported.
Note: Patients may experience multiple events of different severity in different treatment periods, thus the number of patients reported in each treatment period per severity may not add up to the number of patients reported for the entire treatment period, as the highest severity is reported for each treatment period.

Table 49: Summary of TEAEs by maximal severity per SOC (reported in ≥ 5% in any group) for the entire treatment period – SAF and aSAF (TROIKA)

SOC	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)	HD201 N=238 n (%)	EU-Herceptin N=242 n (%)	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)
Skin and subcutaneous tissue disorders	**211 (84.4)**	**210 (83.3)**	**16 (6.7)**	**13 (5.4)**	**214 (85.6)**	**210 (83.3)**
Mild (Grade 1)	54 (21.6)	46 (18.3)	14 (5.9)	10 (4.1)	56 (22.4)	46 (18.3)
Moderate (Grade 2)	147 (58.8)	156 (61.9)	2 (0.8)	3 (1.2)	148 (59.2)	156 (61.9)
Severe (Grade 3)	10 (4.0)	8 (3.2)	0	0	10 (4.0)	8 (3.2)
General disorders and administration site conditions	**139 (55.6)**	**135 (53.6)**	**36 (15.1)**	**40 (16.5)**	**148 (59.2)**	**153 (60.7)**
Mild (Grade 1)	76 (30.4)	76 (30.2)	32 (13.4)	35 (14.5)	85 (34.0)	90 (35.7)
Moderate (Grade 2)	60 (24.0)	58 (23.0)	3 (1.3)	5 (2.1)	59 (23.6)	62 (24.6)
Severe (Grade 3)	2 (0.8)	1 (0.4)	1 (0.4)	0	3 (1.2)	1 (0.4)
Fatal (Grade 5)	1 (0.4)	0	0	0	1 (0.4)	0
Blood and lymphatic system disorders	**126 (50.4)**	**120 (47.6)**	**49 (20.6)**	**45 (18.6)**	**135 (54.0)**	**134 (53.2)**
Mild (Grade 1)	40 (16.0)	35 (13.9)	33 (13.9)	30 (12.4)	42 (16.8)	44 (17.5)
Moderate (Grade 2)	43 (17.2)	36 (14.3)	14 (5.9)	15 (6.2)	49 (19.6)	41 (16.3)
Severe (Grade 3)	32 (12.8)	39 (15.5)	2 (0.8)	0	33 (13.2)	39 (15.5)
Life-threatening (Grade 4)	11 (4.4)	10 (4.0)	0	0	11 (4.4)	10 (4.0)
Gastrointestinal disorders	**131 (52.4)**	**129 (51.2)**	**15 (6.3)**	**11 (4.5)**	**137 (54.8)**	**132 (52.4)**
Mild (Grade 1)	88 (35.2)	77 (30.6)	9 (3.8)	7 (2.9)	92 (36.8)	79 (31.3)
Moderate (Grade 2)	40 (16.0)	48 (19.0)	6 (2.5)	4 (1.7)	42 (16.8)	49 (19.4)
Severe (Grade 3)	3 (1.2)	4 (1.6)	0	0	3 (1.2)	4 (1.6)
Investigations	**81 (32.4)**	**84 (33.3)**	**61 (25.6)**	**57 (23.6)**	**107 (42.8)**	**105 (41.7)**
Mild (Grade 1)	41 (16.4)	40 (15.9)	43 (18.1)	34 (14.0)	55 (22.0)	47 (18.7)
Moderate (Grade 2)	18 (7.2)	38 (15.1)	14 (5.9)	22 (9.1)	28 (11.2)	51 (20.2)
Severe (Grade 3)	20 (8.0)	6 (2.4)	4 (1.7)	1 (0.4)	22 (8.8)	7 (2.8)
Life-threatening (Grade 4)	2 (0.8)	0	0	0	2 (0.8)	0
Musculoskeletal and connective tissue disorders	**62 (24.8)**	**58 (23.0)**	**30 (12.6)**	**28 (11.6)**	**80 (32.0)**	**76 (30.2)**

SOC	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)	HD201 N=238 n (%)	EU-Herceptin N=242 n (%)	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)
Mild (Grade 1)	38 (15.2)	45 (17.9)	21 (8.8)	22 (9.1)	50 (20.0)	57 (22.6)
Moderate (Grade 2)	24 (9.6)	13 (5.2)	9 (3.8)	6 (2.5)	30 (12.0)	19 (7.5)
Nervous system disorders	**58 (23.2)**	**57 (22.6)**	**31 (13.0)**	**19 (7.9)**	**78 (31.2)**	**73 (29.0)**
Mild (Grade 1)	47 (18.8)	40 (15.9)	22 (9.2)	16 (6.6)	60 (24.0)	53 (21.0)
Moderate (Grade 2)	11 (4.4)	13 (5.2)	5 (2.1)	3 (1.2)	14 (5.6)	16 (6.3)
Severe (Grade 3)	0	4 (1.6)	4 (1.7)	0	4 (1.6)	4 (1.6)
Cardiac disorders	**44 (17.6)**	**48 (19.0)**	**33 (13.9)**	**41 (16.9)**	**61 (24.4)**	**69 (27.4)**
Mild (Grade 1)	37 (14.8)	37 (14.7)	27 (11.3)	35 (14.5)	49 (19.6)	54 (21.4)
Moderate (Grade 2)	4 (1.6)	10 (4.0)	3 (1.3)	5 (2.1)	6 (2.4)	13 (5.2)
Severe (Grade 3)	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	3 (1.2)	2 (0.8)
Fatal (Grade 5)	2 (0.8)	0	1 (0.4)	0	3 (1.2)	0
Infections and infestations	**47 (18.8)**	**47 (18.7)**	**22 (9.2)**	**27 (11.2)**	**61 (24.4)**	**64 (25.4)**
Mild (Grade 1)	14 (5.6)	17 (6.7)	10 (4.2)	10 (4.1)	22 (8.8)	25 (9.9)
Moderate (Grade 2)	30 (12.0)	26 (10.3)	12 (5.0)	16 (6.6)	36 (14.4)	35 (13.9)
Severe (Grade 3)	3 (1.2)	3 (1.2)	0	1 (0.4)	3 (1.2)	3 (1.2)
Life-threatening (Grade 4)	0	1 (0.4)	0	0	0	1 (0.4)
Injury, poisoning and procedural complications	**34 (13.6)**	**35 (13.9)**	**26 (10.9)**	**37 (15.3)**	**55 (22.0)**	**67 (26.6)**
Mild (Grade 1)	23 (9.2)	20 (7.9)	21 (8.8)	33 (13.6)	40 (16.0)	49 (19.4)
Moderate (Grade 2)	11 (4.4)	14 (5.6)	5 (2.1)	4 (1.7)	15 (6.0)	17 (6.7)
Severe (Grade 3)	0	1 (0.4)	0	0	0	1 (0.4)
Metabolism and nutrition disorders	**41 (16.4)**	**36 (14.3)**	**22 (9.2)**	**20 (8.3)**	**49 (19.6)**	**44 (17.5)**
Mild (Grade 1)	36 (14.4)	30 (11.9)	18 (7.6)	16 (6.6)	40 (16.0)	34 (13.5)
Moderate (Grade 2)	1 (0.4)	5 (2.0)	4 (1.7)	4 (1.7)	5 (2.0)	9 (3.6)
Severe (Grade 3)	4 (1.6)	1 (0.4)	0	0	4 (1.6)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**33 (13.2)**	**25 (9.9)**	**20 (8.4)**	**16 (6.6)**	**45 (18.0)**	**39 (15.5)**
Mild (Grade 1)	26 (10.4)	20 (7.9)	15 (6.3)	12 (5.0)	33 (13.2)	31 (12.3)
Moderate (Grade 2)	7 (2.8)	5 (2.0)	5 (2.1)	4 (1.7)	12 (4.8)	8 (3.2)

SOC	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)	HD201 N=238 n (%)	EU-Herceptin N=242 n (%)	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)
Vascular disorders	**27 (10.8)**	**22 (8.7)**	**14 (5.9)**	**21 (8.7)**	**40 (16.0)**	**38 (15.1)**
Mild (Grade 1)	22 (8.8)	12 (4.8)	9 (3.8)	14 (5.8)	30 (12.0)	21 (8.3)
Moderate (Grade 2)	5 (2.0)	8 (3.2)	5 (2.1)	4 (1.7)	10 (4.0)	12 (4.8)
Severe (Grade 3)	0	2 (0.8)	0	3 (1.2)	0	5 (2.0)
Hepatobiliary disorders	**16 (6.4)**	**15 (6.0)**	**3 (1.3)**	**3 (1.2)**	**17 (6.8)**	**18 (7.1)**
Mild (Grade 1)	12 (4.8)	13 (5.2)	1 (0.4)	2 (0.8)	12 (4.8)	15 (6.0)
Moderate (Grade 2)	4 (1.6)	2 (0.8)	1 (0.4)	1 (0.4)	4 (1.6)	3 (1.2)
Severe (Grade 3)	0	0	1 (0.4)	0	1 (0.4)	0
Reproductive system and breast disorders	**11 (4.4)**	**11 (4.4)**	**3 (1.3)**	**10 (4.1)**	**13 (5.2)**	**21 (8.3)**
Mild (Grade 1)	8 (3.2)	6 (2.4)	2 (0.8)	10 (4.1)	9 (3.6)	16 (6.3)
Moderate (Grade 2)	2 (0.8)	4 (1.6)	1 (0.4)	0	3 (1.2)	4 (1.6)
Severe (Grade 3)	1 (0.4)	1 (0.4)	0	0	1 (0.4)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**11 (4.4)**	**7 (2.8)**	**7 (2.9)**	**7 (2.9)**	**18 (7.2)**	**14 (5.6)**
Mild (Grade 1)	7 (2.8)	1 (0.4)	4 (1.7)	2 (0.8)	11 (4.4)	8 (3.2)
Moderate (Grade 2)	2 (0.8)	6 (2.4)	1 (0.4)	2 (0.8)	3 (1.2)	3 (1.2)
Severe (Grade 3)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.8)	2 (0.8)	2 (0.8)
Life-threatening (Grade 4)	0	0	0	1 (0.4)	0	1 (0.4)
Fatal (Grade 5)	1 (0.4)	0	1 (0.4)	0	2 (0.8)	0
Eye disorders	**13 (5.2)**	**10 (4.0)**	**5 (2.1)**	**3 (1.2)**	**16 (6.4)**	**13 (5.2)**
Mild (Grade 1)	10 (4.0)	8 (3.2)	2 (0.8)	3 (1.2)	10 (4.0)	11 (4.4)
Moderate (Grade 2)	3 (1.2)	2 (0.8)	2 (0.8)	0	5 (2.0)	2 (0.8)
Severe (Grade 3)	0	0	1 (0.4)	0	1 (0.4)	0

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
For incidence of patients, the maximal severity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1) is reported.
Note: Patients may experience multiple events of different severity in different treatment periods, thus the number of patients reported in each treatment period per severity may not add up to the number of patients reported for the entire treatment period, as the highest severity is retained.

Table 50: Summary of patients with ≥ Grade 3 TEAEs by SOC and PT for the entire treatment period – SAF and aSAF (TROIKA)

SOC PT (MedDRA V21.0)	Neoadjuvant period (SAF)		Adjuvant period (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)	HD201 N=238 n (%)	EU-Herceptin N=242 n (%)	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)
TEAEs ≥ Grade 3	**76 (30.4)**	**65 (25.8)**	**15 (6.3)**	**8 (3.3)**	**86 (34.4)**	**70 (27.8)**
Blood and lymphatic system disorders	**43 (17.2)**	**49 (19.5)**	**2 (0.8)**	**0**	**44 (17.6)**	**49 (19.5)**
Neutropenia	32 (12.8)	43 (17.1)	1 (0.4)	0	33 (13.2)	43 (17.1)
Leukopenia	10 (4.0)	6 (2.4)	1 (0.4)	0	11 (4.4)	6 (2.4)
Febrile neutropenia	7 (2.8)	6 (2.4)	0	0	7 (2.8)	6 (2.4)
Anaemia	5 (2.0)	2 (0.8)	0	0	5 (2.0)	2 (0.8)
Investigations	**22 (8.8)**	**6 (2.4)**	**4 (1.7)**	**1 (0.4)**	**24 (9.6)**	**7 (2.8)**
Neutrophil count decreased	9 (3.6)	2 (0.8)	0	1 (0.4)	9 (3.6)	3 (1.2)
White blood cell count decreased	6 (2.4)	1 (0.4)	0	0	6 (2.4)	1 (0.4)
Gamma-glutamyl transferase increased	4 (1.6)	2 (0.8)	1 (0.4)	0	4 (1.6)	2 (0.8)
Alanine aminotransferase increased	3 (1.2)	1 (0.4)	1 (0.4)	0	4 (1.6)	1 (0.4)
Aspartate aminotransferase increased	2 (0.8)	0	1 (0.4)	0	3 (1.2)	0
Ejection fraction decreased	1 (0.4)	0	2 (0.8)	0	3 (1.2)	0
Lymphocyte count decreased	0	0	1 (0.4)	0	1 (0.4)	0
Transaminases increased	1 (0.4)	0	0	0	1 (0.4)	0
Skin and subcutaneous tissue disorders	**10 (4.0)**	**8 (3.2)**	**0**	**0**	**10 (4.0)**	**8 (3.2)**
Alopecia	10 (4.0)	8 (3.2)	0	0	10 (4.0)	8 (3.2)
Metabolism and nutrition disorders	**4 (1.6)**	**1 (0.4)**	**0**	**0**	**4 (1.6)**	**1 (0.4)**
Hyperglycaemia	2 (0.8)	0	0	0	2 (0.8)	0
Hypercalcaemia	1 (0.4)	0	0	0	1 (0.4)	0
Hyperuricaemia	1 (0.4)	0	0	0	1 (0.4)	0
Hyponatraemia	1 (0.4)	0	0	0	1 (0.4)	0
Decreased appetite	0	1 (0.4)	0	0	0	1 (0.4)
Infections and infestations	**3 (1.2)**	**4 (1.6)**	**0**	**1 (0.4)**	**3 (1.2)**	**4 (1.6)**
Bronchitis	1 (0.4)	0	0	0	1 (0.4)	0
Mastitis	1 (0.4)	0	0	0	1 (0.4)	0
Urinary tract infection	1 (0.4)	0	0	0	1 (0.4)	0
Pneumonia	0	1 (0.4)	0	1 (0.4)	0	1 (0.4)
Anal abscess	0	1 (0.4)	0	0	0	1 (0.4)
Tracheobronchitis	0	1 (0.4)	0	0	0	1 (0.4)
Influenza	0	1 (0.4)	0	0	0	1 (0.4)
Septic shock	0	1 (0.4)	0	0	0	1 (0.4)
Gastrointestinal disorders	**3 (1.2)**	**4 (1.6)**	**0**	**0**	**3 (1.2)**	**4 (1.6)**
Diarrhoea	1 (0.4)	3 (1.2)	0	0	1 (0.4)	3 (1.2)
Nausea	1 (0.4)	1 (0.4)	0	0	1 (0.4)	1 (0.4)
Constipation	1 (0.4)	0	0	0	1 (0.4)	0
Haemorrhoids	1 (0.4)	0	0	0	1 (0.4)	0
Cardiac disorders	**3 (1.2)**	**1 (0.4)**	**3 (1.2)**	**1 (0.4)**	**6 (2.4)**	**2 (0.8)**
Cardiomyopathy	1 (0.4)	0	0	0	1 (0.4)	0
Myocardial infarction	1 (0.4)	0	1 (0.4)	0	2 (0.8)	0
Cardiopulmonary arrest	1 (0.4)	0	0	0	1 (0.4)	0
Supraventricular tachycardia	0	1 (0.4)	0	0	0	1 (0.4)
Dilation atrial	0	0	1 (0.4)	0	1 (0.4)	0
Cardiac failure	0	0	1 (0.4)	0	1 (0.4)	0
Cardiac failure chronic	0	0	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Coronary artery disease	0	0	0	1 (0.4)	0	1 (0.4)
Cytotoxic cardiomyopathy	0	0	0	1 (0.4)	0	1 (0.4)
General disorders and administration site conditions	**3 (1.2)**	**1 (0.4)**	**1 (0.4)**	**0**	**4 (1.6)**	**1 (0.4)**
Mucosal inflammation	1 (0.4)	0	0	0	1 (0.4)	0
Chest pain	1 (0.4)	0	0	0	1 (0.4)	0
Sudden death	1 (0.4)	0	0	0	1 (0.4)	0
Asthenia	0	1 (0.4)	0	0	0	1 (0.4)

SOC PT (MedDRA V21.0)	Neoadjuvant period (SAF)		Adjuvant period (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)	HD201 N=238 n (%)	EU-Herceptin N=242 n (%)	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)
Fatigue	0	0	1 (0.4)	0	1 (0.4)	0
Immune system disorders	**2 (0.8)**	**0**	**0**	**0**	**2 (0.8)**	**0**
Hypersensitivity	2 (0.8)	0	0	0	2 (0.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (0.8)**	**0**	**2 (0.8)**	**3 (1.2)**	**4 (1.6)**	**3 (1.2)**
Metastases to central nervous system	1 (0.4)	0	2 (0.8)	1 (0.4)	3 (1.2)	1 (0.4)
Metastases to liver	1 (0.4)	0	0	0	1 (0.4)	0
Metastases to bone	0	0	0	1 (0.4)	0	1 (0.4)
Metastases to spine	0	0	0	1 (0.4)	0	1 (0.4)
Reproductive system and breast disorders	**1 (0.4)**	**1 (0.4)**	**0**	**0**	**1 (0.4)**	**1 (0.4)**
Menstruation irregular	1 (0.4)	1 (0.4)	0	0	1 (0.4)	1 (0.4)
Nervous system disorders	**0**	**4 (1.6)**	**4 (1.7)**	**0**	**4 (1.6)**	**4 (1.6)**
Headache	0	1 (0.4)	0	0	0	1 (0.4)
Peripheral sensorimotor neuropathy	0	1 (0.4)	0	0	0	1 (0.4)
Haemorrhagic stroke	0	1 (0.4)	0	0	0	1 (0.4)
Parkinson's disease	0	1 (0.4)	0	0	0	1 (0.4)
Seizure	0	1 (0.4)	0	0	0	1 (0.4)
Ataxia	0	0	1 (0.4)	0	1 (0.4)	0
Cerebrovascular accident	0	0	2 (0.8)	0	2 (0.8)	0
Cerebrovascular disorder	0	0	1 (0.4)	0	1 (0.4)	0
Cognitive disorder	0	0	1 (0.4)	0	1 (0.4)	0
Dysarthria	0	0	1 (0.4)	0	1 (0.4)	0
Encephalopathy	0	0	1 (0.4)	0	1 (0.4)	0
Hemiparesis	0	0	1 (0.4)	0	1 (0.4)	0
Syncope	0	0	2 (0.8)	0	2 (0.8)	0
Vertebrobasilar insufficiency	0	0	0	0	1 (0.4)	0
Vascular disorders	**0**	**2 (0.8)**	**0**	**3 (1.2)**	**0**	**5 (2.0)**

SOC PT (MedDRA V21.0)	Neoadjuvant period (SAF)		Adjuvant period (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)	HD201 N=238 n (%)	EU-Herceptin N=242 n (%)	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)
Hypertension	0	1 (0.4)	0	1 (0.4)	0	2 (0.8)
Phlebitis	0	1 (0.4)	0	0	0	1 (0.4)
Essential hypertension	0	0	0	1 (0.4)	0	1 (0.4)
Hypertensive crisis	0	0	0	2 (0.8)	0	2 (0.8)
Injury, poisoning and procedural complications	**0**	**1 (0.4)**	**0**	**0**	**0**	**1 (0.4)**
Procedural hypotension	0	1 (0.4)	0	0	0	1 (0.4)
Ear and labyrinth disorders	**0**	**0**	**2 (0.8)**	**0**	**2 (0.8)**	**0**
Vestibular ataxia	0	0	2 (0.8)	0	2 (0.8)	0
Hepatobiliary disorders	**0**	**0**	**1 (0.4)**	**0**	**1 (0.4)**	**0**
Cholangitis	0	0	1 (0.4)	0	1 (0.4)	0
Cholelithiasis	0	0	1 (0.4)	0	1 (0.4)	0
Hepatitis cholestatic	0	0	1 (0.4)	0	1 (0.4)	0
Eye disorders	**0**	**0**	**1 (0.4)**	**0**	**1 (0.4)**	**0**
Open-angle glaucoma	0	0	1 (0.4)	0	1 (0.4)	0
Psychiatric disorders	**0**	**0**	**1 (0.4)**	**0**	**1 (0.4)**	**0**
Depression	0	0	1 (0.4)	0	1 (0.4)	0

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
Note: Patients may experience multiple events of different severity in different treatment periods, thus the number of patients reported in each treatment period per severity may not add up to the number of patients reported for the entire treatment period, as the highest severity is retained.

Table 51: Summary of PTAEs by maximal severity for the post-treatment follow-up period PTAS (TROIKA)

Category	HD201 N=234 n (%)	EU-Herceptin N=242 n (%)
Any PTAEs	64 (27.4)	72 (29.8)
Maximal severity of PTAEs		
Mild (Grade 1)	41 (17.5)	45 (18.6)
Moderate (Grade 2)	16 (6.8)	14 (5.8)
Severe (Grade 3)	5 (2.1)	10 (4.1)
Life-threatening (Grade 4)	0	0
Fatal (Grade 5)	2 (0.9)	3 (1.2)

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; PTAEs: Post-treatment adverse events
% calculated based on N for each treatment group
For incidence of patients, the maximal severity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1) is reported.

Overall, the most frequently reported TEAEs by PT during the entire treatment period in both treatment groups were 'alopecia', 'nausea', 'neutropenia', 'asthenia' and 'anaemia'.

During the entire treatment period, ≥ Grade 3 TEAEs were reported in 86 patients (34.4%) in the HD201 treatment group and 70 patients (27.8%) in the EU-Herceptin treatment group. The most reported SOCs were 'blood and lymphatic system disorders', 'investigations', and 'skin and subcutaneous tissue disorders'.

2.7.5.1.1. Serious adverse event/deaths/other significant events

Phase I study TROIKA-1

There was one SAE of thumb fracture reported in TROIKA-1, in a subject treated with EU-Herceptin. No fatal events were reported.

Phase III study TROIKA

Table 52: Summary of SAEs during entire study by SOC and PT - SAF and aSAF(TROIKA)

SOC PT (MedDRA V21.0)	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 (N = 250)	EU-Herceptin (N = 252)	HD201 (N = 238)	EU-Herceptin (N = 242)	HD201 (N = 250)	EU-Herceptin (N = 252)
	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae
Any serious TEAEs	16 (6.4) 22	12 (4.8) 17	8 (3.4) 8	6 (2.5) 7	24 (9.6) 30	17 (6.7) 24

Blood and lymphatic system disorders	**8 (3.2) 9**	**5 (2.0) 5**	**0**	**0**	**8 (3.2) 9**	**5 (2.0) 5**
Febrile neutropenia	6 (2.4) 6	4 (1.6) 4	0	0	6 (2.4) 6	4 (1.6) 4
Anaemia	2 (0.8) 2	0	0	0	2 (0.8) 2	0
Neutropenia	1 (0.4) 1	1 (0.4) 1	0	0	1 (0.4) 1	1 (0.4) 1
Infections and infestations	**3 (1.2) 3**	**4 (1.6) 5**	**1 (0.4) 1**	**2 (0.8) 2**	**4 (1.6) 4**	**5 (2.0) 7**
Bronchitis	1 (0.4) 1	0	0	0	1 (0.4) 1	0
Mastitis	1 (0.4) 1	0	0	0	1 (0.4) 1	0
Urinary tract infection	1 (0.4) 1	0	0	0	1 (0.4) 1	0
Pneumonia	0	3 (1.2) 3	0	1 (0.4) 1	0	3 (1.2) 4
Influenza	0	1 (0.4) 1	0	0	0	1 (0.4) 1
Septic shock	0	1 (0.4) 1	0	0	0	1 (0.4) 1
Erysipelas	0	0	0	1 (0.4) 1	0	1 (0.4) 1
Opisthorchiasis	0	0	1 (0.4) 1	0	1 (0.4) 1	0

SOC PT (MedDRA V21.0)	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 (N = 250)	EU-Herceptin (N = 252)	HD201 (N = 238)	EU-Herceptin (N = 242)	HD201 (N = 250)	EU-Herceptin (N = 252)
	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae
Immune system disorders	**2 (0.8) 2**	**1 (0.4) 2**	**0**	**0**	**2 (0.8) 2**	**1 (0.4) 2**
Hypersensitivity	2 (0.8) 2	1 (0.4) 2	0	0	2 (0.8) 2	1 (0.4) 2
Cardiac disorders	**2 (0.8) 2**	**1 (0.4) 1**	**2 (0.8) 2**	**1 (0.4) 1**	**4 (1.6) 4**	**2 (0.8) 2**
Myocardial infarction	1 (0.4) 1	0	1 (0.4) 1	0	2 (0.8) 2	0
Cardio-respiratory arrest	1 (0.4) 1	0	0	0	1 (0.4) 1	0
Supraventricular tachycardia	0	1 (0.4) 1	0	0	0	1 (0.4) 1
Cardiac failure chronic	0	0	1 (0.4) 1	0	1 (0.4) 1	0
Cytotoxic cardiomyopathy	0	0	0	1 (0.4) 1	0	1 (0.4) 1
Gastrointestinal disorders	**2 (0.8) 2**	**0**	**0**	**0**	**2 (0.8) 2**	**0**
Diarrhoea	2 (0.8) 2	0	0	0	2 (0.8) 2	0
Metabolism and nutrition disorders	**1 (0.4) 2**	**0**	**0**	**0**	**1 (0.4) 2**	**0**
Hyperglycaemia	1 (0.4) 1	0	0	0	1 (0.4) 1	0
Hyponatraemia	1 (0.4) 1	0	0	0	1 (0.4) 1	0
General disorders and administration site conditions	**1 (0.4) 1**	**0**	**0**	**0**	**1 (0.4) 1**	**0**
Sudden death	1 (0.4) 1	0	0	0	1 (0.4) 1	0
Investigations	**1 (0.4) 1**	**0**	**0**	**0**	**1 (0.4) 1**	**0**
Liver function test abnormal	1 (0.4) 1	0	0	0	1 (0.4) 1	0
Nervous system disorders	**0**	**2 (0.8) 3**	**2 (0.8) 2**	**0**	**2 (0.8) 2**	**2 (0.8) 3**
Seizure	0	1 (0.4) 2	0	0	0	1 (0.4) 2
Haemorrhagic stroke	0	1 (0.4) 1	0	0	0	1 (0.4) 1
Cerebrovascular accident	0	0	2 (0.8) 2	0	2 (0.8) 2	0
Injury, poisoning and procedural complications	**0**	**1 (0.4) 1**	**1 (0.4) 1**	**0**	**1 (0.4) 1**	**1 (0.4) 1**
Post-procedural haematoma	0	1 (0.4) 1	0	0	0	1 (0.4) 1
Post-procedural inflammation	0	0	1 (0.4) 1	0	1 (0.4) 1	0
Reproductive system and breast disorders	**0**	**0**	**1 (0.4) 1**	**1 (0.4) 1**	**1 (0.4) 1**	**1 (0.4) 1**
Colpocele	0	0	0	1 (0.4) 1	0	1 (0.4) 1

SOC PT (MedDRA V21.0)	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 (N = 250)	EU-Herceptin (N = 252)	HD201 (N = 238)	EU-Herceptin (N = 242)	HD201 (N = 250)	EU-Herceptin (N = 252)
	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae
Uterine polyp	0	0	1 (0.4) 1	0	1 (0.4) 1	0
Vascular disorders	**0**	**0**	**0**	**2 (0.8) 2**	**0**	**2 (0.8) 2**
Essential hypertension	0	0	0	1 (0.4) 1	0	1 (0.4) 1
Hypertensive crisis	0	0	0	1 (0.4) 1	0	1 (0.4) 1
Eye disorders	**0**	**0**	**1 (0.4) 1**	**0**	**1 (0.4) 1**	**0**
Open-angle glaucoma	0	0	1 (0.4) 1	0	1 (0.4) 1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0**	**0**	**1 (0.4) 1**	**0**	**1 (0.4) 1**
Uterine leiomyoma	0	0	0	1 (0.4) 1	0	1 (0.4) 1

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
Note: Patients may experience one event spanning both treatment periods, thus the number of events reported in each treatment period may not add up to the number of events reported for the entire treatment period.

Table 53: Summary of characteristics of serious TEAEs for the entire treatment period – SAF and aSAF (TROIKA)

Category	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 (N = 250)	EU-Herceptin (N = 252)	HD201 (N = 238)	EU-Herceptin (N = 242)	HD201 (N = 250)	EU-Herceptin (N = 252)
	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae
Any serious TEAEs	16 (6.4) 22	12 (4.8) 17	8 (3.4) 8	6 (2.5) 7	24 (9.6) 30	17 (6.7) 24
Characteristics						
Mild (Grade 1)	0	0	0	2 (0.8) 2	0	2 (0.8) 2
Moderate (Grade 2)	1 (0.4) 3	6 (2.4) 7	3 (1.3) 3	1 (0.4) 1	4 (1.6) 6	7 (2.8) 8
Severe (Grade 3)	11 (4.4) 14	5 (2.0) 6	4 (1.7) 4	3 (1.2) 4	15 (6.0) 18	7 (2.8) 10
Life threatening (Grade 4)	2 (0.8) 2	2 (0.8) 4	0	0	2 (0.8) 2	2 (0.8) 4
Fatal (Grade 5)	3 (1.2) 3	0	1 (0.4) 1	0	4 (1.6) 4	0
Study treatment related	0	1 (0.4) 2	1 (0.4) 1	2 (0.8) 2	1 (0.4) 1	3 (1.2) 4
Chemotherapy related	11 (4.4) 14	7 (2.8) 11	0	1 (0.4) 2	11 (4.4) 14	8 (3.2) 13
Outcome						
Recovered/ resolved	13 (5.2)19	10 (4.0) 15	5 (2.1) 5	3 (1.2) 3	18 (7.2) 24	13 (5.2) 18
Recovered/ resolved with sequelae	0	2 (0.8) 2	2 (0.8) 2	3 (1.2) 4	2 (0.8) 2	4 (1.6) 6
Not recovered/ not resolved	0	0	0	0	0	0
Fatal	3 (1.2) 3	0	1 (0.4) 1	0	4 (1.6) 4	0
Action taken						
Dose/administration modification	4 (1.6) 4	5 (2.0) 6	3 (1.3) 3	3 (1.3) 4	7 (2.8) 7	7 (2.8) 10

N: Number of patients within the treatment group, n: number of patients with an event
% calculated based on N for each treatment group.
For incidence of patients, the maximal severity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1), and worst outcome (fatal > not recovered/not resolved > recovered/resolved with sequelae > recovered/resolved) is reported.
*Refers to action, 'reduced', 'delayed', 'interrupted', 'increased', or 'infusion time prolonged' taken on study drug.
Note: Patients may experience multiple events of different severity in different treatment periods, thus the number of patients reported in each treatment period per severity may not add up to the number of patients reported for the entire treatment period, as the highest severity is retained.

Table 54: Summary of any serious PTAEs by SOC and PT for the post-treatment follow-up period - PTAS (TROIKA)

SOC PT (MedDRA V21.0)	HD201 (N = 234) n (%) nae	EU-Herceptin (N = 242) n (%) nae
Any serious PTAEs	**4 (1.7) 4**	**5 (2.1) 5**
Infections and infestations	**2 (0.9) 2**	**2 (0.8) 2**
Pneumonia	0	2 (0.8) 2
Mastitis	1 (0.4) 1	0
Urosepsis	1 (0.4) 1	0
Vascular disorders	**1 (0.4) 1**	**1 (0.4) 1**
Deep vein thrombosis	1 (0.4) 1	0
Hypertension	0	1 (0.4) 1
Hepatobiliary disorders	**0**	**1 (0.4) 1**
Cholelithiasis	0	1 (0.4) 1
Injury, poisoning and procedural complications	**1 (0.4) 1**	**0**
Ligament rupture	1 (0.4) 1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**1 (0.4) 1**
Gastric cancer	0	1 (0.4) 1

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; PTAEs: Post-treatment adverse events
% calculated based on N for each treatment group

Table 55: Summary of characteristics of serious PTAEs for the post-treatment follow-up period - PTAS (TROIKA)

Category	HD201 (N = 234) n (%) nae	EU-Herceptin (N = 242) n (%) nae
Any serious PTAEs	**4 (1.7) 4**	**5 (2.1) 5**
Characteristics		
Mild (Grade 1)	1 (0.4) 1	0
Moderate (Grade 2)	1 (0.4) 1	1 (0.4) 1
Severe (Grade 3)	2 (0.9) 2	4 (1.7) 4
Life threatening (Grade 4)	0	0
Fatal (Grade 5)	0	0
Study treatment related	0	0
Outcome		
Recovered/ resolved	3 (1.3) 3	4 (1.7) 4
Recovered/ resolved with sequelae	1 (0.4) 1	0
Not recovered/ not resolved	0	1 (0.4) 1
Fatal	0	0

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; PTAEs: Post-treatment adverse events
% calculated based on N for each treatment group.
For incidence of patients, the maximal severity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1), and worst outcome (fatal > not recovered/not resolved > recovered/resolved with sequelae > recovered/resolved) is reported.

There were 8 patients with events reported during the treatment period leading to a fatal outcome (7 patients [2.8%] in the HD201 treatment group, and 1 patient [0.4%] in the EU-Herceptin treatment group); 4 events in the neoadjuvant period, and 4 events in the adjuvant period. All cases were reported as either unrelated or unlikely related to both study treatment and chemotherapy. Of the 8 patients, 4 had a fatal outcome due to a serious TEAE (met the seriousness criteria), and 4 had a fatal outcome due to disease progression, or other events secondary to the malignancy under study (incl metastatic lesions). The events in the neoadjuvant period leading to a fatal outcome were 'myocardial infarction' (1 patient [0.4%]), 'cardio-respiratory arrest' (1 patient [0.4%]), 'sudden death' (1 patient [0.4%]), and 'metastases to central nervous system' (1 patient [0.4%]). The events in the adjuvant period leading to a fatal outcome were 'myocardial infarction' (1 patient [0.4%]), 'metastases to central nervous system' (1 patient [0.4%]), 'metastases to bone' (1 patient [0.4%]) and 'metastases to lung' (1 patient [0.4%]).

Table 56: Summary of deaths by SOC and PT for the entire study – safety set (studyTROIKA)

SOC PT	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)	HD201 N=238 n (%)	EU-Herceptin N=242 n (%)	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)
Any death	4 (1.6)	0	3 (1.2)	1 (0.4)	7 (2.8)	1 (0.4)
Cardiac disorders	2 (0.8)	0	1 (0.4)	0	3 (1.2)	0
Myocardial infarction	1 (0.4)	0	1 (0.4)	0	2 (0.8)	0
Cardio-respiratory arrest	1 (0.4)	0	0	0	1 (0.4)	0
General disorders and administration site conditions	1 (0.4)	0	0	0	1 (0.4)	0
Sudden death	1 (0.4)	0	0	0	1 (0.4)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (0.4)	0	2 (0.8)	1 (0.4)	3 (1.2)	1 (0.4)
Metastases to central nervous system	1 (0.4)	0	1 (0.4)	0	2 (0.8)	0
Metastases to bone	0	0	1 (0.4)	0	1 (0.4)	0
Metastases to lung	0	0	0	1 (0.4)	0	1 (0.4)

N: Number of patients within the treatment group, n: number of patients with an event
Note: For patients with events (events of progression, or other events secondary to the malignancy under study [incl. metastatic lesions]) starting and leading to a fatal outcome in different treatment periods, the patient is reported in the treatment period where the event started.

Table 57: Summary of patients with events starting in the post-treatment follow-up period kleading to a fatal outcome by SOC and PT – PTAS (TROIKA)

SOC PT	HD201 N=234 n (%)	EU-Herceptin N=242 n (%)
Any death	5 (2.1)	5 (2.1)

SOC PT	HD201 N=234 n (%)	EU-Herceptin N=242 n (%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**4 (1.7)**	**4 (1.7)**
Metastases to central nervous system	2 (0.9)	1 (0.4)
Metastases to lung	0	2 (0.8)
Breast cancer recurrent	0	1 (0.4)
Metastases to lymph nodes	1 (0.4)	0
Metastases to pancreas	1 (0.4)	0
Metastases	0	1 (0.4)
General disorders and administration site conditions	**1 (0.4)**	**1 (0.4)**
Disease progression	1 (0.4)	1 (0.4)

N: Number of patients within the treatment group, n: number of patients with an event, PT: preferred term, SOC: system organ class.

Note: For patients in the PTAS with events (events of progression, or other events secondary to the malignancy under study [incl. metastatic lesions]) starting in the post-treatment follow-up period till the 6 month follow-up visit and leading to a fatal outcome in the post-treatment follow-up period after the 6-month follow-up visit, the patient is reported in the post-treatment follow-up period where the event started

Table 58: Summary of patients with events starting after onset of treatment with a fatal outcome by SOC and PT - SAF (TROIKA)

SOC PT	HD201 N=250 n (%) nae	EU-Herceptin N=252 n (%) nae
Any death	**16 (6.4) 18**	**10 (4.0) 11**
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**9 (3.6) 11**	**5 (2.0) 6**
Metastases to central nervous system	5 (2.0) 5	1 (0.4) 1
Metastases to lung	1 (0.4) 1	3 (1.2) 3
Breast cancer recurrent	0	1 (0.4) 1
Metastases to bone	1 (0.4) 1	0
Metastases to liver	1 (0.4) 1	0
Metastases to lymph nodes	1 (0.4) 1	0
Metastases to pancreas	1 (0.4) 1	0
Metastases to skin	1 (0.4)1	0
Metastasis	0	1 (0.4) 1
General disorders and administration site conditions	**3 (1.2) 3**	**5 (2.0) 5**
Disease progression	2 (0.8) 2	4 (1.6) 4
Death	0	1 (0.4) 1
Sudden death	1 (0.4) 1	0
Cardiac disorders	**4 (1.6) 4**	**0**
Myocardial infarction	2 (0.8) 2	0
Cardiac arrest	1 (0.4) 1	0
Cardio-respiratory arrest	1 (0.4) 1	0

N: Number of patients within the treatment group, n: number of patients with an event

Adverse events of special interest

TROIKA-1

The TROIKA-1 study protocol specified adverse events of special interest as events associated with suspected cases of infusion-related reactions and anaphylaxis.

Table 59: TEAEs of special interest by SOC and PT (TROIKA-1)

SOC / PT	HD201 N= 35 n	HD201 N= 35 %	EU-Herceptin N= 35 n	EU-Herceptin N= 35 %	US-Herceptin N= 35 n	US-Herceptin N= 35 %
Injury, poisoning and procedural complications	**2**	**5.7**	**7**	**20.0**	**11**	**31.4**
Infusion related reaction	2	5.7	7	20.0	11	31.4
General disorders and administration site conditions	**3**	**8.6**	**3**	**8.6**	–	–
Chest pain	1	2.9	2	5.7	–	–
Pyrexia	1	2.9	1	2.9	–	–
Influenza like illness	1	2.9	–	–	–	–
Gastrointestinal disorders	**1**	**2.9**	**1**	**2.9**	–	–
Nausea	1	2.9	1	2.9	–	–
Nervous system disorders	**2**	**5.7**	–	–	–	–
Headache	2	5.7	–	–	–	–
Cardiac disorders	**1**	**2.9**	–	–	–	–
Tachycardia	1	2.9	–	–	–	–
Vascular disorders	–	–	**1**	**2.9**	–	–
Hypertension	–	–	1	2.9	–	–

SOC = System organ class; PT = preferred term; N = number of subjects in the population; n = number of subjects with event.

Phase III study TROIKA

TEAEs of special interest were defined as noteworthy events for a particular product or class of products that is to be monitored carefully. The TEAEs of special interest were derived based on the mechanism of action and clinical data available in product labelling for trastuzumab. The TEAEs of special interest for this study included cardiotoxicity, infusion-site reactions, and hypersensitivity, haematotoxicity, pulmonary disorders, infections, and oligohydramnios.

Table 60: Overall summary of treatment-emergent adverse events of special interest- safety set (TROIKA)

	Neoadjuvant Period (SAF)		Adjuvant Period (aSAF)		Entire Treatment Period (SAF)	
	HD201	Herceptin®	HD201	Herceptin®	HD201	Herceptin®
	N = 250	N = 252	N = 238	N = 242	N = 250	N = 252
Type	**n (%) nae**	**n (%) nae**	**n (%) nae**	**n (%) nae**	**n (%) nae**	**n (%) nae**
Any TEAE of Special Interest	**205 (82.0%) 903**	**197 (78.2%) 835**	**117 (49.2%) 270**	**111 (45.9%) 236**	**220 (88.0%) 1169**	**213 (84.5%) 1070**
Cardiotoxicity	68 (27.2%) 108	61 (24.2%) 100	54 (22.7%) 85	51 (21.1%) 74	95 (38.0%) 191	89 (35.3%) 174
Infusion-site reactions and hypersensitivity	118 (47.2%) 409	116 (46.0%) 392	35 (14.7%) 63	27 (11.2%) 44	127 (50.8%) 472	121 (48.0%) 436
Haematotoxicity	134 (53.6%) 321	124 (49.2%) 283	51 (21.4%) 100	47 (19.4%) 83	144 (57.6%) 419	142 (56.3%) 365
Pulmonary Disorders	16 (6.4%) 17	14 (5.6%) 19	15 (6.3%) 19	12 (5.0%) 14	29 (11.6%) 36	23 (9.1%) 33
Infections	47 (18.8%) 70	47 (18.7%) 66	22 (9.2%) 25	27 (11.2%) 32	61 (24.4%) 95	64 (25.4%) 98

N = number of patients in the analysis set; n = number of patients with an event; nae = number of adverse events; TEAE = treatment-emergent adverse event.

Table 61: Summary of Serious TEAEs of Special Interest (Entire Treatment Period; SAF) - TROIKA

	HD201 N = 250		Herceptin® N = 252	
Type	**Any**	**Related to Study Treatment**	**Any**	**Related to Study Treatment**
	n (%) nae	**n (%) nae**	**n (%) nae**	**n (%) nae**
Cardiotoxicity	3 (1.2%) 3	1 (0.4%)1	2 (0.8%) 2	1 (0.4%) 1
Infusion-site reactions and hypersensitivity	2 (0.8%) 2	0 (0%) 0	1 (0.4%) 2	1 (0.4%) 1
Haematotoxicity	8 (3.2%) 9	0 (0%) 0	5 (2.0%) 5	0 (0.0%) 0
Pulmonary Disorders	1 (0.4%) 1	0 (0%) 0	0 (0.0%) 0	0 (0.0%) 0
Infections	4 (1.6%) 4	0 (0%) 0	5 (2.0%) 7	0 (0.0%) 0

N = number of patients in the analysis set; n = number of patients with an event; nae = number of adverse events; TEAE = treatment-emergent adverse event.

Cardiotoxicity

Table 62: Summary of cardiotoxic TEAEs occurring in ≥2% of patients by PT reported in any treatment arm for the entire study – SAF and aSAF (TROIKA)

PT (MedDRA V21.0)	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%) nae	EU-Herceptin N=252 n (%) nae	HD201 N=238 n (%) nae	EU-Herceptin N=242 n (%) nae	HD201 N=250 n (%) nae	EU-Herceptin N=252 n (%) nae
Any cardiotoxicity TEAEs of special interest	**68 (27.2) 108**	**61 (24.2) 100**	**54 (22.7) 85**	**51 (21.1) 74**	**95 (38.0) 191**	**89 (35.3) 174**
Sinus tachycardia	15 (6.0) 15	10 (4.0) 10	2 (0.8) 2	7 (2.9) 7	16 (6.4) 17	16 (6.3) 17
Oedema peripheral	13 (5.2) 21	6 (2.4) 6	5 (2.1) 5	8 (3.3) 8	17 (6.8) 26	14 (5.6) 14
Electrocardiogram abnormal	10 (4.0) 10	5 (2.0) 5	10 (4.2) 11	4 (1.7) 4	16 (6.4) 21	9 (3.6) 9
Ejection fraction decreased	11 (4.4) 11	13 (5.2) 13	12 (5.0) 12	9 (3.7) 9	21 (8.4) 22	21 (8.3) 22
Left ventricular dysfunction	4 (1.6) 4	1 (0.4) 1	5 (2.1) 5	2 (0.8) 2	8 (3.2) 9	3 (1.2) 3
Dyspnoea	3 (1.2) 4	5 (2.0) 5	7 (2.9) 9	2 (0.8) 2	9 (3.6) 13	7 (2.8) 7
Tachycardia	3 (1.2) 3	6 (2.4) 6	2 (0.8) 2	1 (0.4) 1	5 (2.0) 5	7 (2.8) 7
Ventricular dyssynchrony	3 (1.2) 3	5 (2.0) 5	2 (0.8) 2	2 (0.8) 2	4 (1.6) 5	7 (2.8) 7
Bundle branch block right	2 (0.8) 2	2 (0.8) 2	4 (1.7) 4	3 (1.2) 3	6 (2.4) 6	5 (2.0) 5
Sinus bradycardia	2 (0.8) 2	1 (0.4) 1	3 (1.3) 3	1 (0.4) 1	5 (2.0) 5	2 (0.8) 2
Electrocardiogram repolarisation abnormality	1 (0.4) 1	4 (1.6) 4	5 (2.1) 6	8 (3.3) 8	6 (2.4) 7	9 (3.6) 12
Left ventricular hypertrophy	1 (0.4) 1	4 (1.6) 4	3 (1.3) 3	4 (1.7) 4	4 (1.6) 4	8 (3.2) 8
Atrial enlargement	1 (0.4) 1	3 (1.2) 3	1 (0.4) 1	2 (0.8) 2	2 (0.8) 2	5 (2.0) 5
Supraventricular extrasystoles	0	4 (1.6) 4	2 (0.8) 2	2 (0.8) 2	2 (0.8) 2	6 (2.4) 6

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
Note: Patients may experience one event spanning both treatment periods, thus the number of events reported in each treatment period may not add up to the number of events reported for the entire treatment period.

ECG

Table 63: Patients with abnormal 12-lead ECGs for entire study period - SAF (TROIKA)

	HD201 N = 250		Herceptin® N = 252	
	Abnormal, NCS	Abnormal, CS	Abnormal, NCS	Abnormal, CS
	n (%)	n (%)	n (%)	n (%)
Baseline	105 (42.0%)	1 (0.4%)	114 (45.2%)	0 (0.0%)
Cycle 5	106 (43.3%)	14 (5.7%)	91 (36.8%)	13 (5.3%)
Before Surgery	97 (40.1%)	18 (7.4%)	94 (38.7%)	17 (7.0%)
Cycle 12	100 (42.9%)	21 (9.0%)	110 (46.4%)	19 (8.0%)
Cycle 16	94 (42.0%)	20 (8.9%)	98 (42.8%)	21 (9.2%)
EOT	91 (40.3%)	17 (7.5%)	113 (46.5%)	17 (7.0%)
6-Month Follow-up	81 (41.8%)	14 (7.2%)	90 (43.1%)	19 (9.1%)
1-Year Follow-up	60 (32.8%)	10 (5.5%)	70 (35.0%)	16 (8.0%)

N = number of patients in the analysis set; n = number of patients within the category; CS = clinically significant; NCS = not clinically significant; EOT = end of treatment.
Percentages were based on the number of patients in the analysis set with available results.

Infusion site reactions and hypersensitivity

Table 64: Summary of Infusion-related reactions and hypersensitivity TEAEs of special interest occurring in ⩾2% of patients by PT reported in any treatment arm for the entire study – SAF and aSAF (TROIKA)

PT (MedDRA V21.0)	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%) nae	EU-Herceptin N=252 n (%) nae	HD201 N=238 n (%) nae	EU-Herceptin N=242 n (%) nae	HD201 N=250 n (%) nae	EU-Herceptin N=252 n (%) nae
Any infusion-site reactions and hypersensitivity TEAEs of special interest	**118 (47.2) 409**	**116 (46.0) 392**	**35 (14.7) 63**	**27 (11.2) 44**	**127 (50.8) 472**	**121 (48.0) 436**
Nausea	86 (34.4) 234	93 (36.9) 234	2 (0.8) 4	1 (0.4) 1	86 (34.4) 238	93 (36.9) 235
Rash	23 (9.2) 40	13 (5.2) 25	3 (1.3) 3	5 (2.1) 5	26 (10.4) 43	17 (6.7) 30
Vomiting	21 (8.4) 32	18 (7.1) 25	1 (0.4) 1	1 (0.4) 1	21 (8.4) 33	18 (7.1) 26
Stomatitis	19 (7.6) 23	14 (5.6) 22	0	0	19 (7.6) 23	14 (5.6) 22
Pyrexia	13 (5.2) 14	11 (4.4) 12	5 (2.1) 6	3 (1.2) 3	17 (6.8) 20	13 (5.2) 15
Headache	9 (3.6) 11	12 (4.8) 16	19 (8.0) 22	11 (4.5) 14	26 (10.4) 33	22 (8.7) 30
Conjunctivitis	5 (2.0) 9	3 (1.2) 3	1 (0.4) 1	1 (0.4) 1	5 (2.0) 10	4 (1.6) 4
Erythema	4 (1.6) 12	5 (2.0) 5	1 (0.4) 1	2 (0.8) 3	5 (2.0) 13	6 (2.4) 8
Dyspnoea	3 (1.2) 4	5 (2.0) 5	7 (2.9) 9	2 (0.8) 2	9 (3.6) 13	7 (2.8) 7
Pruritus	3 (1.2) 4	3 (1.2) 5	4 (1.7) 4	4 (1.7) 4	6 (2.4) 8	7 (2.8) 9
Tachycardia	3 (1.2) 3	6 (2.4) 6	2 (0.8) 2	1 (0.4) 1	5 (2.0) 5	7 (2.8) 7

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group.
Note: Patients may experience one event spanning both treatment periods, thus the number of events reported in each treatment period may not add up to the number of events reported for the entire treatment period.

Haematotoxicity

Table 65: Summary of Haematotoxic TEAEs of special interest occurring in ⩾2% of patients by SMQ and PT reported in any treatment arm for the entire study – SAF and aSAF (TROIKA)

SMQ PT (MedDRA V21.0)	Neoadjuvant period (SAF)		Adjuvant period (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%) nae	Herceptin N=252 n (%) nae	HD201 N=238 n (%) nae	Herceptin N=242 n (%) nae	HD201 N=250 n (%) nae	Herceptin N=252 n (%) nae
Any haematotoxicity TEAEs of special interest	**134 (53.6) 321**	**124 (49.2) 283**	**51 (21.4) 100**	**47 (19.4) 83**	**144 (57.6) 419**	**142 (56.3) 365**
Haematopoietic leukopenia	**99 (39.6) 220**	**93 (36.9) 206**	**32 (13.5) 57**	**32 (13.2) 54**	**110 (44.0) 277**	**107 (42.5) 260**
Neutropenia	69 (27.6) 120	72 (28.6) 123	15 (6.3) 23	14 (5.8) 15	77 (30.8) 143	78 (31.0) 138
Leukopenia	36 (14.4) 55	38 (15.1) 62	19 (8.0) 27	21 (8.7) 30	44 (17.6) 82	51 (20.2) 92
Neutrophil count decreased	13 (5.2) 20	8 (3.2) 8	3 (1.3) 3	2 (0.8) 4	15 (6.0) 23	8 (3.2) 12
White blood cell count decreased	9 (3.6) 13	4 (1.6) 4	1 (0.4) 1	0	10 (4.0) 14	4 (1.6) 4
Febrile neutropenia	8 (3.2) 8	7 (2.8) 7	0	0	8 (3.2) 8	7 (2.8) 7
Lymphopenia	2 (0.8) 2	0	2 (0.8) 2	5 (2.1) 5	3 (1.2) 4	5 (2.0) 5
Haematopoietic erythropenia	**68 (27.2) 93**	**56 (22.4) 75**	**19 (8.0) 22**	**14 (5.8) 17**	**72 (28.8) 113**	**61 (24.2) 91**
Anaemia	68 (27.2) 93	56 (22.2) 74	19 (8.0) 22	14 (5.8) 17	72 (28.8) 113	61 (24.2) 90
Haematopoietic thrombocytopenia	**7 (2.8) 8**	**2 (0.8) 2**	**15 (6.3) 21**	**12 (5.0) 12**	**20 (8.0) 29**	**13 (5.2) 14**
Thrombocytopenia	6 (2.4) 7	2 (0.8) 2	9 (3.8) 14	9 (3.7) 9	13 (5.2) 21	10 (4.0) 11
Platelet count decreased	1 (0.4) 1	0	6 (2.5) 7	3 (1.2) 3	7 (2.8) 8	3 (1.2) 3

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
Note: Patients may experience one event spanning both treatment periods, thus the number of events reported in each treatment period may not add up to the number of events reported for the entire treatment period.

Pulmonary disorders

Table 66: Summary of Pulmonary TEAEs of special interest occurring in ⩾ 2% of patients by PT reported in any treatment arm for the entire study – SAF and aSAF (TROIKA)

PT (MedDRA V21.0)	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%) nae	EU-Herceptin N=252 n (%) nae	HD201 N=238 n (%) nae	EU-Herceptin N=242 n (%) nae	HD201 N=250 n (%) nae	EU-Herceptin N=252 n (%) nae
Any pulmonary disorders TEAEs of special interest	**16 (6.4) 17**	**14 (5.6) 19**	**15 (6.3) 19**	**12 (5.0) 14**	**29 (11.6) 36**	**23 (9.1) 33**
Pulmonary hypertension	8 (3.2) 8	4 (1.6) 4	2 (0.8) 2	5 (2.1) 5	10 (4.0) 10	9 (3.6) 9
Dyspnoea	3 (1.2) 4	5 (2.0) 5	7 (2.9) 9	2 (0.8) 2	9 (3.6) 13	7 (2.8) 7
Tricuspid valve incompetence	2 (0.8) 2	1 (0.4) 1	0	0	2 (0.8) 2	1 (0.4) 1
Atrial enlargement	1 (0.4) 1	3 (1.2) 3	1 (0.4) 1	2 (0.8) 2	2 (0.8) 2	5 (2.0) 5

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
Note: Patients may experience one event spanning both treatment periods, thus the number of events reported in each treatment period may not add up to the number of events reported for the entire treatment period.

Infections

Table 67: Summaryof TEAEs of special interest related to Infections occurring in ⩾ 2% of patients by PT reported in any treatment arm for the entire study – SAF and aSAF (TROIKA)

PT (MedDRA V21.0)	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 N=250 n (%) nae	EU-Herceptin N=252 n (%) nae	HD201 N=238 n (%) nae	EU-Herceptin N=242 n (%) nae	HD201 N=250 n (%) nae	EU-Herceptin N=252 n (%) nae
Any infections TEAEs of special interest	**47 (18.8) 70**	**47 (18.7) 66**	**22 (9.2) 25**	**27 (11.2) 32**	**61 (24.4) 95**	**64 (25.4) 98**
Upper respiratory tract infection	9 (3.6) 11	3 (1.2) 3	2 (0.8) 2	1 (0.4) 1	11 (4.4) 13	4 (1.6) 4
Tracheitis	6 (2.4) 6	0	1 (0.4) 1	1 (0.4) 1	6 (2.4) 7	1 (0.4) 1

Conjunctivitis	5 (2.0) 9	3 (1.2) 3	1 (0.4) 1	1 (0.4) 1	5 (2.0) 10	4 (1.6) 4
Respiratory tract infection	5 (2.0) 5	3 (1.2) 3	2 (0.8) 2	2 (0.8) 2	6 (2.4) 7	5 (2.0) 5
Nasopharyngitis	4 (1.6) 5	7 (2.8) 7	2 (0.8) 2	2 (0.8) 2	5 (2.0) 7	9 (3.6) 9
Respiratory tract infection viral	4 (1.6) 6	3 (1.2) 4	4 (1.7) 4	5 (2.0) 5	6 (2.4) 10	7 (2.8) 9
Rhinitis	3 (1.2) 5	5 (2.0) 12	1 (0.4) 1	4 (1.7) 4	4 (1.6) 6	7 (2.8) 16
Bronchitis	2 (0.8) 2	7 (2.8) 7	2 (0.8) 2	5 (2.1) 5	4 (1.6) 4	11 (4.4) 12
Pharyngitis	2 (0.8) 2	5 (2.0) 7	0	1 (0.4) 1	2 (0.8) 2	6 (2.4) 8

N: Number of patients within the treatment group, n: number of patients with an event, nae: number of adverse events; TEAE: Treatment-emergent adverse events
% calculated based on N for each treatment group
Note: Patients may experience one event spanning both treatment periods, thus the number of events reported in each treatment period may not add up to the number of events reported for the entire treatment period.

Laboratory findings

Haematology

Phase I study TROIKA-1

Table 68: Haematological parameters (TROIKA-1)

Parameter	Day	HD201		EU-Herceptin		US-Herceptin	
		Mean	Min	Mean	Min	Mean	Min
Haemoglobin (g/L)	Baseline	148.1	129	148.0	129	150.9	136
	D3	148.0	134	147.6	124	149.3	133
	D8	141.1	127	144.2	127	144.3	128
	D29	140.8	124	145.0	125	144.4	131
	54/EOS	142.8	125	146.3	113	146.6	133
Haematocrit	Baseline	0.428	0.37	0.423	0.36	0.435	0.39
	D3	0.431	0.39	0.422	0.36	0.429	0.38
	D8	0.409	0.36	0.414	0.35	0.415	0.36
	D29	0.408	0.36	0.416	0.35	0.419	0.37
	54/EOS	0.412	0.36	0.418	0.33	0.419	0.37
Erythrocytes (10^{12}/L)	Baseline	5.054	4.30	5.009	4.00	5.166	4.60
	D3	5.083	4.40	4.939	4.40	5.086	4.50
	D8	4.843	4.20	4.861	4.10	4.938	4.10
	D29	4.826	4.10	4.888	3.90	4.965	4.30
	54/EOS	4.897	4.20	4.933	3.90	5.015	4.30

N: number of subjects in the treatment group; Min: minimum; EOS: End of Study; n: number of subjects with indicated parameter; % is calculated based the number of non-missing values.

Phase III study TROIKA

Table 69: Highest CTCAE Grade for haematology variables for the entire treatment period – SAF and aSAF (TROIKA)

Parameter	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire (SAF)	
	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)	HD201 N=238 n (%)	EU-Herceptin N=242 n (%)	HD201 N=250 n (%)	EU-Herceptin N=252 n (%)
Haemoglobin (g/L), low						
Grade 0	54 (21.8)	76 (30.3)	147 (62.0)	157 (64.9)	46 (18.5)	66 (26.3)
Grade 1	156 (62.9)	135 (53.8)	81 (34.2)	78 (32.2)	159 (64.1)	138 (55.0)
Grade 2	32 (12.9)	38 (15.1)	9 (3.8)	7 (2.9)	37 (14.9)	45 (17.9)
Grade 3	6 (2.4)	2 (0.8)	0	0	6 (2.4)	2 (0.8)
Platelets ($x10^9$/L), low						
Grade 0	223 (89.9)	236 (94.0)	195 (82.3)	197 (81.4)	195 (78.6)	199 (79.3)
Grade 1	24 (9.7)	14 (5.6)	42 (17.7)	45 (18.6)	52 (21.0)	51 (20.3)
Grade 2	1 (0.4)	1 (0.4)	0	0	1 (0.4)	1 (0.4)
Grade 3	0	0	0	0	0	0
Leukocytes ($x10^9$/L), low						
Grade 0	124 (50.0)	123 (49.0)	151 (63.7)	139 (57.4)	100 (40.3)	87 (34.7)
Grade 1	56 (22.6)	71 (28.3)	64 (27.0)	84 (34.7)	67 (27.0)	98 (39.0)
Grade 2	39 (15.7)	40 (15.9)	21 (8.9)	19 (7.9)	51 (20.6)	49 (19.5)
Grade 3	26 (10.5)	15 (6.0)	1 (0.4)	0	27 (10.9)	15 (6.0)
Grade 4	3 (1.2)	2 (0.8)	0	0	3 (1.2)	2 (0.8)
Neutrophils ($x10^9$/L), low						
Grade 0	121 (48.8)	117 (46.8)	187 (78.9)	193 (79.8)	107 (43.1)	102 (40.8)
Grade 1	41 (16.5)	48 (19.2)	34 (14.3)	34 (14.0)	47 (19.0)	56 (22.4)
Grade 2	36 (14.5)	32 (12.8)	16 (6.8)	13 (5.4)	44 (17.7)	37 (14.8)
Grade 3	23 (9.3)	37 (14.8)	0	2 (0.8)	23 (9.3)	39 (15.6)
Grade 4	27 (10.9)	16 (6.4)	0	0	27 (10.9)	16 (6.4)
Lymphocytes ($x10^9$/L), low						
Grade 0	132 (53.2)	161 (64.4)	142 (59.9)	135 (55.8)	107 (43.1)	100 (40.0)
Grade 1	60 (24.2)	48 (19.2)	45 (19.0)	49 (20.2)	56 (22.6)	61 (24.4)
Grade 2	39 (15.7)	35 (14.0)	39 (16.5)	45 (18.6)	63 (25.4)	70 (28.0)
Grade 3	16 (6.5)	5 (2.0)	11 (4.6)	13 (5.4)	21 (8.5)	18 (7.2)
Grade 4	1 (0.4)	1 (0.4)	0	0	1 (0.4)	1 (0.4)
Lymphocytes ($x10^9$/L), high						
Grade 0	237 (95.6)	239 (95.6)	235 (99.2)	241 (99.6)	236 (95.2)	239 (95.6)
Grade 1	0	0	0	0	0	0
Grade 2	11 (4.4)	11 (4.4)	2 (0.8)	1 (0.4)	12 (4.8)	11 (4.4)
Grade 3	0	0	0	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events; Values within the normal range are assigned to Grade 0. N = number of patients in the Safety Set; Percentages were based on the number of patients in the Safety Set with at least one available assessment in the time period.

Biochemistry

Table 70: Highest CTCAE grade for chemistry variables for the entire treatment period - SAF and aSAF (TROIKA)

Parameter	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 (N = 250)	Herceptin (N = 252)	HD201 (N = 238)	Herceptin (N = 242)	HD201 (N = 250)	Herceptin (N = 252)
Albumin (g/L), low						
Grade 0	215 (86.7)	220 (87.6)	215 (90.7)	228 (94.2)	198 (79.8)	212 (84.5)
Grade 1	27 (10.9)	29 (11.6)	22 (9.3)	11 (4.5)	42 (16.9)	34 (13.5)
Grade 2	6 (2.4)	2 (0.8)	0	3 (1.2)	8 (3.2)	5 (2.0)
Sodium (mmol/L), high						
Grade 0	188 (75.8)	202 (80.5)	198 (83.5)	212 (87.6)	175 (70.6)	192 (76.5)
Grade 1	48 (19.4)	42 (16.7)	32 (13.5)	24 (9.9)	56 (22.6)	49 (19.5)
Grade 2	10 (4.0)	4 (1.6)	5 (2.1)	5 (2.1)	13 (5.2)	6 (2.4)
Grade 3	1 (0.4)	2 (0.8)	2 (0.8)	0	3 (1.2)	2 (0.8)
Grade 4	1 (0.4)	1 (0.4)	0	1 (0.4)	1 (0.4%	2 (0.8)
Sodium (mmol/L), low						
Grade 0	223 (89.9)	237 (94.4)	205 (86.5)	215 (88.8)	202 (81.5)	215 (85.7)
Grade 1	22 (8.9)	12 (4.8)	26 (11.0)	21 (8.7)	38 (15.3)	28 (11.2)
Grade 3	3 (1.2)	2 (0.8)	6 (2.5)	3 (1.2)	8 (3.2)	5 (2.0)
Grade 4	0	0	0	3 (1.2)	0	3 (1.2)
Potassium (mmol/L), high						
Grade 0	216 (87.1)	216 (86.1)	211 (89.0)	220 (90.9)	198 (79.8)	204 (81.3)
Grade 1	20 (8.1)	21 (8.4)	16 (6.8)	15 (6.2)	28 (11.3)	29 (11.6)
Grade 2	11 (4.4)	13 (5.2)	6 (2.5)	6 (2.5)	17 (6.9)	16 (6.4)

Parameter	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 (N = 250)	Herceptin (N = 252)	HD201 (N = 238)	Herceptin (N = 242)	HD201 (N = 250)	Herceptin (N = 252)
Grade 3	1 (0.4)	1 (0.4)	4 (1.7)	1 (0.4)	5 (2.0)	2 (0.8)
Potassium (mmol/L), low						
Grade 0	223 (89.9)	223 (88.8)	222 (93.7)	219 (90.5)	216 (87.1)	211 (84.1)
Grade 1	18 (7.3)	21 (8.4)	9 (3.8)	18 (7.4)	24 (9.7)	32 (12.7)
Grade 3	3 (1.2)	6 (2.4)	4 (1.7)	4 (1.7)	3 (1.2)	6 (2.4)
Grade 4	4 (1.6)	1 (0.4)	2 (0.8)	1 (0.4)	5 (2.0)	2 (0.8)
(Ionised) Calcium (mmol/L), high						
Grade 0	195 (78.6)	186 (74.1)	192 (81.0)	191 (78.9)	173 (69.8)	167 (66.5)
Grade 1	49 (19.8)	60 (23.9)	38 (16.0)	49 (20.2)	65 (26.2)	77 (30.7)
Grade 2	3 (1.2)	4 (1.6)	3 (1.3)	1 (0.4)	6 (2.4)	5 (2.0)
Grade 3	1 (0.4)	1 (0.4)	4 (1.7)	0	4 (1.6)	1 (0.4)
Grade 4	0	0	0	1 (0.4)	0	1 (0.4)
(Ionised) Calcium (mmol/L), low						
Grade 0	194 (78.2)	195 (77.7)	196 (82.7)	195 (80.6)	171 (69.0)	173 (68.9)
Grade 1	43 (17.3)	42 (16.7)	26 (11.0)	37 (15.3)	53 (21.4)	58 (23.1)
Grade 2	8 (3.2)	12 (4.8)	11 (4.6)	9 (3.7)	19 (7.7)	17 (6.8)
Grade 3	3 (1.2)	1 (0.4)	3 (1.3)	1 (0.4)	4 (1.6)	2 (0.8)
Grade 4	0	1 (0.4)	1 (0.4%	0	1 (0.4)	1 (0.4)
AST (U/L), high						
Grade 0	125 (50.4)	123 (49.0)	159 (67.1)	153 (63.2)	93 (37.5)	88 (35.1)
Grade 1	114 (46.0)	123 (49.0)	75 (31.6)	84 (34.7)	143 (57.7)	155 (61.8)
Grade 2	6 (2.4)	5 (2.0)	1 (0.4)	5 (2.1)	7 (2.8)	8 (3.2)
Grade 3	2 (0.8)	0	2 (0.8)	0	4 (1.6)	0
Grade 4	1 (0.4)	0	0	0	1 (0.4)	0
ALT (U/L), high						
Grade 0	111 (44.8)	99 (39.4)	161 (67.9)	166 (68.6)	91 (36.7)	79 (31.5)
Grade 1	121 (48.8)	137 (54.6)	72 (30.4)	71 (29.3)	140 (56.5)	152 (60.6)
Grade 2	11 (4.4)	12 (4.8)	2 (0.8)	5 (2.1)	10 (4.0)	17 (6.8)
Grade 3	4 (1.6)	3 (1.2)	2 (0.8)	0	6 (2.4)	3 (1.2)
Grade 4	1 (0.4)	0	0	0	1 (0.4)	0
ALP (U/L), high						
Grade 0	200 (80.6)	198 (78.9)	187 (78.9)	164 (67.8)	172 (69.4)	151 (60.2)
Grade 1	47 (19.0)	52 (20.7)	49 (20.7)	77 (31.8)	74 (29.8)	98 (39.0)
Grade 2	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.8)	2 (0.8)
Grade 3	0	0	0	0	0	0
GGT (U/L), high						
Grade 0	147 (59.3)	138 (55.0)	175 (73.8)	159 (65.7)	130 (52.4)	117 (46.6)
Grade 1	71 (28.6)	81 (32.3)	54 (22.8)	67 (27.7)	87 (35.1)	94 (37.5)
Grade 2	19 (7.7)	24 (9.6)	5 (2.1)	13 (5.4)	19 (7.7)	30 (12.0)
Grade 3	11 (4.4)	8 (3.2)	3 (1.3)	3 (1.2)	12 (4.8)	10 (4.0)
Bilirubin (µmol/L), high						
Grade 0	226 (91.1)	235 (93.6)	217 (91.6)	225 (93.0)	217 (87.5)	222 (88.4)
Grade 1	21 (8.5)	13 (5.2)	17 (7.2)	13 (5.4)	27 (10.9)	21 (8.4)
Grade 2	1 (0.4)	3 (1.2)	3 (1.3)	4 (1.7)	4 (1.6)	8 (3.2)

Parameter	Neoadjuvant (SAF)		Adjuvant (aSAF)		Entire treatment period (SAF)	
	HD201 (N = 250)	Herceptin (N = 252)	HD201 (N = 238)	Herceptin (N = 242)	HD201 (N = 250)	Herceptin (N = 252)
Creatinine (µmol/L), high						
Grade 0	183 (73.8)	196 (78.1)	190 (80.2)	201 (83.1)	170 (68.5)	185 (73.7)
Grade 1	63 (25.4)	52 (20.7)	45 (19.0)	41 (16.9)	74 (29.8)	63 (25.1)
Grade 2	2 (0.8)	3 (1.2)	2 (0.8)	0	4 (1.6)	3 (1.2)

CTCAE = Common Terminology Criteria for Adverse Events; Values within the normal range are assigned to Grade 0. N = number of patients in the Safety Set; n' = Number of patients with at least one available assessment in the time period; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; GGT = gamma glutamyl transferase. Percentages were based on the number of patients in the Safety Set with at least one available assessment in the time period

Vital signs, physical findings, and other observations related to safety

TROIKA-1

All vital sign parameters and their change from baseline were similar across the three treatment groups at all timepoints.

Majority of the subjects had no abnormalities on physical examination between the three threatment groups. A few subjects presented with abnormal but clinically nonsignificant findings in HD201 and US-Herceptin treatment groups. No abnormalities in physical examination were recorded for subjects in the EU-Herceptin treatment group

Majority of the subjects had no injection site symptoms after injection. One subject in the EU-Herceptin treatment group had injection site symptoms prior to injection but had no symptoms after injection. There were no severe injection site symptoms at any time in any of the three treatment groups. Occurrence of symptoms was comparable in the three treatment groups.

Most subjects in the study had normal echocardiogram findings during the study and there were no clinically significant abnormal findings.

TROIKA

No abnormalities were detected regarding vital signs.

Physical examination was normal for most patients in the neoadjuvant period. Post operative scars without pathological changes was a frequently reported abnormal finding in the adjuvant period. Alopecia, a known side-effect of chemotherapy, was the most common abnormal finding reported in the physical examination in both neoadjuvant and adjuvant periods. No further analysis was performed.

No marked shifts in LVEF were observed in majority of the patient population.

In vitro biomarker test for patient selection for safety

Not applicable.

Safety in special populations

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

Immunological events

In TROIKA-1 study, immunogenicity evaluation of HD201, EU-Herceptin and US-Herceptin was one of the secondary objectives of the study. Immunogenicity samples in the study were collected during pre-dose (baseline), Day 15, Day 29, Day 43 and Day 54 post-dose. In the Phase 3 study, TROIKA, immunogenicity evaluation of HD201 and EU-Herceptin was one of the secondary objectives of the study. Blood samples for immunogenicity assessment were collected at Screening (prior to dosing), before surgery, before Cycle 5 (tested only if before surgery sample is positive for ADA]), before Cycle 10, before Cycle 14, EOT and at the 1-year post-treatment follow-up visit.

TROIKA-1

One subject of the EU-Herceptin group tested positive on day 1 for ADAs and did not test positive at any time after injection. It was subsequently determined to be negative for NAbs.

TROIKA

Table 71: Overall positive incidences of ADA in TROIKA -SAF population (TROIKA)

Timepoint	HD201 N=250		Herceptin N=252	
	n'	n (%)	n'	n (%)
Baseline	249	2 (0.8)	251	1 (0.4)
Before Surgery*	241	1 (0.4)	241	1 (0.4)
Before Cycle 10	29	0	29	0
Before Cycle 14	124	1 (0.8)	131	2 (1.5)
EOT	220	6 (2.7)	238	5 (2.1)
1-Year Follow-up	184	14 (7.6)	198	7 (3.5)

N= number of available patients within the group; n'= number of available patients per timepoint; n= number of patients with confirmed positive ADA results; %= Percentages are calculated based on number of patients with an available assessment; *=Two Before Surgery ADA positive patient's samples was also tested for Before Cycle 5 ADA and reported as negative.

All samples confirmed positive for ADA were negative for NAb.

Safety related to drug-drug interactions and other interactions

Formal studies to assess the potential drug-drug interaction studies with HD201 have not been carried out. This is acceptable for a biosimilar application

Discontinuation due to adverse events

In the entire treatment period, any TEAEs leading to dose/administration modification or study treatment discontinuation were comparable between the two treatment groups (83 patients [33.2%] with 172 TEAEs and 78 patients [31.0%] with 160 TEAEs in HD201 and EU-Herceptin treatment groups, respectively).

Post marketing experience

Not applicable.

2.7.6. Discussion on clinical safety

Safety similarity data was available from the Phase 1 pharmacokinetic (PK) study in healthy volunteers (TROIKA-1), and the Phase 3 confirmatory efficacy and safety study in patients with HER2-positive EBC (TROIKA).

Assessment of safety and tolerability of HD201, EU-Herceptin and US-Herceptin was a secondary objective of the TROIKA-1 study.

For the TROIKA study where the study consisted of two treatment periods (neoadjuvant and adjuvant treatment periods), the analysis of safety during the neoadjuvant treatment period and the integrated analysis of both treatment periods (entire treatment period) was performed for the safety set (SAF), and for the adjuvant SAF (aSAF) sets. The analysis of safety during the post-treatment follow-up period was performed for the post-treatment analysis set (PTAS).

In total, 607 subjects (502 patients with HER2-positive EBC and 105 healthy volunteers) were exposed to at least one dose of study drug in the entire clinical development. 285 subjects received HD201, and 287 subjects received EU-Herceptin, and 35 subjects received US-Herceptin.

Overall, the total number of subjects exposed as well as the mean cumulative dose are considered sufficient to judge upon the safety of HD201 and no dissimilarities were observed in terms of exposure.

Adverse events in healthy subjects (TROIKA-1 study)

Overall, the proportion of subjects who experienced at least one TEAE was 77.1% in the HD201 treatment arm, 85.7% in the EU-Herceptin arm and 82.9% in the US-Herceptin arm. Across all treatment groups, the most frequently reported TEAEs by SOC, were nervous system disorders (31.% HD201, 22.9% EU-Herceptin, 31.4% US-Herceptin), injury, poisoning and procedural complications (14.3% HD201, 25.7% EU-Herceptin, 20.0% US-Herceptin), infections and infestations (17.1% HD201, 20.0% EU-Herceptin, 34.3% US-Herceptin), general disorders and administration site conditions (20.0% HD201, 22.9% EU-Herceptin, 5.7% US-Herceptin), and respiratory, thoracic and mediastinal disorders (14.3% HD201, 20.0% EU-Herceptin, 11.4% US-Herceptin). All TEAEs were mild to moderate in severity.

The proportion of subjects who experienced at least 1 TEAE was similar between the three treatment groups. TEAEs of moderate severity occurred in 1 subject (2.9%) in the HD201 treatment group, while 12 moderate severity TEAEs were reported in 9 subjects (25.7%) in the EU-Herceptin treatment group and 9 moderate severity TEAEs were reported for 6 subjects (17.1%) in the US-Herceptin treatment group. Further, TEAEs of special interest (AEs associated with IRR, cutaneous, respiratory, cardiovascular, and gastrointestinal symptoms) in the HD201 treatment group were reported in 7 subjects (20.0%) with 10 TEAEs, compared to the other treatment groups (EU-Herceptin – 12 subjects [34.3%] with 12 TEAEs, and US-Herceptin – 11 subjects [31.4%] with 11 TEAEs). There were no AEs leading to discontinuation or withdrawal from the TROIKA-1 study.

Overall, the safety data were balanced between the three treatment arms in the TROIKA-1 study and no unexpected safety findings were reported.

Adverse events in female patients with HER2-positive EBC (TROIKA study)

The following time periods (and their respective database lock) and safety analysis groups were evaluated for the study:

Entire treatment period consisting of Neoadjuvant period and surgery (database lock date of 22 September 2020) and Adjuvant period (database lock date of 15 December 2020).

Post-treatment follow-up period (database lock date of 02 February 2022).

During the **neoadjuvant treatment period**, similar proportions of subjects reported TEAEs in the HD201 group (98.4%) and the Herceptin group (96.4%), and similar numbers of TEAEs were reported in both groups.

Serious TEAEs were reported for 6.4% of patients in the HD201 treatment group and 4.8% in the EU-Herceptin treatment group. TEAEs related to study treatment were reported for 34.4% of patients in the HD201 treatment group and 35.7% in the EU-Herceptin treatment group. TEAEs related to chemotherapy were reported for 97.2% of patients in the HD201 treatment group and 94.4% in the EU-Herceptin treatment group. TEAEs with intensity of Grade 3 or higher were reported for 30.4% of patients in the HD201 treatment group and 25.8% in the EU-Herceptin treatment group. TEAEs leading to discontinuation of study treatment were reported for 2.4% of patients in the HD201 treatment group and 1.2% in the EU-Herceptin treatment group. TEAEs leading to dose/administration modification or discontinuation of study treatment were reported for 27.6% of patients in the HD201 treatment group and 24.2% of patients in the EU-Herceptin treatment group.

There were higher proportions of patients observed with findings (≥ Grade 3) suggesting haematotoxicity in the HD201 arm as compared to the EU-Herceptin arm. The number [%] of patients observed with "Neutrophil count decreased" were 9 [3.6%] in the HD201 treatment group as compared to 2 [0.8%] in the EU-Herceptin treatment group. Moreover, the number [%] of patients observed with "White blood cell count decreased" were 6 [2.4%] in the HD201 treatment group as compared to 1 [0.4%] in the EU-Herceptin treatment group. According to the applicant, these events were attributed to the chemotherapy treatment, and all events resolved without sequelae. It is acknowledged that absolute number of patients in the HD201 group with "Neutrophil count decreased" or "White blood cell count decreased" were low and that most cases apparently were adequately resolved without sequalae. However, since both treatment groups received chemotherapy during the neoadjuvant period, the imbalance between the treatment groups cannot reliably be attributed to the chemotherapy.

During the **adjuvant treatment period**, similar proportions of subjects reported TEAEs in the HD201 group (68.9%) and the Herceptin group (69.0%), with a slightly higher number of TEAEs reported in the HD201 treatment group compared to the Herceptin group (678 compared to 625).

Serious TEAEs were reported for 3.4% of patients in the HD201 treatment group and 2.5% of patients in the EU-Herceptin treatment group. TEAEs related to study treatment were reported for 31.1% of patients in the HD201 treatment group and 30.6% in the EU-Herceptin treatment group. TEAEs with intensity of Grade 3 or higher were reported for 6.3% of patients in the HD201 treatment group and 3.3% in the EU-Herceptin treatment group. TEAEs leading to discontinuation of study treatment were reported for 4.6% of patients in the HD201 treatment group and 3.7% in the EU-Herceptin treatment group. TEAEs leading to dose/administration modification or discontinuation of study treatment were reported for 8.8% of patients in the HD201 treatment group and 10.7% in the EU-Herceptin treatment group.

The number of patients who experienced any SAE was slightly higher in the HD201 group compared to the EU-Herceptin group (9.6% and 6.7% of patients in the HD201 and EU-Herceptin group, respectively, across the entire treatment period). However, the number of treatment related SAEs was comparable between groups and the overall higher incidence of SAEs in the HD201 group was probably related to the concomitantly administered chemotherapy during the neoadjuvant period.

During the **post-treatment follow up period**, PTAEs were reported for 64 patients (27.4%) in the HD201 treatment group and 72 patients (29.8%) in the EU-Herceptin treatment group. Grade 3 or higher PTAEs were reported in 7 patients (3.0%) in the HD201 treatment group and 13 patients (5.4%) in the EU- Herceptin treatment group. Serious PTAEs were reported for 4 patients (1.7%) in the HD201 treatment group and 5 patients (2.1%) in the EU-Herceptin treatment group.

PTAEs related to study treatment were reported for 21 patients (9.0%) in the HD201 treatment group and 23 patients (9.5%) in the EU-Herceptin treatment group. No serious PTAEs related to study treatment were reported during the post-treatment follow up period.

Immunogenicity

ADA-assay

A Precipitation and Acid Dissociation (PandA) ECLA method was developed and validated at AGILEX Biolabs to determine anti-trastuzumab antibodies in human serum. ECL measurement was performed using commercial equipment . As a positive control, human anti-Trastuzumab was used. HD201, EU- and US-Herceptin were used to spike samples for the confirmatory assay and to assess drug tolerance. The control matrices were female HER-positive early breast cancer serum samples from subjects in the clinical study TROIKA and pooled human serum from normal subjects.

All critical reagents and antibodies were well described.

The method was validated for its precision, selectivity and specificity, drug tolerance, stability and drug interference. Intra- and inter-assay precision was below 20%. Screening assay sensitivity was at 15.6 ng/mL. Screening and confirmatory cut-point statistical calculations were presented. The confirmatory cut-point was 20.6% for HD201, 20.1% for EU-Herceptin and 20.3% for US-Herceptin. Cut points were estimated in 42 female human serum samples with HER2-positive early breast cancer. Drug tolerance was investigated by spiking varying levels of HD201, EU- or US-Herceptin into positive control samples. The assay was tolerant for up to 250 µg/mL HD201, EU- or US-Herceptin.

The minimum required dilution was 1 in 25. Short-term stability at room temperature was confirmed for 25 hours and 28 minutes and for 15 freeze/thaw cycles. Drug target interference was investigated with anti-Trastuzumab spiked into diseased human serum containing HER2. 37 ng/mL of ADA was detectable in the presence of up to 200 µg/mL of HER2.

Overall, the method for detection of anti-Trastuzumab antibodies in human serum was well described and developed. It is considered state of the art and valid for its intended use.

NAb assay

Neutralising antibodies were detected based on a reduction of trastuzumab-dependent ADCC response using a luciferase reporter gene system. ADCC activity was measured by luminescence. After initial validation, the method was re-validated to include a pre-treatment step to achieve higher drug tolerance.

All critical reagents, drugs, matrices and antibodies including lot numbers are well described. The assay was validated for its precision, sensitivity, selectivity, drug tolerance. Intra-assay precision was below 20% for all controls tested. Inter-assay precision was below 20% for MPC (4 of 5 runs) and HPC. The low positive control precision was 55.45% and thus, did not meet the acceptance criteria. The high variability is not expected to impact screening analysis. Drug tolerance was evaluated by spiking controls with various concentrations of HD201. The tolerance for the HPC and MPC was 100000 ng/mL and for the LPC 50000 ng/mL. For selectivity assessment, anti-trastuzumab reference standard was spiked into drug naïve sera. All sampled passed the acceptance criteria. Assay sensitivity was determined to be 265 ng/mL.

Specificity, stability and cut-point determination were assessed at previous validations. Specificity of effector and target cell lines and the specificity of neutralizing anti-trastuzumab antibodies was investigated and met the acceptance criteria. For stability, room temperature and freeze/thaw stability were evaluated. Human anti-trastuzumab antibodies were stable at room temperature in human serum

for at least 4 hours and stable for 4 freeze/thaw cycles. The confirmation cut point was determined to be 47.5% in normal human serum.

Taken together, presented assay for detection of neutralising antibodies in human serum by a cell based ADCC assay was well described and established. It measures the neutralisation of ADCC activity after addition of anti-HD201 or anti-Herceptin antibodies. It is considered valid for its intended use.

ADA/NAb data

In the TROIKA-1 study, overall, only 1 sample (in the EU-Herceptin treatment arm) was confirmed ADA positive but with a low titre value.

In the Phase 3 TROIKA study, the overall incidence of ADA was similar between the HD201 and the EU-Herceptin treatment arms. None of the confirmed ADA positive patients in the HD201 and EU-Herceptin treatment arms of the TROIKA study experienced any anaphylactic or allergic reactions due to the study drugs. Results indicate similar incidence and titres of anti-drug antibodies for HD201 and EU-Herceptin. Any treatment-emergent immune response was similar between the two treatment arms. There was no effect on safety parameters in the study associated with the presence of ADAs. Incidence of infusion-related reactions were similar across the treatment arms. In addition, none of the confirmed ADA positive patients in the HD201 and EU-Herceptin treatment arms tested positive for NAbs.

Overall, immunogenicity was shown to be low in all studies and comparable to Herceptin.

2.7.7. Conclusions on the clinical safety

Exposure in the TROIKA study seems appropriate for the intended target population.

Based on the findings in the TROIKA-1 and TROIKA biosimilarity studies, the safety profiles of the HD201 and Herceptin treatment groups are broadly similar and are in line with the known safety profile of Herceptin.

2.8. Risk Management Plan

The Safety Specification (Part II, SI-SVIII) from RMP version 0.1, dated 24July 2023 is assessed below.

2.8.1. Safety concerns

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP which is in line with the reference product's (Herceptin) summary of safety concerns.

Table 72: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Cardiac dysfunction Infusion – related reaction (IRRs) Oligohydramnios

Summary of safety concerns	
Important potential risks	None
Missing information	Safety of Docetaxel 75 mg / m^2 vs 100 mg / m^2

2.8.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.8.3. Risk minimisation measures

Table 73: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk Cardiac dysfunction	**Routine risk communication:** SmPC Section 4.2: Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for monitoring to identify patients who develop cardiac dysfunction is included in Section 4.4 of SmPC. Clinical recommendation for managing LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.2 of SmPC. **Other risk minimisation measures beyond the product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine.
Important identified risk Infusion-related reactions	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Guidance on observation period after administration has been adequately captured in Section 4.2 of SmPC. **Other risk minimisation measures beyond the product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine.
Important identified Risk Oligohydramnios	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy, and lactation **Routine risk minimisation activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Tuznue or if a patient becomes pregnant while receiving Tuznue or within 7 months following last dose of

	Tuznue, close monitoring by a multidisciplinary team is desirable. This has been adequately covered in Section 4.6 of SmPC. **Other risk minimisation measures beyond the product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine.
Important missing information Safety of docetaxel 75mg/m² vs 100mg/m²	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Precautions to be taken prior to administration for the prevention of Safety of 75mg/m² vs 100mg/m² docetaxel dose are included in SmPC Section 4.2. **Other risk minimisation measures beyond the product information:** None

2.8.4. Conclusion

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

2.9. Pharmacovigilance

2.9.1. Pharmacovigilance system

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

2.9.2. Periodic Safety Update Reports submission requirements

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

2.10. Product information

2.10.1. 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.*.

2.10.2. Additional monitoring

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

3.1. Comparability exercise and indications claimed

HD201 has been developed as a similar biological medicinal product to the reference medicinal product Herceptin (Roche Registration Limited). HD201 (trastuzumab) is a recombinant humanised IgG1 monoclonal antibody targeted against the human epidermal growth factor receptor 2 (HER2). Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and thereby inhibits the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of ADCC and ADCP. The same therapeutic indications as granted for Herceptin for intravenous administration in the EU (EU/1/00/145/001) are proposed for HD201.

A 3-way pairwise analytical biosimilarity exercise was performed comparing HD201 DP lots to EU-Herceptin, HD201 DP to US-Herceptin, and EU-Herceptin to US-Herceptin. The quality attributes (QAs) were determined based on the quality target product profile (QTPP). Overall, the identified QTPP is acknowledged. Each quality attribute was evaluated for criticality using a risk ranking approach, which assessed the possible impact of the attribute on clinical safety and efficacy. The classification and assignment of QA under the proposed tiers 1-3 are acceptable. The quality attributes were stratified into three statistical tiers. For tier 1 quality attributes, equivalence testing was selected as an approach to evaluate the biosimilarity of HD201 and Herceptin. Tier 2 QAs were assessed by a quality range approach. For Tier 3 quality attributes evaluation was performed using descriptive raw data and/or graphical comparison. The overall approach is accepted. Biosimilarity assessment of HD201 DP (150 mg presentation and 420 mg presentation), EU-Herceptin. Of note HD201 and Herceptin lots included in the pivotal clinical studies are included in the biosimilarity exercise as well. Thus HD201 material representative for the commercial process was also used in the Phase 3 clinical trial (DS process D, DP process 2-II).

Overall, the provided data set accumulated to support biosimilarity of HD201 with the reference material EU-Herceptin is considered comprehensive and support the biosimilarity claim.

3.1. Results supporting biosimilarity

Quality

A 3-way pairwise analytical biosimilarity exercise was performed comparing HD201 FP lots to EU-Herceptin, HD201 FP to US-Herceptin, and EU-Herceptin to US-Herceptin. The quality attributes were determined based on the quality target product profile (QTPP).

All analytical methods used for the similarity assessment have been validated. Overall, the descriptions and validation data that have been provided for the analytical methods used for the analytical comparability exercise are considered sufficient and indicate that the methods are suitable for the intended purpose.

Each quality attribute was evaluated for criticality using a risk ranking approach, which assessed the possible impact of the attribute on clinical safety and efficacy. The classification and assignment of QA under the proposed tiers 1-3 are acceptable. The quality attributes were stratified into three statistical tiers. For tier 1 quality attributes, equivalence testing was selected as an approach to evaluate the

biosimilarity of HD201 and Herceptin. Tier 2 QAs were assessed by a quality range approach. For Tier 3 quality attributes evaluation was performed using descriptive raw data and/or graphical comparison. The overall approach is accepted.

The biosimilarity assessment included HD201 FP (150 mg presentation and 420 mg presentation) and EU-Herceptin. This includes HD201 and Herceptin lots included in the pivotal clinical studies.

Table 79: Analytical similarity overview

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Primary structure	Primary sequence	LC-TUV-MS/MS Peptide mapping	Identical primary sequence
	N- and C-terminal sequence	LC-TUV-MS/MS Peptide mapping	Identical N- and C-terminal sequence
	N-terminal sequence	Edman degradation sequencing	Identical heavy and light chain N-terminal sequence
	Total mass	LC-TUV-MS	Highly similar total mass
	Extinction coefficient	UV spectroscopy	Highly similar
General	Protein content	UV spectroscopy	Highly similar
Higher order structure	Secondary structure	Far UV circular dichroism (CD)	Highly similar spectra and secondary structure
	Secondary structure	Fourier transform infrared spectroscopy (FT-IR)	Highly similar spectra and secondary structure
	Tertiary structure	Fluorescence	Similar
	Thermodynamic stability	Differential scanning calorimetry (DSC)	Highly similar transition temperatures
	Free thiol	Ellman test	Highly similar free thiol content
	Disulfide bond	LC-TUV-MS/MS Peptide mapping	Identical disulfide bridging patterns
Glycosylation	Site specific N-glycosylation	LC-TUV-MS/MS Peptide mapping	Identical glycosylation site (Asn-300)
	High mannose	LC-FLR-MS	Highly similar
	Afucosylated glycan + high mannose	LC-FLR-MS	Similar
	Afucosylated glycan	LC-FLR-MS	Similar with marginal differences. No impact on FcγRIIIa binding and ADCC activity observed
	Galactosylated glycan	LC-FLR-MS	Highly similar

Molecular parameter	Attribute	Methods for control and characterization	Key findings
	Sialylation	LC-FLR	Lower total sialylation, Neu5Ac, and Neu5Gc content in HD201
	Non-glycosylated heavy chain	Capillary electrophoresis sodium dodecyl sulfate (CE-SDS; reduced)	Highly similar
Purity	Intact IgG	CE-SDS (non-reduced)	Similar with justifiable differences
	Sum of LC and HC	CE-SDS (reduced)	Highly similar
	Sum of fragment	CE-SDS (non-reduced)	Similar with justifiable differences
	Monomer	Size exclusion high-performance liquid chromatography (SE-HPLC)	Similar. Higher purity in HD201 compared to EU-Herceptin
	HMW	SE-HPLC	Similar. Lower aggregates in HD201 compared to EU-Herceptin
	Dynamic light scattering (DLS)	DLS	Highly similar
Charge variants	Charge variant profile	Cation exchange high performance liquid chromatography (CEX-HPLC)	Similar percentage of main, acidic and basic species observed in HD201 compared to EU-Herceptin
		Capillary isoelectric focusing (cIEF)	Highly similar main peak pI and similar percentage of main, acidic and basic species observed between HD201 and EU-Herceptin
Modifications	Total isomerisation	Isomerisation kit	Similar
	Isomerisation	LC-TUV-MS/MS	Similar
	Deamidation	Peptide mapping	Similar
	Oxidation	Peptide mapping	Similar
Biological activity	Anti-proliferation assay	Cell-based assay	Equivalent antiproliferative activity
	ADCC activity	Reporter assay	Equivalent ADCC activity
	ADCC activity	Primary PBMCs	Equivalent ADCC PBMC activity
	ADCP activity	Reporter assay	Equivalent ADCP activity
	CDC assay	Cell-based assay	Similarly lack of CDC activity

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Binding affinity	HER2 binding	Bio-layer interferometry (BLI)	Equivalent binding affinity to HER2
	FcγRIIa binding (R and H variants)	BLI	Highly similar
	FcγRIIb binding	BLI	Highly similar
	FcγRIIIa binding (V and F variants)	BLI	Highly similar
	FcγRIIIb binding	BLI	Highly similar
	FcγRI binding	BLI	Highly similar
	FcRn binding	BLI	Highly similar
	Inhibition of VEGF secretion	ELISA	Similar inhibition of VEGF secretion
	C1q binding	ELISA	Highly similar
Degradation profile	High pH stress Thermal stress Oxidative stress Photo stress	SE-HPLC, CE-SDS, CEX-HPLC, Peptide mapping, Extinction coefficient, Antiproliferation assay, HER2 binding, Fcγ receptor binding by BLI	Similar degradation profile

Regarding the tier1 QAs, HER 2 binding and antiproliferative activity are comparable between HD201 and the reference product. The ADCC activity for both V and F Variant, were assessed using ADCC reporter bioassays, which quantify biological activity on nuclear factor of activated T-cells (NFAT) response element (RE) pathway activation. SKBR3 cell line over expressing HER2 were used as target cells for both the assays. The effector cells used for ADCC-V and ADCC-F reporter bioassays were genetically engineered Jurkat T cells that express FcγRIIIa V or F respectively, and a luciferase reporter gene driven by NFAT-RE. ADCC activity (FcγRIIIa V) seems slightly lower for HD201 but this is due to the inclusion of process B derived material. The intentional change from Process B to Process C in order to match quality profile of Herceptin can be considered successful as relative potency derived for ADCC-V activity is more aligned to results for Herceptin after introduction of Process C. Despite this, the equivalence margin was met. The ADCC activity for F Variant of FcγRIIIa is comparable. This is not unexpected and confirmed by structure-function relationship analysis. The ADCC activity using PBMC was also determined and overall the data indicate that HD201 has similar *in vivo* ADCC activity as Herceptin under these more physiological conditions compared to the NK cell assay. Despite the more physiological conditions the intended differences seen between the batches form the three different manufacturing processes B, C, and D is retained indicating that the assay is sufficiently sensitive. ADCP activity of HD201 and Herceptin samples were determined using FcγRIIa-H ADCP reporter bioassay kit. HER2-overexpressing SKBR3 breast cancer cell lines were used as target cells. The effector cells used were genetically engineered Jurkat T cell expressing FcγRIIa-H receptor (G988A) and a luciferase reporter gene driven by NFAT-RE. The ADCP activity is considered comparable. Peptide Mapping and a N- and C-terminal sequencing via peptide mapping confirmed the amino acid sequence similarity between the HD201 and the reference materials. Sequence identification was investigated using LC-TUV-MS and was shown to cover 100% of the light and heavy chain sequence of Trastuzumab.

For tier 2 QAs, binding affinity of HD201, EU- and US-Herceptin to Fcγ receptors were determined. The intended process change (B to C) in order to align the critical quality attributes seem to be reflected in the binding affinity towards the high affinity FcγRIIIa (V variant) as process B derived HD201 material

shows slightly lower binding affinities which are more aligned with the reference material after the process change. The effect cannot be observed for binding toward FcγRIIIa (F variant). With regard to FcγRIIIb binding slightly lower binding affinities observed for HD201 are driven by process B material. Protein concentration was determined by UV-Vis Spectroscopy. The extinction coefficient was compared experimentally and found nearly comparable. In the biosimilarity exercise, the extinction coefficient used for protein concentration measurement was experimentally determined for each lot individually. The current extinction coefficient is employed for UV protein quantification to align with Herceptin and what is used for HD201 release. N-glycan profiling was conducted. Lower values (min-max) of afucosylation+high mannose/afucosylation are observed for process B derived HD201 material clearly outside of the quality range of Herceptin. The difference is diminished after the intended process change to process C. No significant differences were observed for galactosylation, sialylation, Neu5Ac and Neu5Gc levels (present at very low levels). Total mass analysis was measured by UPLC/LC-MS and is qualified as a Tier 2 CQA, therefore a quality range test was performed to evaluate comparability. The total mass of the two main glycoforms G0F(2) and G0F(1)/G1F(1) were within quality range of EU- and US-Herceptin. Regarding purity under non-reduced conditions, the purity min-max ranges were similar for HD201 and EU-Herceptin lots. It is concluded that HD201 and Herceptin are highly comparable in terms of their purity. The profile of charged variants displays some variability for both HD201 and the reference product. During development the profiles were aligned and can be considered sufficiently comparable. With regard to other modifications such as isomerisation, deamidation, and oxidation no significant differences are observed although the degree of variability seems higher for HD201. With FT-IR, secondary structures including α-helix, β-sheet, β-turns and random coils were analysed.

Regarding Tier 3 QAs, C1q binding of HD201 and Herceptin indicates no significant binding activity and the difference observed is not meaningful. Accordingly, CDC activity is not observed and is not part of the mechanism of action of trastzumab.

Structure-function analysis was performed and the known correlation between %afucosylation, FcγRIIIa binding and ADCC activity was confirmed. This further supports the process change from B to C to increase afucosylation levels.

A forced degradation study was included in the biosimilarity exercise between HD201 and Herceptin. The study included thermal forced degradation at 40°C, high pH forced degradation, photo-induced forced degradation, and oxidative forced degradation. Samples were analysed by SEC-HPLC, CE-SDS, CEX-HPLC, peptide mapping, extinction coefficient, HER2 binding and Fcγ-receptor binding. HD201 showed a similar degradation profile than EU- and US-Herceptin in the thermal stress study. No significant differences were observed between HD201 and Herceptin lots in the high pH forced degradation study. Similar degradation profiles were detected between HD201, EU- and US-Herceptin in the photostability study. A minor difference was observed for FcRn binding. However, this observed difference does not preclude biosimilarity. Oxidative stress study was performed on HD201, EU- and US-Herceptin. No significant differences were observed in degradation profiles of HD201, EU- and US-Herceptin. When exposed to different stress conditions, when certain QA are affected, similar trends, degradation patterns, modifications, and binding affinities were observed for HD201 and Herceptin. Thus, forced degradation study results support biosimilarity.

In conclusion, the applicant has addressed the analytical similarity between HD201 and the reference product EU-Herceptin in an extensive comparability study.

Non-clinical

Non-clinical evidence to support the demonstration of biosimilarity between HD201 and EU-authorised Herceptin is based on extensive in-vitro comparability studies conducted under non-GLP conditions. No additional non-clinical studies are included in this MAA, which is acceptable.

Clinical

Two studies TROIKA-1 and TROIKA were performed. The first one was a standard phase I bioequivalence study. The second one contained an assessment of bioequivalence based on the C_{trough} value before each treatment cycle.

For TROIKA-1, the bioanalytical methods were properly validated. The PK and statistical methods essentially followed standard procedures and the sample size has been adequately estimated.

TROIKA was a Phase III study with a PK component, consisting of the analysis of the C_{trough} values before each treatment cycle. At each of the before cycles 5, 8, and 14, the 90% confidence interval on the ratio of geometric means of the C_{trough} level of the two treatments is contained within the defined equivalence interval [80.00%; 125.00%], implying that bioequivalence of HD201 to Herceptin for steady-state trough level can be accepted. At before Cycle 10, only 57 samples were available for analysis and the mean ratio (90% CI) between the treatment groups (115.4% [93.8%; 142.0%] was not contained within the 80% - 125% equivalence margin possibly due to the small sample size.

In a study design based on scientific advice, the pivotal TROIKA study met its primary and secondary endpoints indicating equivalence in terms of efficacy between the proposed biosimilar (HD201) and the reference product in the EBC indication. The Applicant provided a sufficient rationale for why data from the TROIKA trail could support the indication in gastric metastatic cancer.

The primary analysis of the primary efficacy variable was based on a 95% CI on the difference in tpCR rate between the treatment groups for the PPS. Equivalence between the two groups was to be concluded if the 95% CI on the difference between the two treatment groups in tpCR rate was entirely situated within the interval [-15%; 15%]. The locally assessed tpCR rate in HD201 and EU-Herceptin treatment groups in the PPS was 45.0% and 48.7%, respectively. The difference between the two groups (HD201-Herceptin) was -3.8% with 95% CI ranging from -12.8% to 5.4%. Since this interval falls within the pre-defined equivalence margin of [-15%; 15%], it can be concluded that HD201 and EU-Herceptin are equivalent.

Based on the findings in the TROIKA-1 and TROIKA biosimilarity studies, the safety profiles of the HD201 and Herceptin treatments groups are broadly similar and are in line with the known safety profile of Herceptin.

3.2. Uncertainties and limitations about biosimilarity

Quality

Overall, the provided data set accumulated to support biosimilarity of HD201 with the reference material EU-Herceptin is considered comprehensive and support the biosimilarity claim.

Non-clinical

N/A

Clinical

Efficacy

There were several concerns raised due to critical and major findings from GCP inspections and re-inspections at the Sponsor as well as study sites in Russia Thailand and sites monitored by a CRO in Spain. However, GCP issues were considered resolved as sensitivity analyses on the PPS excluding affected patients were provided. However, these sensitivity analyses only excluded some of the respective study sites in turn but not all of them at once, while in fact data reliability for all inspected

sites was questioned. Hence, the Applicant was asked to prepare additional sensitivity analyses by excluding all data for which credibility concerns had been raised. As these analyses resulted in 95% CI ([-11.0%, 9.0%] in the PPS and [-10.5%; 8.9%] in the mFAS) which were lying well within the acceptance range of (-15%, 15%), the issue was considered resolved. Submitted efficacy results for the screening, neoadjuvant and surgery period are based on re-monitored data, which were presented in the CSR Version 3.0 (01. February 2021) along with data for the adjuvant treatment period. Primary efficacy outcome was within the equivalence acceptance margin, suggesting biosimilarity from an efficacy point of view. Further, secondary endpoints and supplementary analyses support results from the primary endpoint.

Safety

There were higher proportions of patients observed with findings (≥ Grade 3) suggesting haematotoxicity in the HD201 arm as compared to the EU-Herceptin arm. It is acknowledged that absolute number of patients in the HD201 group with "Neutrophil count decreased" or "White blood cell count decreased" were low and that most cases apparently were adequately resolved without sequalae. However, since both treatment groups received chemotherapy during the neoadjuvant period, the imbalance between the treatment groups cannot reliably be attributed to the chemotherapy.

3.3. Discussion on biosimilarity

HD201 has been developed as biosimilar to Herceptin. The active substance trastuzumab is manufactured using a typical manufacturing process for monoclonal antibodies. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

An analytical biosimilarity exercise was performed comparing HD201 FP lots to EU sourced Herceptin. The QAs were determined based on the QTPP. Each quality attribute was evaluated for criticality using a risk ranking approach, which assessed the possible impact of the attribute on clinical safety and efficacy. Structure-function analysis was performed and the known correlation between %afucosylation, FcγRIIIa binding and ADCC activity was confirmed. Overall, the provided data set accumulated to support biosimilarity of HD201 with the reference product is considered comprehensive. The material generated with Process D, which is intended to be the commercial material, is considered highly similar to the EU reference product Herceptin.

Concerns were raised since AS material used in pivotal clinical studies, mostly derived from process B and C, could not be considered comparable to the material produced by the proposed commercial manufacturing process, process D. An overview of previously submitted data, as well as data from re-analysis of samples and newly generated data were submitted indicating that the differences seen between material from the different processes are not clinically meaningful which was reassuring.

Overall, the provided data set accumulated to support biosimilarity of HD201 with the reference material EU-Herceptin is considered comprehensive and support the biosimilarity claim. Tuznue is considered approvable as a proposed biosimilar to Herceptin.

3.4. Extrapolation of safety and efficacy

The indications granted for the reference product EU-Herceptin are all claimed for the trastuzumab biosimilar Tuznue. These include: HER2 positive metastatic breast cancer, HER2 positive early breast cancer and HER2 positive metastatic breast cancer.

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

3.5. Additional considerations

Not applicable.

3.6. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Outcome

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

Metastatic breast cancer

For the treatment of adult patients with HER2-positive (MBC):

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

Early breast cancer

Tuznue 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 HD201 therapy, for locally advanced (including inflammatory) disease or tumours >2 cm in diameter (see sections 4.4 and 5.1).

Tuznue 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.

Tuznue in combination with capecitabine or 5-fluorouracil and cisplatin 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.

Tuznue should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by Immunohistochemistry (IHC) 2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see sections 4.4 and 5.1).

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

to be implemented by the Member States

Not applicable.