19 May 2022
EMA/CHMP/902445/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Tuznue

International non-proprietary name: trastuzumab

Procedure No. EMEA/H/C/005066/0000

Note

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

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Administrative information

Name of the medicinal product:	Tuznue
Applicant:	Prestige Biopharma Belgium Terhulpensesteenweg 449 3090 Overijse BELGIUM
Active substance:	Trastuzumab
International Non-proprietary Name/Common Name:	trastuzumab
Pharmaco-therapeutic group (ATC Code):	Other antineoplastic agents, monoclonal antibodies (L01XC03)
Therapeutic indication(s):	Breast cancer *Metastatic breast cancer* Tuznue is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC): - as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments. - in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

	- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease. - in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab. *Early breast cancer* 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 Tuznue 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 is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not

	received prior anti-cancer treatment for their metastatic disease. Tuznue should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by 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).
Pharmaceutical form(s):	Powder for concentrate for solution for infusion
Strength(s):	150 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

ADA	Anti Drug Antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AM	Main acidic peak
API	Active pharmaceutical ingredient
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
CAPA	Corrective and preventive actions
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 Organisation
CSR	Clinical Study Report
Ctrough	Trough Concentration
CV	Coefficient of Variation
DLS	Dynamic light scattering
DP	Drug product
DS	Drug substance
DSC	Differential scanning calorimetry
EBC	Early Breast Cancer
ECG	Electrocardiogram
eCRF	Electronic case report form
EFS	Event-Free Survival
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ER	Estrogen Receptor
Ph.Eur	European Pharmacopeia
FAS	Full Analysis Set
FISH	Fluorescence in Situ Hybridisation
FTIR	Fourier transform infrared spectroscopy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good manufacturing practice
GS/MS	Gas chromatography mass spectrometry
HCD	Host cell DNA
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
ICH	International Council on Harmonisation
ICP-OES	Inductively-coupled plasma optical emission spectroscopy
IG	Immunogenicity

IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
IMP / IP	Investigational Medicinal Product
IPC	In-process controls
LC-MS	Liquid chromatography mass spectrometry
LMW	Low molecular weight
LOQ	Lower limit of quantitation
MA	Marketing authorisation
MAA	Marketing authorisation application
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
Ph. Eur.	European pharmacopeia
PI	Isoelectric point
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
RMP	Risk Management Plan
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 Hybridisation
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	United States pharmacopeia
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 3 May 2019 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 I of Regulation (EC) No 726/2004.

The applicant applied for the following indication

Breast cancer

Metastatic breast cancer

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

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

Early breast cancer

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 Tuznue 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 is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Tuznue should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by 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).

1.2. Legal basis, dossier content and multiples

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.

This application is submitted as a multiple of Hervelous simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen reference product is:

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
17 November 2011	EMEA/H/SA/2212/1/2011/III	David Brown and Joao Manuel Lopes de Oliveira
9 November 2017	EMEA/H/SA/2212/1/FU/2017/II	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: Eva Skovlund Co-Rapporteur: Ondřej Slanař

The application was received by the EMA on	3 May 2019
The procedure started on	23 May 2019
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 August 2019
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 August 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 August 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 September 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	08 October 2020
The following GMP and GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection (GCP/2019/022) at the sponsor site in Singapore, 1 investigator site in Thailand and 1 investigator site in Russia between 09 September 2019 and 11 October 2019. – A GCP re-inspection (GCP/2021/04) at the sponsor site in Singapore, a CRO in Spain and an investigator site located also in Spain between 14 September 2021 and 19 November 2021. The outcome of the inspection carried out was issued on	09 March 2020 31 December 2021
– A GMP inspection at 2 DS manufacturers in Republic of Korea between 09 November 2021 and 16 November 2021. The outcome of the inspections carried out was issued on	15 February 2022 and 25 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	27 November 2020

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	10 December 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 February 2021
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 March 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 March 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 December 2021
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	12 January 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 January 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 March 2022
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	6 April 2022
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	21 April 2022
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	13 May 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Tuznue on	19 May 2022

2. Scientific discussion

2.1. Problem statement

Not applicable

2.2. About the product

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

Trastuzumab as 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.

Tuznue (trastuzumab) also referred HD201 has been developed as a biosimilar to the reference product Herceptin (trastuzumab) authorised in the European Union (EU) via the Centralised Procedure in 2000, claiming the same therapeutic indications than those of the reference product for the treatment of HER2-positive early and metastatic breast cancer (EBC and MBC), and metastatic gastric cancer (MGC).

Efficacy and safety study in early breast cancer patients are provided, and the other indications are sought to be extrapolated.

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. This is an application for a biosimilar trastuzumab. 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.

The clinical programme was initiated with the aim to show biosimilarity between both products in the setting of metastatic breast cancer (MBC), and extrapolating similarity to the other indications in case biosimilarity was confirmed in MBC in regard to quality, non-clinical, PK, pharmacodynamic and clinical aspects.

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

2.3. Quality aspects

2.3.1. Introduction

The finished product (FP) is presented as powder for concentrate for solution for infusion containing 150 mg of trastuzumab as active substance (AS).

Other ingredients are: L-histidine hydrochloride monohydrate, L-histidine, α,α-trehalose dihydrate, and polysorbate 20.

The product is available in 20 mL clear glass vials with rubber stopper. Each carton contains one vial.

The formulation, dosage, strength upon reconstitution, and administration are the same as for the originator Herceptin.

2.3.2. Active substance

2.3.2.1. General information

The active substance, trastuzumab (company code HD201), is a humanised monoclonal antibody (mAb) developed by Prestige Biopharma Limited as a biosimilar product to the EU-approved Herceptin (trastuzumab).

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}. β-sheet represents the major secondary structure found in HD201 and this is followed by α-helix and β-turn.

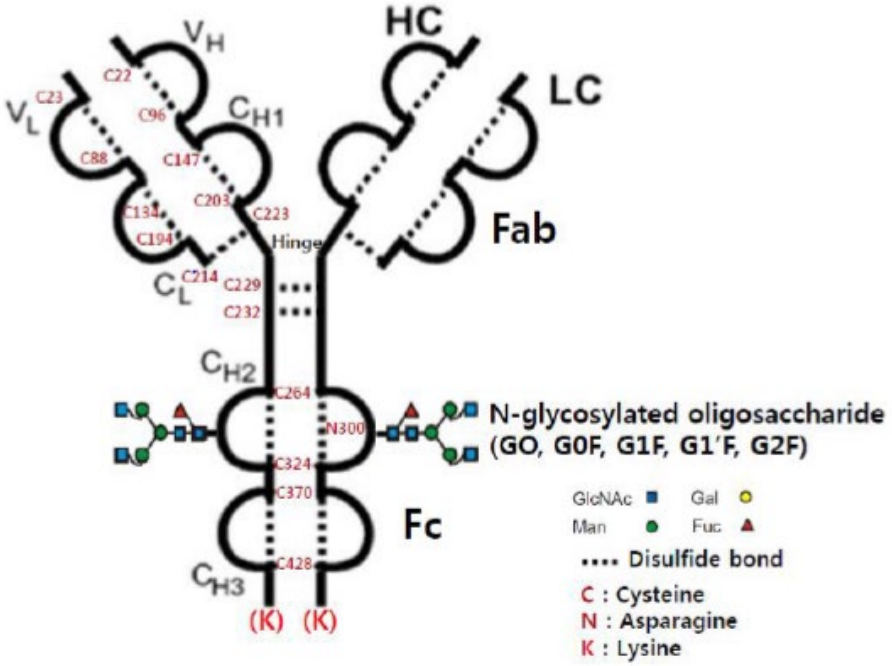


Figure 1: Schematic diagram of HD201 glycosylation sites and inter- and intra-disulphide bridges.

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).

2.3.2.2. Manufacture, process controls and characterisation

Tuznue master cell bank (MCB), working cell bank (WCB), and AS were manufactured at two non-EU contract manufacturing organisations. One of these sites was also responsible for stability and release testing of the AS.

Pre-approval inspections were requested and carried out during the evaluation procedure for both sites. A major objection was raised in view of the absence of valid EU GMP certificates included in the MAA. Following the inspection, the requested GMP certificates have been provided and the major objection was considered resolved.

In addition, comparability and similarity studies have been performed in Singapore.

Description of manufacturing process and process controls

The production cell line is a Chinese Hamster Ovary (CHO) cell line transfected with an expression vector encoding HD201. The manufacturing process of HD201 AS consists of upstream and downstream processes. In-process controls (IPCs) are conducted at every step throughout the whole manufacturing process. The detailed information of both IPCs and in-process tests (IPTs) is described in the dossier.

The upstream manufacturing process begins with thawing of WCB and serial cell culture expansion. A production bioreactor is used for production, which is followed by harvest steps.

The downstream process is composed of purification and formulation processes and includes chromatography and filtration steps, final formulation and bulk filling.

At day 120, a major objection was raised on the lack of adequate documentation to demonstrate a consistent, validated manufacturing process and control strategy for the active substance. To address this major objection, Module 3.2.S.2 has been rewritten, with significant additions made to the presentation and content. In general, the AS manufacturing process has been described in detail and has been properly validated. Critical process parameters (CPP), critical process controls (CPC) or critical quality attributes (CQA) are described and justified. Information and justification for process parameters and process controls used to maintain the process in a validated and qualified state is adequately presented. There are no intermediates from the manufacturing process of HD201 AS.

Information on filter reusability is provided in the dossier, and the maximum number of membrane reuse is defined.

Control of materials

All the MCB/WCB have been adapted and cultured in serum-free culture media with no materials of animal or human origin. The monoclonality of the MCB is also confirmed by fluorescence *in situ* hybridisation (FISH) method. HD201 WCB and MCB have been characterised in terms of growth profile, viable cell density, antibody production (titre), identity, purity, genetic stability and safety (non-viral and viral adventitious agents) in accordance with ICH guidelines Q5D and Q5A(R1).

All raw materials and reagents used in the manufacture are provided, and tests are performed either at the supplier (certificate of analysis provided) and/or at the manufacturer before the materials are accepted by the production quality system used for manufacturing. The compendial raw materials were tested according to Pharmacopoeial monographs, while the non-compendial raw materials were tested according to internal test procedures.

Cells are grown in suspension culture using chemically defined media with supplements or additives of non-animal and non-human origin. Therefore, HD201 AS and FP are free of TSE (Transmitting Animal

Spongiform Encephalopathy)/ BSE (Bovine Spongiform Encephalopathy). BSE/TSE-Free declaration of each material is provided in Module 3.2.A.2.

Process validation

The HD201 AS manufacturing process was validated by demonstrating that the process, when executed within defined process parameter ranges, consistently produces AS that meets predefined acceptance criteria. The initial process validation encompassed upstream and downstream manufacturing steps for three HD201 batches. Variability was observed between these three batches. In order to support the repeatability of the AS manufacturing process, an additional five batches have been included in the process validation study.

As indicated in the section above, issues relating to validation were raised as part of the major objection on the manufacturing process. As these were adequately addressed, the active substance manufacturing process is considered properly validated.

Media and buffer hold time validation studies were conducted at small scale under conditions and in containers representative of the full-scale manufacturing process. Clearance studies were conducted on process- and product-related impurities before and after each unit operation of the downstream purification process for process validation batches. Stability was evaluated by several assays to reveal possible degradation or contamination.

Manufacturing process development

Manufacturing of HD201 AS has been performed using four different manufacturing processes, namely process A, process B, process C and process D (commercial), across 3 different manufacturing sites to support various studies. Differences between the processes include scale, manufacturing sites, and changes to the feed media. Several development studies were conducted during the development phase of HD201 AS manufacturing from non-clinical/Phase I to Phase III clinical trials. The study reports are included in the dossier.

To evaluate comparability between lots produced in the different manufacturing processes, a series of comparability testing strategies were employed.

In relation to the demonstration of comparability, the applicant applied an inconsistent approach in setting comparability acceptance criteria, which was not endorsed. In addition, several quality attributes with high criticality fall outside the predefined comparability acceptance criteria, as outlined below.

Regarding the functional characterisation studies, the provided results for HER2 binding potency do not support comparability as a substantial number of tested batches (A, B, D process) fall outside of the comparability range based on process C material. In addition, lots manufactured by process D display a lower rate of (dissociation constant) KD change than process B and C lots upon heat stress. Highly variable results for FcγRIIIa (V variant) and FcγRIIIa (F variant) do not support the overall comparability claim. A drift towards stronger FcγRIIIa binding affinity was identified for process C and D. Process A and B material cannot be concluded as comparable to representative commercial material in these attributes. This variability in results is further substantiated in relative ADCC activity where results for V variant show approximately 50-200% potency range regardless of the differences in glycan structure, and results for F variants show that process B material is not comparable to C and D material. This also relates to the observed major differences in glycosylation profile (afucosylation, high mannose content and galactosylation). FcγRIIa (R variant) binding affinity was not consistent between produced batches as the B and D batches are shifted towards stronger binding affinity to FcγRIIa (R variant). The applicant does not expect any negative impact on the ADCP activity, however

considering the high variability of ADCP bioassay results, the CHMP considers that no firm conclusion can be made in this regard.

In summary, in the comparability exercise, several quality attributes with high criticality directly impacting the mode of action or which can have an impact on efficacy, safety, pharmacokinetic and immunogenicity, demonstrate significant variation between the manufacturing processes used during clinical development and the proposed commercial manufacturing process. The applicant's justification for these differences are based on a claimed insignificant impact on *in vitro* and clinical efficacy as well as pharmacokinetics, which according to the applicant supports comparability between the processes. However, the clinical studies were not designed or powered to demonstrate comparability for the manufacturing processes, and hence cannot be used to conclude whether the differences in quality attributes have an adverse impact upon safety or efficacy. Considering the significant differences observed in quality attributes between material from the different manufacturing processes, the applicant's conclusion that these studies demonstrate comparability is not supported. A major objection raised at day 120 in relation to the lack of comparability between clinical and commercial material remains unresolved despite the opportunities given to address the concerns identified, further details are provided below.

In several rounds of responses during the procedure the applicant provided additional data and clarifications, and multiple re-analyses and adjustments of the dataset (adding/withdrawing data). Some of the points covered by the major objection were considered adequately addressed but many issues remained unresolved. In particular, the post hoc comparability analysis approach in the last two assessment rounds was considered poorly justified and not acceptable.

AS manufacturing processes are not considered comparable, and the FP comparability can therefore not be concluded. This is also reflected in the differences observed in the FP comparability exercise.

In conclusion, multiple quality attributes with high criticality directly impacting the mode of action or which can have an effect on efficacy and safety demonstrate significant variation between the manufacturing processes used during clinical development and the proposed commercial manufacturing process. The underlying differences in the data are not resolved by the applicant's continuous re-analysis of the data. Therefore, considering the extent of differences seen in the batch data for multiple quality attributes of high criticality, the batches from the manufacturing processes used to generate clinical material cannot be considered comparable to the commercial process material.

In conclusion, the clinical trial material is not considered representative of the proposed commercial material.

Characterisation

Following a major objection raised at day 120 on the inadequate information provided in relation to the characterisation of the active substance, the section on elucidation of structure and other characteristics was completely re-written. The new information and data were considered adequate and consequently the major objection was resolved.

The structure and biological properties have been characterised using orthogonal, state-of-the art analytical methods. The intact and total molecular mass was determined, and the amino acid sequence was identified. The presence of C- and N-terminal variants, oxidation, deamidation, isomerisation and glycation was assessed and disulfide structure as well as free sulfhydryl groups were analysed.

Glycoanalysis comprised the identification of the oligosaccharide pattern, N- and O-linked glycosylation and site occupancy. Charge and size variants were identified, and their physicochemical and biological characteristics determined. The higher order structure was evaluated by orthogonal methods. The

biological characterisation included binding (including HER2, FcγRIIIa (V and F), FcγRIIa (R and H), and FcRn) and functional (including proliferation inhibition, ADCC, ADCP) activity covering Fab and Fc related functions of HD201. Structure-function relationship studies on ADCC activity and glycosylation are presented, and this is further addressed in the biosimilarity section below.

Product-related impurities include aggregates, fragments and truncated forms, charge variants and modifications (deamidation, oxidation, isomerisation) and glycosylation such as afucosylation, galactosylation, mannosylation, and sialylation may be generated depending on the media used during production, or in cases of improper storage or handling. Process-related impurities include HCP, residual DNA, residual insulin, endotoxin, antifoam, and residual solvents may be derived from cell substrates, cell culture media or downstream processing (e.g., processing reagents or column leachables).

As demonstrated in the assessment conducted on three commercial batches of HD201, process-related impurities such as residual DNA and insulin are effectively removed after the harvest stage and are not detectable in the subsequent purification steps. Residual solvents including ethanol and acetic acid are removed after CEX-HPLC. HCP and antifoam are removed after AEX-HPLC. Endotoxin is removed after virus filtration. Product-related impurities from these 3 lots were largely unaffected by the downstream purification. Nevertheless, the levels of process- and product-related impurities in these three lots were within the routine release criteria. Likewise, the levels of impurities in all the other HD201 DS lots produced for use in the non-clinical, clinical phase 1, clinical phase 3 and process validation were also within the routine release criteria.

2.3.2.3. Specification

The specifications and test methods for routine release tests of the HD201 active substance include testing for appearance, identity, purity, content, potency, and general tests.

At day 120 a major objection was raised as the proposed specifications were considered inadequate to control the active substance. In response the applicant has made appropriate changes to the active substance specification. Upon request, pharmacopoeial and analytical method references have been included as well.

The revised specifications are considered adequate and consequently the major objection was resolved.

Analytical methods

At day 120 a major objection was raised in view of the inadequate information presented for several of the analytical methods. In response, adequate method descriptions were provided and validation of the (non-compendial) methods in accordance with ICH guidelines was confirmed. Consequently the major objection was considered resolved.

Technology transfer reports for assays performed at different sites are provided.

Batch analysis

Batch analysis data, used in the developmental phase, clinical trial phase and process validation phase of the active substance were provided.

In response to a major objection raised at day 120, the applicant has made adjustments to the batch nomenclature, to ensure it is clear and unambiguous. The major objection was consequently considered adequately resolved.

Reference materials

In the initial dossier submitted, the history of the reference standards used during development was not appropriately described and data ensuring appropriate qualification and storage of the current reference standard was missing. Therefore a major objection was raised. To address this major objection the applicant provided additional information on the current and previously used reference standard lots.

Herceptin is used as the primary reference standard while in-house reference standards are selected from HD201 FP samples. The history of the reference standards used during development has been described. Qualification of the current and future reference standards is presented as well. The proposed testing panel for reference standard qualification is considered sufficient.

Container closure

The container closure systems are considered appropriate for the storage of HD201 AS. The applicant has updated the dossier with additional information on the HD201 AS container closure systems, as requested. Specifications for biological reactivity, physicochemical tests, and sterility testing are provided.

Risk assessment for consumables in HD201 manufacture process and risk assessment for the HD201 AS storage containers are presented. Leachable studies are ongoing with available data up to 12 months. The applicant committed to submitting additional data up to 36 months.

2.3.2.4. Stability

The stability data of process validation batches, clinical trial phase III batches, and clinical trial phase I/non-clinical batches have been included in the dossier. The long-term stability studies for the commercial batches are still on-going.

The presented data supports the proposed shelf-life for the AS stored in the proposed storage conditions.

A stressed stability study for HD201 AS is included in the dossier.

Data from a photostability study have been provided. The changes in the purity profile when comparing AS stored in visible light and in the dark at 25±2°C are considered to be significant. Actions have been taken to prevent light exposure to HD201 AS.

2.3.3. Finished medicinal product

2.3.3.1. Description of the product and Pharmaceutical development

The HD201 finished product (FP) is supplied as a sterile, preservative-free, lyophilised powder in a 20 mL glass vial sealed with a rubber stopper. Each vial of FP contains 150 mg of HD201 AS and is formulated with the same excipients as the EU reference product Herceptin. The finished product is to be reconstituted in 7.2 mL of sterile water to form a single-dose formulation of 25 mg/mL. An overfill of 4% (v/v) during the filling process ensures that the labelled dose of 150 mg can be withdrawn from each vial.

HD201 FP is formulated with L-histidine hydrochloride monohydrate, L-histidine, α, α-trehalose dihydrate and polysorbate 20. All the excipients used in the formulation of HD201 FP comply with Ph. Eur. requirements and were tested according to the general guidelines with quality reference standard in the Ph.Eur. The quality of each of these excipients fulfils the requirements defined in the relevant monograph. Analytical procedures used to test the FP excipients are performed per current compendial

methods, and therefore, validation of the procedure is not required. No excipients of human or animal origin are used in the manufacture of HD201 FP.

The composition of HD201 FP has not changed during the course of development. Formulation studies are presented, and the formulation of HD201 is identical to the reference product. Stability of the commercial formulation has been confirmed. The applicant has investigated the effect of different pH over a 12-day period. Stress studies are presented and discussed.

During the developmental phase of HD201, different manufacturing sites and scales have been employed. An overview of FP batches, manufacturing sites and purpose has been provided.

HD201 FP is manufactured by a conventional process consisting of formulation, filling, stoppering, capping, lyophilisation and packaging. Manufacturing changes and comparability studies are summarised in the comparability section for active substance above. See also the discussion in the active substance section with regard to FP comparability, which remains an outstanding major objection.

The primary packaging materials are in compliance with Ph. Eur, with a nominal capacity of 20 mL. The vials are sealed with a rubber stopper which complies 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. The primary packaging materials are subjected to quality control tests performed at the HD201 FP manufacturing sites. Extractable risk assessment for the rubber stoppers is provided, and quality certificates from the respective primary materials suppliers and a certificate of analysis (CoA) for the quality control tests conducted at the FP manufacturing sites, are included in the dossier. The container closure system is considered to be suitable for storage of HD201 FP.

2.3.3.2. Manufacture of the product and process controls

The intended commercial manufacturing site of HD201 FP is responsible for import of AS, manufacturing of FP, in-process testing, packaging and release of finished product. A valid EU GMP certificate and manufacturer's authorisation, in addition to a QP declaration for the manufacturers of MCB, WCB and AS in South Korea, have been provided. EU GMP certificate and license have been presented for the release testing site of HD201 FP.

The dossier contains tables listing the names, addresses, and responsibilities of all manufacturers.

At the time of submission of the MAA, a second (non-EU) commercial manufacturing site was included. At day 120 a major objection was raised relating to the absence of adequate GMP certification for the non-EU manufacturing and testing sites.

In response to the day 120 List of Questions (LoQ) the applicant decided to withdraw the non-EU site which was missing adequate GMP certification as FP manufacturer. This was not supported as the dossier is based on data (quality and clinical) from FP manufactured at this site, and the withdrawal puts in question the validity of this critical data. It is therefore noteworthy that the HD201 FP used in the clinical trials, has been manufactured at a site which does not hold an EU GMP certificate.

The inclusion of the remaining site as commercial FP manufacturer was considered premature considering the lack of critical data (e.g., validation data) and in the day 120 LoQ the applicant was advised to withdraw this site and resubmit it through a variation application once the necessary data had been generated. Nevertheless, as noted above, the applicant chose to withdraw the non-EU site and maintain the EU site as the commercial manufacturing site for FP. Adequate data to support the intended commercial manufacturing site of HD201 FP has subsequently been provided (see below).

Issues relating to the GMP status for the other non-EU sites have been resolved.

In the FP manufacturing process, AS is diluted with formulation buffer, followed by filling, stoppering, capping, lyophilisation and packaging.

Overall, the manufacturing process is described in sufficient detail. The manufacturing process of HD201 FP is a standard process that includes AS thawing, pooling and mixing, preparation and addition of formulation buffer, filtration, aseptic filling, lyophilisation, and sealing. After packaging, the vials are subjected to QC testing prior to release.

At day 120 a major objection was raised in relation to the absence of an evaluation of the criticality of process parameters and in-process testing as part of the process validation. The justification of acceptance criteria for measured parameters was not provided and there were inconsistencies in the dossier in relation to process parameters and IPCs. In response, the applicant has provided a description of process risk assessment, control strategy, process characterisation, risk assessment of process parameters and overview of critical process parameters and non-critical process parameters. Based on the responses, it can be concluded that all steps of the manufacturing process are continuously monitored through the in-process control (IPC) tests. The applicant has presented IPCs for each process step and associated acceptance criteria. Acceptance criteria for IPC have been justified appropriately with a risk assessment.

Another major objection was raised on the proposed sterilisation process and aseptic manufacturing as their suitability was not considered adequately demonstrated. The validation data for the sterilisation steps was missing and the process description was not considered adequate.

At the time of submission, the process validation was done independently by the two contract manufacturers of HD201 FP. More detailed information for both manufacturing sites, including validation data, was requested at day 120. However, following the withdrawal of the non-EU manufacturing site the process validation report for the non-EU site is no longer included in the dossier.

Process validation for the manufacturing process of HD201 FP at the intended commercial manufacturing site is now completed with three consecutive batches. Overall, the presented documentation on control of critical steps together with the PPQ activity are considered acceptable. Process parameters including holding times are considered to be validated by PPQ runs. Validation of the sterile filtration steps was conducted using viability (bactericidal test), bacterial challenge tests, chemical compatibility tests, and leachable tests. During the sterilisation process there three disposable filter are used and these have been clearly specified. Media fill report for re-validation was provided. The submitted results (sterile filtration validation, leachable test, media fill) confirm process validation.

In view of the responses provided the major objections raised in relation to the finished product manufacture and validation were considered adequately resolved.

During process validation of the lyophilisation step for the second validation batch, several vials had water content higher than the upper specification. The applicant has performed an investigation and has justified why the freeze-drying procedures can nevertheless be considered qualified and why no additional batch data are required to support the validation. The justification can be supported in the light of the root-cause analysis, CAPA plan and the fact that water content is controlled as part of the finished product specification.

The applicant has conducted a transport validation study to support the transport of the FP from the manufacturing site to the distribution centres and warehouses in the EU. However, there are no analytical results presented. Data should be provided to demonstrate that the quality of the product is maintained if transported according to the defined conditions (outstanding issue).

2.3.3.3. Product specification

The finished product release and shelf-life specifications include testing for appearance, identity, purity, content/potency, polysorbate 20, pH, osmolality, water content (for FP powder), endotoxin, sterility, uniformity of dosage units, visible particles and sub-visible particles (after reconstitution).

The test methods and acceptance criteria for HD201 AS and FP have been selected based on general pharmacopoeial requirements as well as specific requirements generated from in-house data from clinical trial batches. Most of the specification criteria are the same as for the AS specifications. The applicant has discussed and justified the specification and acceptance criteria based on lot release data and stability data.

With responses to the Day 120 LoQ, the specifications have been revised.

To address a major objection raised at day 180, a risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with ICH Q3D. Batch analysis data was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

Analytical methods

A summary of each of the analytical procedures used to test the FP is provided in the dossier. The methods used for release and stability testing of FP are mostly the same methods that are used for AS. The compendial methods are conducted in accordance with Ph. Eur. guidelines. Validation reports of analytical procedures used to test the FP, and verification of compendial methods, have been provided.

At day 120 a major objection was raised in relation to the transfer of analytical methods to the EU release testing site. Although the technical transfer of analytical methods had been completed, qualification and analysis of batches for two methods had not been provided and was requested. Following completion of the technical transfer of the analytical methods the requested data was provided and the major objection was considered resolved.

Batch analysis

Three batches of HD201 FP manufactured at the non-EU site and three batches manufactured at the intended commercial manufacturing site have been tested to comply with the established quality specifications. Batch analysis data are provided together with copies of certificates of analysis (CoAs).

Reference materials

Please refer to the AS section as the same reference materials are used for AS and FP.

Container closure

The primary packaging for HD201 FP consists of a 20 mL glass vial with rubber stopper and aluminium cap seal which comply with the Ph. Eur. guidelines. The same vial, rubber stopper and cap are used for all the batches produced.

The primary packaging materials are suitable as containers of HD201 FP. Each site performed their own QC testing of the primary packaging material prior to use. The vial and stopper components are compliant with Ph. Eur. monographs for primary containers and closures. Summaries of QC testing of vials, rubber stoppers, and caps are included in the dossier. Extractable and leachable risk assessment is adequately presented.

2.3.3.4. Stability of the product

Stability programs are in line with ICH Q5C and are performed with a primary packaging equivalent with commercial packaging. Long term studies are run at 5 ± 3°C and accelerated studies at 25 ± 2°C, 60 ± 5% RH.

For non-clinical and clinical phase I batches long term stability data for 36 months and 12 months accelerated stability data are presented. The stability studies for the three clinical phase III batches of HD201 FP manufactured at the non-EU site (commercial scale) are currently ongoing. Long-term stability data are available for up to 24 months. Accelerated stability studies are completed with 6 months data available. For stability batches produced at the proposed commercial manufacturing site 24 months long-term data and 6 months accelerated data are presented. The applicant has trended and discussed the results of the stability data.

The applicant claims that stability of the FP is demonstrated for 24 months at 2-8°C based on real-time data from the proposed commercial manufacturing site and supportive data from clinical batches produced at the non-EU site. This approach is accepted.

Data have been provided to support the proposed in-use conditions as outlined in the SmPC. Stability of the reconstituted product and infusion solution at the declared conditions is considered demonstrated.

2.3.3.5. Adventitious agents

Testing for viral and non-viral adventitious agents of the cell banks and unprocessed bulk harvest identified no adventitious agents. Adequate information is presented regarding the monitoring programme for adventitious agents of the MCB and WCB. Routine monitoring of adventitious virus for each unprocessed bulk harvest will be performed. The examination of adventitious agents in HD201 LIVCA has been conducted and a brief summary of results are provided.

Viral clearance studies for the Phase I and Phase III manufacturing processes are presented. The validity of the performed Phase III viral clearance study for the commercial process is sufficiently justified. The aged resin maintained adequate viral clearance capacity.

2.3.3.6. Biosimilarity

The biosimilarity exercise addressed primary structure, higher order structure, size and molecular variants, charge variants, glycosylation, biological activity and immunochemical properties. Significant concerns have been raised throughout the procedure with regards to the presented biosimilarity exercise. At day 120 a major objection was raised on various aspects of the biosimilarity exercise,

including the design and rationale of the biosimilarity exercise, the limited number of batches included, the data evaluation approach, and the proposed testing panel.

Following several rounds of responses, several of the points raised have been adequately addressed. However, two major objections remain outstanding in relation to the biosimilarity exercise. These relate to structural differences identified and the absence of established structure function relationships in the presented data. Concerns are also raised on the representativeness of the presented Herceptin quality profile. As presented, HD201 is not considered to be similar to EU-licensed Herceptin with respect to the presented biological and physicochemical biosimilarity data. These aspects are discussed below in detail.

The applicant presents a biosimilarity exercise of HD201 AS and FP batches produced using the commercial manufacturing process. The similarity ranges were established for quantitative key quality parameters using data from EU-licensed Herceptin batches. To establish the analytical similarity between HD201 and EU-Herceptin, a 3-tier approach was used. The use of a 3-tier approach is generally acceptable and the criticality assessment of quality attributes is considered satisfactory, however ranges applied are considered too wide. Tier 1 quantitative attributes were assessed by equivalency testing, while Tier 2 and 3 quantitative attributes were assessed by the quality range approach. The Tier 3 quality range is considered too wide. However, graphical comparison may be performed for those attributes. All qualitative attributes were assessed using descriptive raw data and / or graphical comparison to Herceptin regardless of their criticality scoring.

The validation reports for all the analytical methods are presented.

The analytical tests were performed on HD201 FP, originating from different AS batches, to assess their performance against lots of EU-Herceptin for similarity evaluation. Clinically relevant HD201 lots were included, and the EU-Herceptin lots included are considered suitable. The applicant has removed the US Herceptin batches from the biosimilarity exercise and chosen to not include them as supportive data. The biosimilarity exercise addressed primary structure, higher order structure, size and molecular variants, charge variants, glycosylation, biological activity and immunochemical properties.

For all the Tier 1 quality attributes, HD201 is considered statistically equivalent to that of EU-Herceptin. These include critical functional assays for HER2 binding, anti-proliferation and ADCC, as well as FcγRIIa, FcγRIIIa, FcγRIIb and FcγRIIIb binding.

For primary structure of HD201, subunits and amino acid composition were confirmed and verified via LC-MS and Edman degradation N-terminal sequencing. The applicant demonstrates 100% sequence coverage for both heavy and light chain of HD201 and EU-Herceptin, and the issue of incomplete coverage raised during the procedure is considered resolved. Disulphide linkage was confirmed by non-reduced LC-MS. N-glycosylation site was identified using peptide mapping analysis. Molecular weight and isoelectric point (pI) were determined by dynamic light scattering and capillary isoelectric focusing, respectively. The extinction coefficient was determined using UV spectroscopy. The data supports the claim of similarity of primary structure between the HD201 and EU-Herceptin.

N-linked glycan profiling was conducted by UPLC-FLR-MS. The analysis identified that G0F-GN, G0, G0F, Man5, G1, G1', G1F, G1F' and G2F peaks were detected in both HD201 and EU-Herceptin. All the high mannose, afucosylated and galactosylated glycans of HD201 met the similarity acceptance criteria for EU-Herceptin. The N-linked glycan profiling found that the total levels of sialylation and Neu5Ac were much lower in HD201 than those in EU-Herceptin. The Neu5Gc level of all the HD201 lots were within the EU- Herceptin similarity range. It is agreed the low sialylation levels seen (<5%) may have no significant impact on the potency and immunogenicity of HD201. Furthermore, as no difference was identified in ADCC between HD201 and EU-Herceptin it could be agreed that the differences observed in glycan profiles may have no impact on clinical efficacy for trastuzumab. Total mass analysis by LC-

MS show higher relative abundance of G0F(1)/G1F(1) -Lys(2) in some HD201 batches, though no subsequent difference in biological activity is observed.

Higher order structure was assessed using far-UV CD, FT-IR, Near-UV CD, FL and DSC. No significant differences were observed between HD201 and the reference medicinal product. Purity of HD201 has been evaluated by SE-HPLC, CE-SDS and SEC. Lower levels of HMWS and higher levels of monomers are detected in HD201 than in the reference medicinal product. The charge heterogeneity of HD201 was evaluated by CEX-HPLC and IEF. The applicant provided a justification for observed differences in acidic and basic peaks of HD201 in comparison to EU-approved, and similarity is supported by orthogonal assays.

Modifications, including isomerisation deamidation and oxidation were compared. The majority of isomerisation species for HD201 fall outside the range for EU-Herceptin. Differences in Met107, Met 255 and Met 366 oxidation are observed between HD201 and EU-Herceptin. These could impact stability, though no impact on HER2 binding nor FcRn is observed. The applicant implemented continual monitoring of oxidation levels in the aged HD201 batches from different manufacturing batches. If a consistent increase in oxidation level will be observed, corrective actions such as additional monitoring of the oxidation levels in the release tests and stability tests will be implemented.

Though the biological function parameters of HD201 were all similar to those of EU Herceptin following the equivalence testing, it cannot be excluded that the differences in structural attributes observed will impact PK or efficacy. As requested, the applicant has presented a structure function relationship for glycosylation, FcγRIIIa binding and ADCC (PBMC) activity. With the exception of FcγIIIa, the analysis indicated correlation between structural variations and biological function in extended analysis when using HD201 batches for several of the structural attributes in line with expectations established in published literature. However, the applicant is unable to replicate the correlations when analysing the Herceptin and HD201 batches presented in the biosimilarity exercise.

This is not in line with the established literature for Herceptin, where differences in ADCC and FcγRIIIa binding correlate with differences in afucosylation in the presented ranges. This raises significant concerns on the quality profile presented for the reference medicinal product. In response to this concern, the applicant has withdrawn batch data which were out of validated assay range. The approach is poorly explained and is not considered acceptable as the withdrawal of results may introduce a bias in the data. The applicant has further argued that a structure function relationship is absent for some quality attributes within the assessed ranges, with some references to literature. The applicants interpretation of the literature is not supported as the conclusions are contrary to published data[1].

Analysis of hydrophobic variants by RP-HPLC indicate differences in HD201 main peak as well as HB1 variants. Lower main peak purity results for HD201 were attributed to the increase of HB1 variants. HB1 variants were identified as disordered structures which may impact stability of HD201 compared to the reference product, however further functional characterisation of HB1/HB2 variants was not provided. Functional characterisation of HB1 variants of HD201 should be performed and the results should be provided to support the proposed conclusion that no impact on safety or efficacy is expected (outstanding issue).

For batches of Herceptin presented in the biosimilarity analysis, the variability in the data and the wide ranges for several CQAs are unexpected and not in line with the known variability of the reference product. The applicant makes references to the quality drift in quality attributes of the reference

[1] Kim S, Song J, Park S, et al. Drifts in ADCC-related quality attributes of Herceptin: Impact on development of a trastuzumab biosimilar. *MAbs*. 2017;9(4):704-714. doi:10.1080/19420862.2017.1305530

product described in the literature to justify some of the variability. Whereas this is acknowledged, the justification does not address deficiencies in the structure function relationship and the impact on the biosimilarity exercise. The applicant has presented justifications referring to analytical errors and methodological errors identified during an internal investigation and has removed the data from the analysis and recalculated the ranges. Though the explanation is acknowledged, the justification raises concerns of data integrity and reliability. In addition, the revised quality ranges for critical quality parameters including ADCC activity, HER2 binding, anti-proliferation and afucosylation are still considered well outside the range for Herceptin reported in the literature. Therefore, significant concerns remain on the representativeness of the data and the presented biosimilarity exercise. In addition, the applicant claims that EU-Herceptin lots have wider range than HD201 AS lots because three lots of EU-Herceptin were tested close to the expiry date. This is an unsubstantiated claim and not supported.

In conclusion, the presented quality profile of Herceptin is not considered to be representative of the reference medicinal product. Significant concerns have been identified in relation to the presented biosimilarity exercise which preclude a conclusion of biosimilarity between Tuznue/Hervelous and EU-sourced Herceptin. Therefore, the credibility of the presented analytical biosimilarity assessment is questioned and based on the data provided biosimilarity to the reference product cannot be considered established.

2.3.3.7. Post approval change management protocol(s)

Post approval change management protocols (PACMPs) were included in the MAA and covered future QC testing site addition, changes to primary packaging material for the FP, changes to the FP batch size and the lyophilisation process.

Justifications for the proposed changes have been provided. The PACMPs include descriptions of planned testing and evaluation, deliverables are identified, and criteria are defined. Evaluation of comparability of pre-change and post-change FP batches is included in the PPQ protocol. The PACMPs are considered approvable.

2.3.4. Discussion on chemical, and pharmaceutical aspects

HD201 has been developed as a biosimilar product to the reference product, Herceptin (trastuzumab).

At day 120 of the procedure twelve major objections and 135 other concerns on quality aspects were raised by the CHMP. The major objections were raised in relation to missing GMP certificates, manufacturing process, comparability between the clinical and commercial material, characterisation, specifications, batch nomenclature, analytical methods, reference standards, lack of data supporting the proposed second finished product manufacturer, sterilisation process and aseptic manufacturing, and biosimilarity. GMP inspections were also requested for several of the sites involved.

In response to the day 120 LoQ, the applicant provided what could be considered as an entirely new dossier. However, clear responses to the questions were often missing, as well as a confirmation that only changes directly related to the questions have been introduced. A general major objection was raised in this regard at day 180. In addition, a new major objection was raised relating to the absence of a risk evaluation on the potential presence of nitrosamine impurities.

Through multiple rounds of responses several of the major objections raised at day 120 and 180 could be satisfactorily resolved, as discussed in the above sections of this report. However, at the time of opinion three major objections remained unresolved. These relate to the following deficiencies:

- The clinical trial material is not considered representative of the proposed commercial material: Multiple quality attributes with high criticality directly impacting the mode of action or which can have an effect on efficacy, safety, pharmacokinetic and immunogenicity, demonstrate significant variation between the manufacturing processes used during clinical development and the proposed commercial manufacturing process. Therefore, the batches from the different clinical manufacturing processes cannot be considered comparable to the commercial process material.
- Significant concerns identified in the presented biosimilarity exercise preclude a conclusion of biosimilarity between HD201 and EU-sourced Herceptin. The approach taken by the applicant to address the identified concerns by post hoc re-analysis of data, including arbitrary exclusion or inclusion of certain data, is not considered acceptable. It is rather creating uncertainty around the credibility of the results presented and the integrity of the data.
- Data provided on the quality profile for the reference product are not in line with the known quality profile of the reference product (including ADCC activity, HER2 binding, anti-proliferation, afucosylation), creating further uncertainty around the credibility of the results presented and the integrity of the data. Therefore, it cannot be concluded whether the currently presented data ranges fully represent the underlying variability for the reference product.

Therefore, from the quality perspective HD201 is not considered approvable as a biosimilar to its reference product Herceptin.

In addition, as outlined in the sections above, the following other concerns remained outstanding at the time of opinion. It is however noted that the applicant stated during the oral explanation that actions would be taken to address these points:

- Functional characterisation of HB1 variants of HD201 should be performed and the results should be provided.
- The testing frequency for the methionine oxidation test is not considerate adequate and should be extended to testing of FP after 24 months of storage.
- The dossier should be updated to include information on the back-up storage site for cell banks.
- Analytical results of the transport validation study should be presented to demonstrate that the quality of the product is maintained if transported according to the defined conditions.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

In conclusion, based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for Tuznue/Hervelous is currently not approvable from the quality point of view since the unresolved major objections preclude a recommendation for a positive opinion.

The CHMP considers that:

- Multiple quality attributes with high criticality directly impacting the mode of action or which can have an effect on efficacy and safety demonstrate significant variation between the manufacturing processes used during clinical development and the proposed commercial manufacturing process. The underlying differences in the data are not resolved by the applicant's continuous re-analysis of the data. Therefore, considering the extent of differences seen in the batch data for multiple quality attributes of high criticality, the batches from the

manufacturing processes used to generate clinical material cannot be considered comparable to the commercial process material. In conclusion, the clinical trial material is not considered representative of the proposed commercial material.

- Significant concerns have been identified in relation to the presented biosimilarity exercise which preclude a conclusion of biosimilarity between Tuznue/Hervelous and EU-sourced Herceptin. The poor structure-function relationship between ADCC activity, Fc binding and glycosylation, is raising significant concerns on the data presented. In addition, the data indicates decreased stability for the proposed biosimilar in comparison to Herceptin. Some of the data presented outside the validated parameter range of the respective assays have been withdrawn, with questionable exclusion of batches to justify the data. This is creating uncertainty around the credibility of the results presented and the integrity of the data. Furthermore, the presented quality profile of the reference medicinal product is not considered to be representative of the known quality profile of the reference medicinal product. This raises further significant concern on the reliability of the data presented and the overall analytical biosimilarity exercise. Thus, the credibility of the presented analytical biosimilarity assessment is highly questioned and based on the data provided biosimilarity to the reference product cannot be considered established.

2.3.6. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

The non-clinical programme consists of two pharmacodynamics (PD) studies in mice xenograft models, a tissue cross-reactivity study with normal human tissue, single dose pharmacokinetic studies in mice and Cynomolgus monkeys, and a 4-week repeat-dose toxicity study in Cynomolgus monkeys. All studies were done in comparison with Herceptin. Except for single dose PK studies in mice and monkeys, all studies were GLP compliant.

2.4.2. Pharmacology

In vitro assays were conducted in order to address biocomparability between HD201, Herceptin-EU and Herceptin-US (See Quality Aspects).

In vivo studies were conducted in xenograft mice models, comparing the pharmacology of HD201 to Herceptin-EU and Herceptin-US. Further, a tissue cross-reactivity (TCR) study was conducted with normal human tissue, comparing the potential cross-reactivity of HD201 (HD201P-1101) and Herceptin.

Primary pharmacodynamic studies

Two PD studies were conducted in mouse (Balb/c nude) xenograft BT474 breast cancer models to compare anti-tumour effects following twice weekly intravenous (iv) infusions of 2 and 10 µg HD201 (drug substance and drug product). In both studies, all animals were subcutaneously injected with Estradiol on day 1 followed by subcutaneous administration of 200µl of BT474 cells (1 X 10^7

cells/mouse) on day 3 for tumour development. Similar tumour suppressive effects were observed with HD201 drug product and EU-sourced Herceptin. Further, similar suppressive effects were observed between HD201 drug product and Herceptin of non-specified origin.

Study HD201-PHA02-NUM1101

In the first study, HD201 drug substance (HD201 DS, batch number HD201S-1006) was compared to Herceptin lot B1573. After tumour development, animals were treated IP from day 21 with respective drugs at a dose level of 2 and 10 µg/animal twice weekly for 5 to 8 times. Progression of the tumour was determined by measuring the tumour volume twice weekly. Statistical analysis demonstrated comparable and concentration dependent tumour suppression effects after twice weekly dosing of HD201 DS and Herceptin (Table 1, Figure 2).

Table 1: Mean tumour volume from day 21 to day 38 in xenograft mice administered HD201 DS or Herceptin (Study HD201-PHA02-NUM1101)

Test groups	Mean tumour volume (mm^3)		
	Day 21	Day 28	Day 38
Herceptin - B1573 (10 µg)	312.5 ± 27.6	257.8 ± 31.8	160.9 ± 12.3
HD201S-1006 (10 µg)	305.7 ± 18.4	249.5 ± 29.1	157.9 ± 28
Herceptin - B1573 (2 µg)	318.9 ± 23.7	314.5 ± 23.3	259.7 ± 34.1
HD201S-1006 (2 µg)	308.5 ± 24.1	329.1 ± 29.3	264.5 ± 16.1

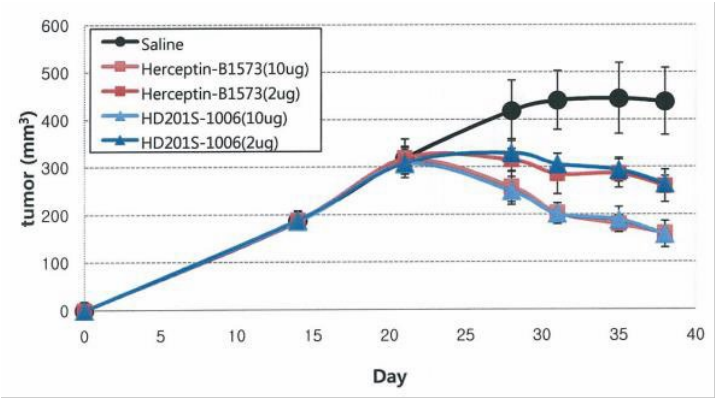


Figure 2: Comparison of tumour growth inhibitory activity of HD201 drug substance (HD201S-1006) and Herceptin (B1573) in breast cancer induced mouse xenograft Model.

Study HD201-PHA02-MBG1101

In the second study, HD201 drug product (HD201 DP, batch number HD201P-1101) was compared to Herceptin lot H0750B01. After tumour development, animals were treated IP from day 7 with respective drugs at a dose level of 2 and 10 ug/animal twice weekly for 8 times. Progression of the tumour was determined by measuring the tumour volume twice weekly. Statistical analysis demonstrated comparable and concentration dependent tumour suppression effects after twice weekly dosing of HD201 DP and Herceptin (Table 2,

Figure 3).

Table 2: Mean tumour volume from day 21 to day 38 in xenograft mice administered HD201 DP or Herceptin (Study HD201-PHA02-MBG1101)

Test groups	Mean tumour volume (mm^3)		
	Day 7	Day 21	Day 32
Herceptin-H0750B01 (10 µg)	205 ± 21.3	144.5 ± 10.4	106.2 ± 9.4
HD201P-1101 (10 µg)	216.5 ± 34.8	146.2 ± 7.9	111.7 ± 7.6
Herceptin-H0750B01 (2 µg)	198 ± 26.2	188 ± 25.8	177.8 ± 14
HD201P-1101 (2 µg)	209.3 ± 33.5	188 ± 25.8	176 ± 17.9

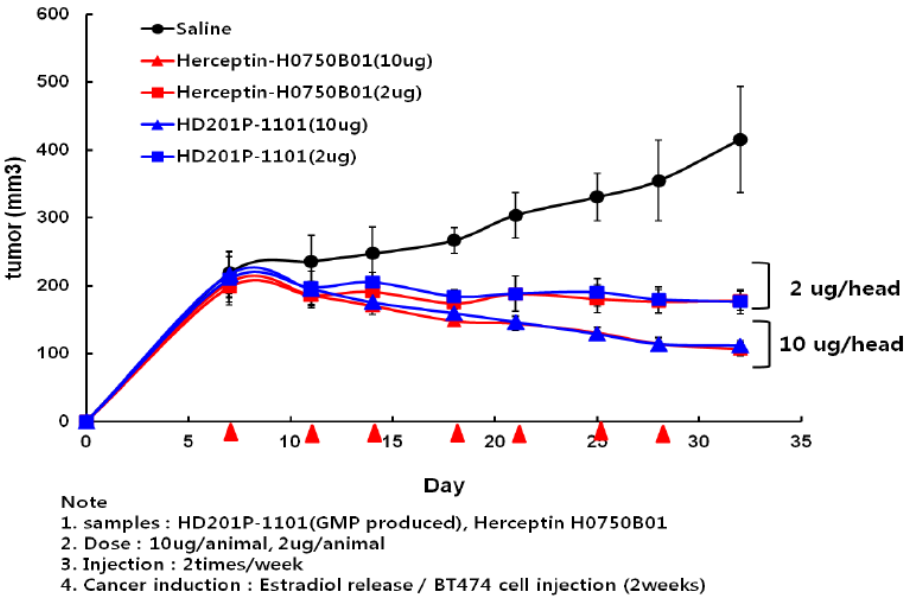


Figure 3: Comparison of tumour growth inhibitory activity of HD201 Drug Product (HD201P-1101) and Herceptin (H0750B01) in breast cancer induced mouse xenograft Model.

Comparability studies have to be conducted with an EU-sourced product. The Herceptin-lot used in study HD201-PHA02-MBG1101 is an EU sourced lot. However, the origin of Herceptin lot B1537 used in study HD201-PHA02-NUM1101 has not been clarified, and the validity of the study is therefore questioned. The studies do, however, indicate comparable pharmacodynamic effects between HD201 and Herceptin in the xenograft models.

Secondary pharmacodynamics

A tissue cross-reactivity study (TCR) of FITC-conjugated HD201 and Herceptin in normal tissues (Study No. 20018560, GLP)

A GLP-compliant tissue cross-reactivity (TCR) study was conducted comparing the potential cross-reactivity of HD201 (HD201P-1101) and EU-Herceptin (H0750B01) in cryosections of normal human tissues from three healthy donors. The study also aimed to determine the cellular localisation of HD201 in a range of normal human tissues and hence identify sites, other than target sites, with which the antibody cross-reacts.

FITC-conjugated test articles were applied at concentrations of 1, 5 and 10 µg/mL. Both HD201-FITC and Herceptin-FITC produced staining of several neural tissue elements. Staining of arachnoid cap cells

and peripheral neural tissues (perineural sheath cells, ganglion, and Schwann cells) was consistent with the expression of HER2 in these tissues. In the placenta, decidual cells were stained with HD201-FITC and Herceptin-FITC, consistent with the expression of HER2. In testis and lung, mesothelium stained with HD201-FITC and Herceptin-FITC; however, no literature was available describing HER2 expression in this tissue. The staining in these tissue elements might represent either a previously unrecognised site of HER2 expression or unexpected tissue cross-reactivity.

Tissue cross-reactivity studies are not considered suitable to detect subtle changes in critical quality attributes and are thus not considered relevant for assessing comparability (EMA/CHMP/BMWP/403543/2010). Safety pharmacology and pharmacodynamics drug interaction studies were not performed.

2.4.3. Pharmacokinetics

Pharmacokinetic properties of HD201 and EU-Herceptin were characterised in mouse and non-human primate models, by validated and GLP-compliant analytical methods.

Methods of analysis

An overview of the analytical methods are presented in Table 3.

Table 3: Analytical methods and validation reports for HD201, Herceptin and ADA formation

Type of Study	Test System	Test Article	Method of Administration	GLP Compliance	Study Number	Testing Facility	CTD Location
Analytical methods and validation							
PK assay validation	NHP (Cyno) serum	Herceptin® (Lot No. B1600B01 and H0750B01 (Czech Republic))	*in vitro*	Yes	999-767	MPI Research Inc. 54943 North Main Street Mattawan, Michigan 49071-8353 USA	Annex 4.2.2.1-1
	NHP (Cyno) serum	HD201 (Lot No. HD201P-1101)	*in vitro*	Yes	1843-009	MPI Research Inc. 54943 North Main Street Mattawan, Michigan 49071-8353 USA	Annex 4.2.2.1-2
	Mouse serum	HD201 (Lot No. HD201P-1001 and HD201S-1002) Herceptin® (Lot No. B1573)	i.v.	No	10-MK-527N-Annex 1	Preclinical Research Center, Chemon Inc. 334, Jeil-ri, Yangji-myeon, Cheoin-gu, Yongin-si, Gyeonggi-do, 449-826, Korea	Annex 4.2.2.1-3
	Mouse serum	HD201 (Lot No. HD201P-1101 and HD201P-1201) Herceptin® 440mg (Lot No. 983303 (San Francisco, USA)) Herceptin® (Lot No. H0901B01 (Mannheim, Germany))	i.v.	Yes	12-MK-327N-Appendix III	Preclinical Research Center, Chemon Inc. 334, Jeil-ri, Yangji-myeon, Cheoin-gu, Yongin-si, Gyeonggi-do, 449-826, Korea	Annex 4.2.2.1-4
Anti-drug antibody assay validation	NHP (Cyno) serum	Herceptin® (Lot No. B1600B01 and H0750B01 (Czech Republic))	*in vitro*	Yes	999-769	MPI Research Inc. 54943 North Main Street Mattawan, Michigan 49071-8353 USA	Annex 4.2.2.1-5
	NHP (Cyno) serum	HD201 (Lot No. HD201P-1101)	*in vitro*	Yes	1843-011	MPI Research Inc. 54943 North Main Street Mattawan, Michigan 49071-8353 USA	Annex 4.2.2.1-6
Neutralizing binding antibody assay validation	NHP (Cyno) serum	HD201 (Lot No. HD201P-1101)	*in vitro*	Yes	1843-010 (Terminated)	MPI Research Inc. 54943 North Main Street Mattawan, Michigan 49071-8353 USA	Annex 4.2.2.1-7
Formulation analysis validation	HPLC-UV	HD201 (Lot No. HD201P-1101) Herceptin® (Lot No. B1600B01)	*in vitro*	Yes	1843-012	MPI Research Inc. 54943 North Main Street Mattawan, Michigan 49071-8353 USA	Annex 4.2.2.1-8

An ELISA method was developed validated to quantify anti-HER2 antibody using Herceptin and HD201 in mouse serum. The analytical method showed acceptable results in terms of linearity, precision and accuracy for both test articles, with CV ≤20% and a recovery range of 80% to 120%. There was no significant effect on the analytical results for up to 3 freeze/thaw cycles.

An electro chemiluminescent ligand binding method was developed and validated for the quantitative measurement of Herceptin and HD201 in cynomolgus monkey serum. The assay demonstrated acceptable accuracy and precision with CV ≤20% and a recovery range of 80% to 120%. Short-term stability was established for at least 4 hours at ambient conditions and freeze/thaw stability up to 3 cycles at -10 to -30°C and -50 to -90°C. Long-term storage stability was established for up to 70 days at -50 to -90°C. The assay had a good range (0.98 to 125 ng/mL) and was highly sensitive with LLOQ of 0.977 ng/mL in neat serum.

A quasi-quantitative immunogenicity method was successfully validated to detect the presence of anti-Herceptin or anti-HD201 antibodies in NHP serum. The corrective factor (CF) were 0.0128 for Herceptin and 0.0141 for HD201. The assay was specific to the respective antibodies. QC low and QC high samples were detected in 0.25 and 2 µg/mL for Herceptin® and 0.5 and 4 µg/mL for HD201

respectively. Anti- Herceptin and anti-HD201 antibodies were stable in serum throughout the duration of freeze/thaw cycles, at ambient conditions for up to 4 hours, at -10 to -30°C and -50 to -90°C for up to 77 days.

A cell based neutralising antibody assay was designed and validated to measure the ability of anti-HD201 antibodies in inhibiting BT-474 cell proliferation. Sponsor supplied method was used for method optimisation but the study was terminated as per the sponsor's request during the method feasibility and development phase due to the absence of anti-HD201 antibodies in the analysed serum samples.

An HPLC-UV assay for HD201 and Herceptin in saline over a concentration range of 0.1 to 25 mg/mL using a multipoint calibration curve was successfully validated. The method was accurate, precise and linear and was specific for the quantification of analyte in vehicle.

Absorption

Single dose pharmacokinetics study of HD201 and Herceptin in ICR mice (study no 10-MK-527N, non-GLP)

The first study in ICR mice was to determine and compare the pharmacokinetic parameters of HD201 and Herceptin and to examine and compare the pharmacokinetic profile and systemic exposure of HD201 and Herceptin in female animals via single i.v. dose administration at 10 mg/kg. Three groups (G1, G2 and G3) of 9 animals each, were administered with the test article HD201 Drug Product (Lot No. HD201P-1001), HD201 Drug Substance (Lot No. HD201S-1002) and Herceptin (B1573) respectively at a dose volume of 5 mL/kg. It was concluded that both HD201 Drug Product and HD201 Drug Substance displayed similar pharmacokinetics profile to the reference drug, Herceptin at 10 mg/kg (see Table 4), although AUC_{last} of HD201 was slightly higher (about 4.0~8.4%) than that of Herceptin.

Table 4: Pharmacokinetic parameters for HD201 and Herceptin in ICR mice after iv dose of 10 mg/kg

Groups	Test Article	Pharmacokinetic parameters			
		AUC_{last} (ng*h/mL)	AUC_{inf} (ng*h/mL)	C_0 (ng/mL)	$T_{1/2}$ (h)
G1	HD201P-1001	33579303	38078953	230792	241
G2	HD201S-1002	32201654	37247603	256359	241
G3	Herceptin-B1573	30964470	34723401	238938	229

Comparative pharmacokinetics assessment of Herceptin® 440 mg, Herceptin® 150 mg and 2 types of HD201 in ICR mouse (study no 12-MK-327N, GLP)

The second study in ICR mice was to examine and compare the pharmacokinetic profiles of US-Herceptin (Lot. 983303, 440 mg/vial), EU-Herceptin (Lot. H0901B01, 150 mg/vial) and two lots of HD201 (HD201P-1101 and HD201P-1201) in female ICR mice via single i.v. dose administration at 10 mg/kg. Four groups (G1, G2, G3 and G4) of 9 animals each were administered with the test articles at a dose volume of 5 mL/kg. It was concluded that the systemic exposure and pharmacokinetic properties of HD201 (HD201P-1101 and HD201P-1201) was similar across the two strengths of Herceptin (440 mg and 150 mg) (Table 5).

Table 5: Mean pharmacokinetic parameters for Herceptin and HD201 in ICR mice after single iv dose of 10 mg/kg

Parameter and units	G1	G2	G3	G4
	US-Herceptin, 440 mg/vial	EU-Herceptin, 150 mg/vial	HD201P-1101	HD201P-1201
$T_{1/2}$ (hr)	229.5 ± 15.0	230.6 ± 1.4	240.4 ± 7.1	256.7 ± 22.5
C_0 (ug/mL)	271.1 ± 23.7	230.0 ± 53.9	267.7 ± 37.5	242.5 ± 27.1
AUC_{last} (hr*ug/mL)	29,069.9 ±1,712.5	27,223.2 ±565.7	28,643.8 ±2,999.2	28,696.1 ±1,353.3
CL (mL/hr/kg)	0.306 ± 0.021	0.324 ± 0.008	0.305 ± 0.031	0.300 ± 0.018

Single dose pharmacokinetics study of HD201 in Cynomolgus monkeys (study no 1843-013, non-GLP)

Female Cynomolgus monkeys weighing between 2-5 kg were used to determine and compare the pharmacokinetic parameters of HD201 and Herceptin via single intravenous infusion. Four groups (G1, G2, G3 and G4) of 3 animals each, were administered with 5 mg/kg/dose and 25 mg/kg/dose of HD201 (Lot No. HD201P-1101) and EU-Herceptin (Lot No. H0750B01) at a dose volume of 10 mL/kg.

The serum concentration data collected at 48 hours post-dose in all dose groups was anomalous, possibly due to sample switching/processing error. Thus, the anomalous 48 hours post-dose data were excluded from the PK analysis and interpretation. The serum concentration profile and pharmacokinetic parameters of HD201 and Herceptin were considered similar after dose administration of 5 and 25 mg/kg. Systemic exposure ($AUC_{0-\infty}$ and AUC_{0-720}) increased in proportion to dose between 5 and 25 mg/kg for both test compounds (Table 6).

Table 6: Mean (±SD) pharmacokinetic parameters for Herceptin and HD201 in female monkeys after a single iv dose

PK Parameter	Dose groups			
	Herceptin, 5 mg/kg	**Herceptin, 25 mg/kg**	**HD201, 5 mg/kg**	**HD201, 25 mg/kg**
$AUC_{0-\infty}$ (hr*µg/mL)	31400± 6020	198000±60900	32300±6160	181000±74200
AUC_{0-720} (hr*µg/mL)	30700±5750	173000±41800	30500±5220	156000±46200
CL (mL/min/kg)	0.00271±0.000508	0.00229±0.000857	0.00264±0.000453	0.00261±0.00114
$T_{1/2}$ (hr)	114±7.43	211±88.7	168±35.6	203±169
V_{ss} (mL/kg)	33.6±4.56	39.1±1.55	38.1±4.49	40.7±7.92

In mice, similar PK parameters (C_{max}, AUC, $T_{1/2}$ and CL) were observed following single iv administrations of HD201, EU-Herceptin and US-Herceptin at 10 µg/kg.

In Cynomolgus monkeys, serum concentration data obtained 48 hours post-dose were anomalous across the groups and were therefore excluded from further analysis. Following this exercise, serum concentration profile and pharmacokinetic parameters (C_{max}, AUC, $T_{1/2}$, CL and V_{ss}) of HD201 and EU-Herceptin were considered similar after dose administration of 5 and 25 mg/kg.

Studies on distribution, metabolism and excretion were not performed.

2.4.4. Toxicology

No single dose toxicity studies were performed. The lack of single-dose toxicity studies is considered acceptable.

A 4-week intravenous toxicity study on HD201 and Herceptin in cynomolgus monkeys with a 4-week recover period (study no 1843-014, GLP)

A 4-week GLP compliant intravenous dose toxicity study was conducted in order to compare toxicity, pharmacodynamics, toxicokinetics and immunogenic response of HD201 (lot no HD201P-1101) and EU-Herceptin (lot no H0750B01).

Herceptin and HD201 were administered to female cynomolgus monkeys at a dose level of 0, 5, or 25 mg/kg/dose and a dose volume of 10 mL/kg for all groups. Drugs were administered weekly for 4 consecutive weeks via 1-hour intravenous infusion. Following the treatment period, two animals in

each group treated with vehicle, Herceptin 25 mg/kg and HD201 25 mg/kg were maintained for a 4-week recovery period.

Evaluated parameters included clinical observations, body temperatures, body weight, food consumption, indirect blood pressures, ophthalmoscopic examinations, ECG, haematology, coagulation, clinical chemistry, urinalysis parameters, macroscopic evaluations and organ weights. Blood samples for serum concentration analysis and TK evaluation were collected at pre-dose, and approximately at 0.25, 0.5, 2, 6, 12, 24, 48, 72, 96, 144 and 168 hours post dose on Day 1, 15 and 22. Blood samples for immunology evaluations were collected during pre-test and prior to the terminal and recovery necropsy.

There was no HD201- or Herceptin-related effects or toxicity on clinical observations, body temperatures, body weight, food consumption, indirect blood pressures, ophthalmoscopic examinations, ECG, haematology, coagulation, clinical chemistry, urinalysis parameters, macroscopic evaluations and organ weights. Test article-related microscopic findings were limited to the injection site. Changes were more pronounced in the Herceptin-treated animals; however, following the recovery period, the incidence and/or severity of the changes was reduced indicating reversibility. No Herceptin or HD201 related changes were observed in the relative percentage or absolute cell counts of lymphocyte, monocyte, mature T cell, CD4+ T cell, CD 8+ T Cell, B cell, and NK cell populations. Systemic exposure increased in proportion to dose between 5 and 25 mg/kg/dose for both compounds, and systemic exposure to Herceptin and HD201 was similar on Day 1 and Day 22 (Table 7).

Table 7: Mean (± SD) toxicokinetic parameters for Herceptin and HD201 in female Cynomolgus monkeys after weekly intravenous doses

	Day 1				Day 22			
	Herceptin		HD201		Herceptin		HD201	
	5 mg/kg	25 mg/kg	5 mg/kg	25 mg/kg	5 mg/kg	25 mg/kg	5 mg/kg	25 mg/kg
$AUC_{0-\infty}$ (hr· µg/mL)	21600 ±7460	134000 ±33500	14800 ±5580	109000 ±12400	NA	NA	NA	NA
AUC_{0-168} (hr·µg/mL)	12100 ±2210	61100 ±8060	9610 ±2090	61300 ±4700	29500 ±4340	144000 ±33200	24600 ±10500	156000 ±25900
CL (mL/min/kg)	0.00423 ±0.00147	0.00327 ±0.000792	0.00651 ±0.00313	0.00386 ±0.000508	0.00129 ±0.000590	0.00135 ±0.000464	0.00269[a]	0.00146 ±0.000589
$T_{1/2}$ (hr)	128 ±32.3	190 ±75.4	103 ±39.1	135 ±23.0	233 ±117	205 ±47.8	80.2[a]	163 ±116
V_{ss} (mL/kg)	45.1 ±4.84	50.8 ±10.8	50.7 ±2.47	45.2 ±4.73	21.6 ±3.18	23.0 ±5.27	22.3[a]	19.1 ±5.14
Accumulation ratio[b]	NA	NA	NA	NA	1.45 ±0.337	1.11 ±0.344	1.65 ±0.225	1.50 ±0.386

NA – not applicable
b: AUC0-168 on Day 22/AUC0-∞ on Day 1.
a: Where no SD is given, the mean comprises fewer than 3 observations.

Based on these findings, there were no apparent differences detected in toxicity, toxicokinetic, or immunogenic response between non-human primates receiving Herceptin and HD201 at 5 and 25 mg/kg/dose.

Immunogenicity of HD201 and EU-Herceptin was assessed as part of the 4-week toxicology study in monkeys (study no 1843-014). Blood samples were collected from the femoral vein of all animals

during pre-test, prior to terminal and recovery necropsies for determining the presence of anti-drug (HD201 or Herceptin) antibody level.

In all Herceptin-treated animals, anti-Herceptin antibodies were absent during pre-test, terminal and recovery collections, with the exception of weak positive signals in a single control and a single 25 mg/kg/dose Herceptin animal at the recovery collection. The positive response for the control animal was thought to be non-specific since this animal was not exposed to Herceptin; however, the positive response for 25 mg/kg/dose Herceptin animal was thought to be test article related. It was concluded that high concentration of circulating Herceptin could be masking the detection of anti-drug antibodies at the recovery collection.

In the control group animals, anti-HD201 antibodies were absent throughout the pre-test, terminal, and recovery collections. One of the animals in HD201 group with 5 mg/kg/dose exhibited presence of anti-HD201 antibodies prior to HD201 administration. Another animal in HD201 group with 25 mg/kg/dose showed presence of anti-HD201 antibodies during pre-test, terminal and recovery collections. As these animals showed positive response prior to HD201 administration, the terminal and recovery positive responses were not likely due to HD201 exposure. The non-specific nature of antibody response of the latter animal were also supported by the fact that the response remained positive even in the presence of approximately 857 µg/mL circulating levels of HD201 as measured at 168 hours post Day 22 dose administration. This concentration of HD201 exceeds the drug tolerance limit of immunoassay which was determined to be 4 µg/mL HD201 for QC high samples and 0.5 µg/mL HD201 for QC low samples during assay validation.

Except for the mentioned animals, the remaining animals in the 5 mg/kg/dose and 25 mg/kg/dose did not exhibit any anti-HD201 antibodies during pre-test, terminal or recovery sampling, and thus there was no difference in immunogenicity response between HD201 and Herceptin.

Overall, there were no apparent differences in clinical observations, body temperatures, body weight, food consumption, indirect blood pressures, ophthalmoscopic examinations, ECG, haematology, coagulation, clinical chemistry, urinalysis parameters, macroscopic evaluations or organ weights between non-human primates receiving Herceptin or HD201 at 5 and 25 mg/kg/dose. Findings in monkeys indicate low levels of immunogenicity, and there was no apparent difference in immunogenicity response between HD201 and Herceptin following repeated dosing for 4 weeks.

Local tolerance endpoints were incorporated in the repeat-dose toxicity study. Similar, reversible macroscopic and microscopic findings were observed in both treatment groups, although somewhat more pronounced in the Herceptin groups.

Studies on genotoxicity, carcinogenicity, and reproduction and developmental toxicity were not conducted.

2.4.5. Ecotoxicity/environmental risk assessment

HD201 is a monoclonal antibody, unlikely to pose a significant risk to the environment. Environmental risk assessment studies are therefore not required, in accordance with EMEA/CHMP/SWP/4447/00.

2.4.6. Discussion on non-clinical aspects

As indicated in Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), a stepwise approach should be applied when evaluating non-clinical biosimilarity. Step 1 comprises a number of comparative *in vitro* studies. As the *in vitro* assays may be more specific and sensitive than studies in animals, these assays

are considered paramount in the nonclinical comparability exercise. Based on the *in vitro* assay findings, a decision should then be made as to the extent of what, if any, *in vivo* work will be required.

Following assessment of the applicant's response to D180 LoQ, there were remaining MOs concerning the in vitro comparability and biosimilarity exercises.

Repeated dose toxicity studies in non-human primates is usually not recommended for similar biological products (EMA/CHMP/BMWP/403543/2010). However, the 4-week comparative toxicity study in monkeys was performed according to relevant guidelines that applied at that time. Tissue cross-reactivity studies are not considered suitable to detect subtle changes in critical quality attributes and are thus not considered relevant for assessing comparability (EMA/CHMP/BMWP/403543/2010).

The drug substance and drug product lots of HD201 used for the non-clinical *in vivo* studies were produced during the early developmental phase (PI). However, no data have been provided to confirm that the PI-batches are representative for the product intended for marketing. Thus, the *in vivo* studies conducted with these early lots of HD201 cannot be considered clinically relevant.

2.4.7. Conclusion on the non-clinical aspects

As *in vitro* assays are considered more specific and sensitive than in vivo studies, the biocomparability assays are considered paramount in the nonclinical comparability exercise for HD201. The CHMP considered that non-clinical *in vivo* studies provided by the applicant are not sufficient to overcome several unresolved MOs concerning the in vitro comparability and biosimilarity exercises.

2.5. Clinical aspects

2.5.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. Further to the GCP inspection integrated report (GCP/2021/004) for the phase III TROIKA study, a new clinical study report had to be issued excluding patients from clinical sites where there were critical findings.

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. However, the requested outcomes of the GCP inspections of the investigator that performed the TROIKA-1 study were not submitted (**OC**).

- **Tabular overview of clinical studies**

Study phase	Study code EudraCT	Dose	Study title	Number of subjects/ patients	Study period
Phase I	EAGLE-I-12 2012-000805-56	6 mg/kg single dose	A Phase I, Double-blind, Randomised, Parallel Group Study to Demonstrate the Equivalent Pharmacokinetic Properties of a Single Intravenous Dose of HD201	73	21 Nov 2012 to 01 Feb 2014

Study phase	Study code EudraCT	Dose	Study title	Number of subjects/ patients	Study period
			and Herceptin in Healthy Male Subjects		
Phase III	TROIKA 2016-004019-11	8 mg/kg bolus followed by 6 mg/kg every 3 weeks in combination with chemotherapy	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	503	19 Feb 2018 to 13 Jan 2022
Phase I	TROIKA-1 2018-004776-36	6 mg/kg single dose	A Double-blind, Randomized, Parallel Group Study to Demonstrate the Equivalent Pharmacokinetic Properties of a Single Intravenous Dose of HD201 Versus EU-Herceptin and US-Herceptin, in Healthy Male Subjects	105	09 April 2019 to 16 Sep 2019

2.5.2. Clinical Pharmacology

2.5.2.1. Pharmacokinetics

Two clinical studies were submitted with the initial application to support PK similarity between HD201 and Herceptin: One pivotal phase I study (EAGLE-I-12), and a phase III study (TROIKA) where PK was a secondary endpoint. During the procedure (On Day 121), another phase I study (TROIKA-1) was submitted. TROIKA-1 is now considered to be the pivotal PK study, and the EAGLE-I-12 study is considered to be supportive.

Analytical methods

EAGLE-I-12

The quantitative ELISA method for the determination of HD201 or trastuzumab in human serum for the supportive phase I study EAGLE-I-12 was validated and demonstrated to be suitable for the analysis of human serum samples in the calibration range of 2-70 ug/ml with a MRD of 1:1000. The samples are stable for up to 440 days at -20°C±10°C and at <-65°C. Stability of HD201 and trastuzumab in human whole blood was also established for up to 24 hours at room temperature.

An immunoassay method was acceptably validated for the detection of anti-trastuzumab antibodies in human serum using an Electrochemiluminescent (ECLA) methodology, utilising MSD (Meso-Scale Discovery) technology.

The cell-based antibody-dependent cell-mediated cytotoxicity (ADCC) method for the detection of neutralizing anti-HD201 or anti-trastuzumab antibodies in human serum has been validated using a human anti- trastuzumab antibody as the positive control.

TROIKA

For the phase III bioanalytical validation for the detection of anti-herceptin antibodies (trastuzumab) in human female serum, the presented validation met the pre-set acceptance criteria and this assay can be considered suitable for its intended use of detection of anti- trastuzumab in female human serum.

The method has been re-validated based on current guidelines. After re-validation of the adjusted ADA method all ADA samples were re-analysed. All final subject ADA data have been obtained using a new method ALM-425 and the TROIKA CSR has been updated with the new analytical results from the ALM-425 method.

TROIKA-1

The analytical methods used to determine trastuzumab and anti-HD201/ anti-trastuzumab antibodies (ADA) were the same as those used in the previously submitted study TROIKA:

In order to determine and quantify the amount of HD201 and trastuzumab reference product in human serum samples, validation studies were conducted using an enzyme linked immunosorbent assay (ELISA) method. For the detection of anti-HD201/ anti-trastuzumab antibodies (ADA) in human serum samples, method validation was performed using an electrochemiluminescent (ECLA) method. Cut point of anti-HD201/ anti-trastuzumab antibodies was also determined by analysing drug-naïve samples from subjects through box-plot method.

An overview and summary of the bioanalytical studies that were carried out across the various phases are listed in the clinical summary (below).

- **Tabular summary of the bioanalytical studies**

Sl #	Analytical Lab	Project number/code/Job number	Study type	Study title	Studies involved	Module section
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	Module 5.3.1.4, Annex 5314-1
2	ICON	2548/003b (500702)	Long term stability	Long term stability report for the determination of HD201 or trastuzumab in human serum by ELISA	EAGLE-I-12	Module 5.3.1.4, Annex 5314-2
3	ICON	2548/003c (500703)	ADA method validation	Validation for the detection of anti-HD201 or anti-trastuzumab antibodies in human serum by an electrochemiluminescent assay (ECLA)	EAGLE-I-12	Module 5.3.1.4, Annex 5314-4
4	ICON	2548/003d (500705)	NAb method validation	Validation for the detection of neutralizing anti-HD201 or anti-trastuzumab antibodies in human serum by a cell based ADCC assay	EAGLE-I-12	Module 5.3.1.4, Annex 5314-6
5	ICON	2548/003f (500773)	PK-Sample analysis report (Bioanalytical report)	PK immunoassay sample analysis report for the determination of HD201 or trastuzumab (Herceptin) in human serum by quantitative ELISA	EAGLE-I-12	Module 5.3.1.4, Eagle-pkimmunoassay-elisa
6	ICON	2548/003g (500704)	ADA-Sample analysis report (Bioanalytical report)	Immunoassay sample analysis report for the detection of anti-HD201 or anti-trastuzumab (Herceptin) antibodies in human serum by electrochemiluminescent assay (ECLA)	EAGLE-I-12	Module 5.3.1.4, Eagle-immnuoassayrep-ecla
7	AGILEX	VAL322	PK-Method transfer validation	Validation of a method transfer for the detection of trastuzumab in human serum	TROIKA and TROIKA-1	Module 5.3.1.4, Annex 5314-7
8	AGILEX	VAL322	Report Addendum 01	Validation of a method transfer for the detection of trastuzumab in human serum	TROIKA and TROIKA-1	Module 5.3.1.4, Report Pk-validation Val322-Addendum 01
9	AGILEX	VAL322	Report Addendum 02	Validation of a method transfer for the detection of trastuzumab in human serum	TROIKA and TROIKA-1	Module 5.3.1.4, Report Pk-validation Val322-Addendum 02
10	AGILEX	VAL323 (Old method)	ADA method validation	Validation of an electrochemiluminescent method for the detection of anti-Herceptin antibodies in human serum	TROIKA and TROIKA-1	Module 5.3.1.4, Annex 5314-8
11	AGILEX	VAL323 (Old method)	Report Addendum 01	Validation of an electrochemiluminescent method for the detection of anti-Herceptin antibodies in human serum	TROIKA and TROIKA-1	Module 5.3.1.4, Report ADA-validation Val323-Addendum 01
12	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	Module 5.3.1.4, Report ADA-validation Val425
13	AGILEX	GAY	Bioanalytical report (PK and ADA)	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	TROIKA	Module 5.3.1.4, Report Bioanalytical GAY
14	AGILEX	GCC	Bioanalytical report (PK and ADA)	Double-blind, randomised, parallel group study to demonstrate the equivalent pharmacokinetic properties of a single intravenous dose of HD201 versus EU-Herceptin and US-Herceptin in healthy male	TROIKA-1	Module 5.3.1.4, Report Bioanalytical GCC
15	AGILEX	GCC	Report Amendment 01	Double-blind, randomised, parallel group study to demonstrate the equivalent pharmacokinetic properties of a single intravenous dose of HD201 versus EU-Herceptin and US-Herceptin in healthy male	TROIKA-1	Module 5.3.1.4, Report Bioanalytical GCC-Amendment 01
16	CAI	GLP19001	NAb partial method validation	Method validation-Detection of neutralizing anti-trastuzumab antibodies in human serum by a cell based ADCC assay	TROIKA	Module 5.3.1.4, Report Nab-validation GLP19001
17	CAI	GLP20004	NAb sample analysis report	Sample analysis report for detection of neutralizing anti-trastuzumab antibodies in human serum by a cell based ADCC assay	TROIKA	Module 5.3.1.4, Report Bioanalytical GLP20004

CAI: Cell Assay Innovations

Determination of trastuzumab in human serum by ELISA:

Partial validation has been presented for the method transfer from ICON (EAGLE-I-12) to AGILEX (TROIKA-1) for the determination of trastuzumab in human serum. The results are summarised below.

Bioanalytical Lab	AGILEX		
Project Code	VAL322		
Matrix	Human serum		
Analyte	HD201	EU-Herceptin	
Batch/Lot No.	HD201-17001, conc.: 21mg/mL	N3006H02, conc.: 21mg/mL	
Technique	ELISA method read on Spectramax Paradigm Plate Reader		
Sample Assay Volume	10 µL		
Minimum Required Dilution (MRD)	1 in 1000		
Calibration Range	1.00 µg/ml to 100 µg/ml. Anchor points: 1.00 µg/ml and 100µg/ml. LLOQ = 2.00 µg/ml, ULOQ 70.0 µg/ml		
Calibration Fit	4PL with no weighting (concentrations vs. mean ODs)		
Inter - Assay	Precision (% CV)	Between 5.2 and 9.0% (n=12)	Between 3.5 and 11.8% (ULOQ and LLOQ n=12, QCH, QCM and QCL n=16)
	Accuracy (% Bias)	Between -6.4 and -2.5% (n=12)	Between -6.0 and -1.6% (ULOQ and LLOQ n=12, QCH, QCM and QCL n=16)
	Total Error	Between 7.7 and 14.8% (n=12)	Between 7.5 and 17.8% (ULOQ and LLOQ n=12, QCH, QCM and QCL n=16)
Intra - Assay	Precision (% CV)	Between 3.5 and 9.4% (n=6)	Between 2.7 and 9.1% (n=6)
	Accuracy (% Bias)	Between -9.0 and 0.9% (n=6)	Between -2.4 and 2.0% (n=6)
	Total Error	Between 4.0 and 16.5% (n=6)	Between 5.0 and 9.7% (n=6)
Selectivity and Specificity	Healthy	12 out of 12 sera samples non-spiked were BLQ {<LLOQ) 6 out of 6 sera samples spiked at LLOQ with HD201 and 4 out of 6 sera samples spiked at LLOQ with EU-Herceptin met criteria. Overall 10/12 met criteria (83.3%)	
	Haemolysed (approx 275mg/dL)	Individual non-spiked was BLQ {<LLOQ) Individual spiked to LLOQ with HD201 or EU-Herceptin met criteria	
	Lipaemic	Individual non-spiked was BLQ {<LLOQ) Individual spiked to LLOQ with HD201 or EU-Herceptin met criteria	
	Diseased State (Breast Cancer HER2 positive)	9 out of 10 sera samples non-spiked were BLQ (<LLOQ) 5 out of 5 sera samples spiked at LLOQ with HD201 and 4 out of 5 sera samples spiked at LLOQ with EU-Herceptin met criteria. Overall 9/10 met criteria (90%)	
Batch Size	31 samples in duplicate per plate		
Dilutional Integrity#	No prozone effect observed. Maximum acceptable dilution for study samples in 1 in 2500 in Sample Dilution Buffer after 1000 MRD		

In conclusion, 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) and precision and accuracy for all parameters passed the tested set criteria successfully.

Long-term stability was determined and provided as an addendum to the bioanalytical validation report.

Project Code		VAL322 (Addendun 02)		
Analyte		HD201	EU-Herceptin	US-Herceptin
Batch/Lot No.		HD201-18002-1, conc.: 21.0mg/mL	N3006H02, conc.: 21mg/mL	3268203, conc.:21.0mg/mL
Stability	Long Term Stability:	Up to 189 days at nominal -20°C* (*study is ongoing*)	Up to 175 days at nominal -20°C* (*study is ongoing*)	Not assessed
		Up to 635 days at nominal -80°C	Up to 635 days at nominal -80°C	Not assessed
	Stock Stability (in Water)	Up to 319 days at nominal -80°C	Up to 641 days at nominal -80°C	Up to 513 days at nominal -80°C

^ - As per conclusion of the validation conducted at ICON Labs (Project Number 2548/003a & 2548/003b, a single assay was considered suitable for quantification of all three analytes. Therefore, stability data generated with Biosimilar analyte is considered valid for the other two drugs, wherever not assessed
* - LTS assessment on-going

Determination of HD201 or trastuzumab ADA using electrochemiluminescent methodology:

The validated analytical method ALM-425 was used for anti-drug antibodies detection in Agilex. The validation results VAL-425 are summarised below:

Category	Details				
Bioanalytical laboratory	AGILEX				
Project code	VAL425				
Matrix	Human serum (healthy and disease state)				
Analyte	Anti-trastuzumab (Lot no: 1807)				
Technique	PandA format				
Sample volume	10 µL				
MRD	1 in 25-fold				
Batch size	48 in duplicate, including samples and controls				
Relative assay sensitivity (ng/mL)	15.6				
PC concentrations (ng/mL)	**LPC**	**MPC (Validation studies only)**	**HPC**		
	37.0	100	5000		
Screening/titre cut point assessment methodology	Data was log transformed, cut point is multiplicative				
Screening cut point NF	1.17				
Titre cut point normalisation factor (TNF)	1.25				
Confirmation cut point(s)	**HD201**	**EU-Herceptin**		**US-Herceptin**	
	20.6%	20.1%		20.3%	
Control acceptance limits (NC: RLU, PCs: S/N)	**Control**	**Lower Limit**		**Upper Limit**	
	NC	NA		118	
	LPC	1.49		2.48	
	MPC	2.27		5.64	
	HPC	97.6		238	
Screening assay precision (NC: RLU, PCs: S/N)		**Inter-assay precision**		**Intra-assay precision[$]**	
	Control	%CV	n	%CV	n

Category	Details				
	NC	12.3	68	7.2	6
	LPC	9.8	68	6.3	6
	MPC	16.5	64	8.2	6
	HPC	16.3	68	18.0	6
Confirmatory assay precision (HD201) (NC: RLU, PCs: S/N)		Inter-assay precision		Intra-assay precision	
	Control	%CV	n	%CV	n
	NC	13.2	55	5.3	6
	LPC	9.0	18	6.7	6
	MPC	5.4	18	2.4	6
	HPC	0.1	18	0.0	6
Confirmatory assay precision (EU-Herceptin) (NC: RLU, PCs: S/N)		Inter-assay precision		Intra-assay precision	
	Control	%CV	n	%CV	n
	NC	8.3	55	8.5	6
	LPC	7.7	18	6.4	6
	MPC	5.3	18	1.8	6
	HPC	0.1	18	0.0	6
Confirmatory assay precision (US-Herceptin) (NC: RLU, PCs: S/N)		Inter-assay precision		Intra-assay precision	
	Control	%CV	n	%CV	n
	NC	10.8	55	4.0	6
	LPC	9.6	18	3.8	6
	MPC	5.9	18	1.6	6
	HPC	0.1	18	0.2	6
Titre assay precision	Inter-assay precision		Intra-assay precision		
	% CV	n	% CV	n	
	27.7	36	0.0	6	
Titre dilution scheme	Dilution factors assessed were 1 in 2				
Drug tolerance	Drug	ADA concentration (ng/mL)		Drug concentration (µg/mL)	
	HD201	37.0		250	
	EU-Herceptin	37.0		250	
	US-Herceptin	37.0		250	
Selectivity and specificity	Individuals meeting acceptance criteria				
	Assay	Level	Disease state individuals	Normal haemolysed	Normal lipaemic
	Screening	Blank	7/10[X1]	0/1[X1]	1/1
		LPC	10/10	1/1	1/1
		HPC	10/10	1/1	1/1
Stabilities	Freeze thaw cycles (nominal -80°C to RT°)		Short-term stability (RT°)		
	15		24 hrs 28 mins		
HER2 interference	37.0 ng/mL of ADA was detectable even in the presence of 200 µg/mL of interfering agent				

$ = Highest values reported among 3 drugs for intra-assay precision
^ = Out of targeted acceptance criteria, no notable impact.
X1 = Acceptance criteria not met: haemolysed sample (unspiked and 30% individual samples (unspiked) positive in the screening assay.

The quantitative ELISA method for the determination of HD201 and trastuzumab reference in human serum, performed at the Agilex analytical site, was partly validated and demonstrated to be precise and accurate for the analysis of human serum samples in the calibration range (LLOQ to ULOQ) of 2-70 ug/ml with a MRD of 1:1000. Overall, the samples are stable for up to 189 days (HD201)/175 days (EU-Herceptin) at -20°C±10°C and 635 days at <-80°C.

The electrochemiluminescent methodology for the determination of HD201 or trastuzumab ADA in human serum, as performed at the Agilex analytical site, was partly validated and demonstrated to be precise and accurate.

Studies

In the phase I studies (TROIKA-1 and EAGLE-I-12), $AUC_{0\text{-}inf}$ was considered the primary endpoint. Equivalence was concluded if the 90% CI for the ratio of geometric means of test product/reference product was completely contained within the acceptance interval of 0.8 to 1.25. C_{max}, $AUC_{0\text{-}t}$, $t_{½}$, C_L and V_d were regarded as secondary endpoints. In the phase III study (TROIKA) trough serum concentrations at pre-dose of Cycles 5 and 8 were initially recorded. Based on a request on Day 120, C_{trough} was additionally determined at pre-dose of cycles 10 and 14 using available stored samples. Equivalence for C_{trough} was concluded if these 90% CIs were completely within the acceptance interval of -20% to 20%. The number and percentage of subjects with C_{trough} concentration of at least 20 µg/mL at pre-dose were summarised by treatment group and cycle.

TROIKA-1 (pivotal phase 1 PK study, submitted on Day 121)

Mean (±SD) trastuzumab serum concentration-time profiles by treatment group are presented in Figure 7 below:

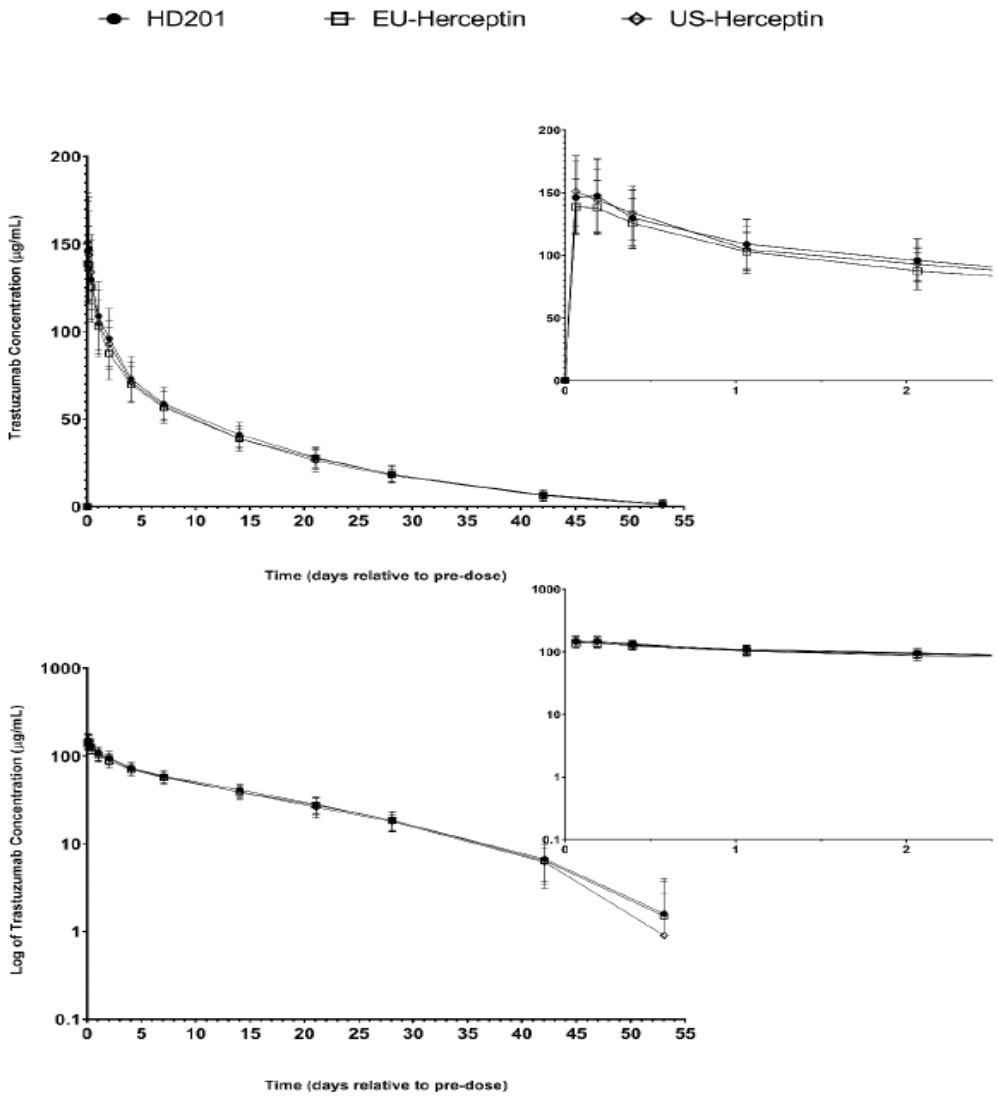


Figure 4: Mean (+SD) trastuzumab serum concentration-time profiles

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.

Summary of trastuzumab serum PK parameters by treatment group are presented in Table 8 below.

Table 8: 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.

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 $AUC_{0\text{-}inf}$. This indicates that the applied sampling schedule ensured the majority of AUC was captured and the range of times across which K_{el}

was estimated was greater than twice the resultant $T_{1/2el}$. All summarised PK parameters were therefore considered to be reliably estimated.

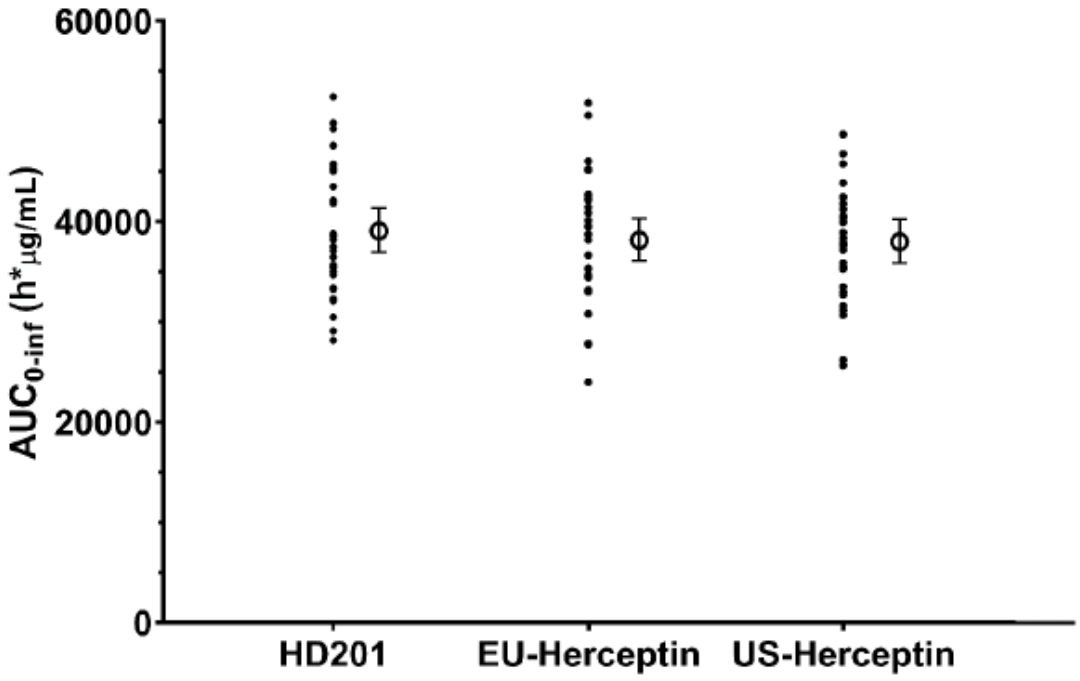
Overall, systemic exposure, based on $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} after administration of HD201, EU-Herceptin, or US-Herceptin was similar.

The inter-subject variability based on $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}last}$, was characterised by a geometric CV ranging from 15.3% to 17.6%. For C_{max} 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%).

The $T_{1/2el}$ was similar across treatments with mean half-life of 234 h, 243 h, and 238 h after administration of HD201, EU-Herceptin, and US-Herceptin respectively.

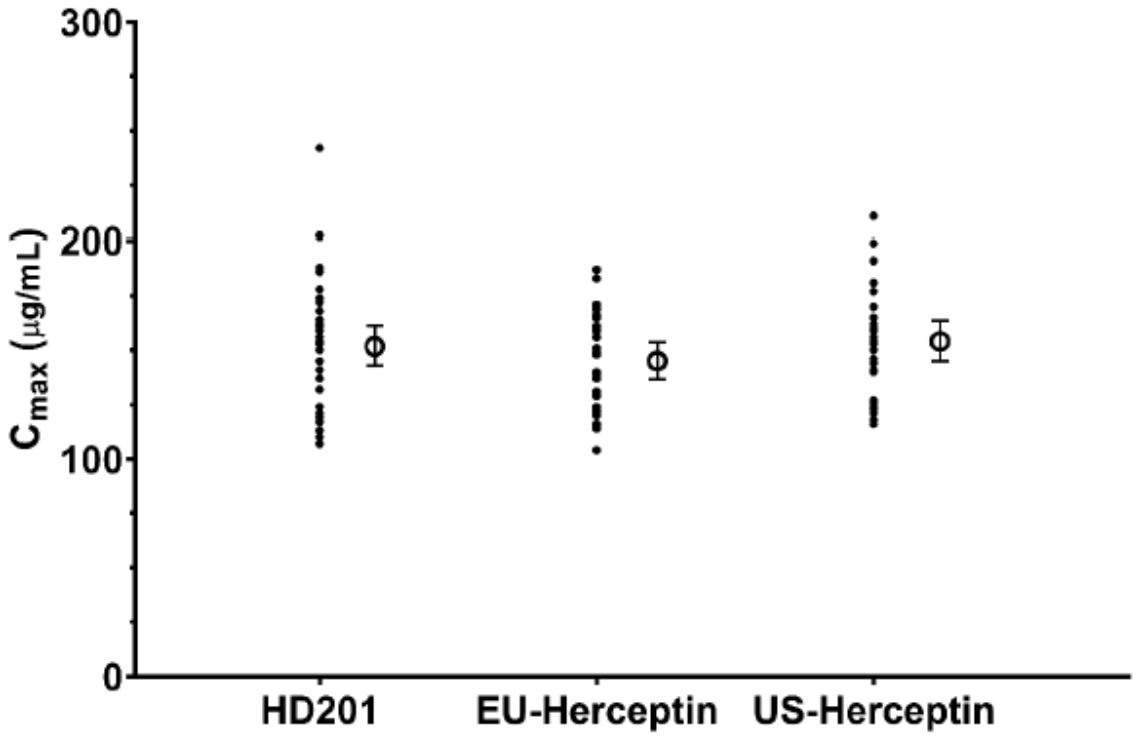
Clearance of trastuzumab was consistent across treatments with mean clearance of 12.5, 12.6, and 12.1 mL/h after administration of HD201, EU-Herceptin, and US-Herceptin respectively.

The volume of distribution was consistent across treatments with mean volume of 4.2, 4.4, and 4.1 L after administration of HD201, EU-Herceptin, and US-Herceptin respectively.



Individual $AUC_{0\text{-}inf}$ data for the PKP population are plotted per treatment group; n = 32 for HD201, n = 34 for EU-Herceptin, n = 31 for US-Herceptin. Open circles and error bars indicate the geometric mean and 95% CI for each treatment group.

Figure 5: Scatterplot of trastuzumab $AUC_{0\text{-}inf}$



Individual C_{max} data for the PKP population are plotted per treatment group; n = 32 for HD201, n = 34 for EU-Herceptin, n = 31 for US-Herceptin. Open circles and error bars indicate the geometric mean and 95% CI for each treatment group.

Figure 6: Scatterplot of trastuzumab C_{max} comparing treatments and sites

The results of the statistical analysis and sensitivity analysis of the equivalent PK properties of HD201 and Herceptin are presented in Table 9. For both the primary analysis and the sensitivity analysis, the 90% CI for the ratio of geometric means of HD201/Herceptin were contained within the acceptance interval of 0.8 to 1.25 for both $AUC_{0\text{-}inf}$ and C_{max} thus demonstrating equivalent PK properties of HD201 and Herceptin.

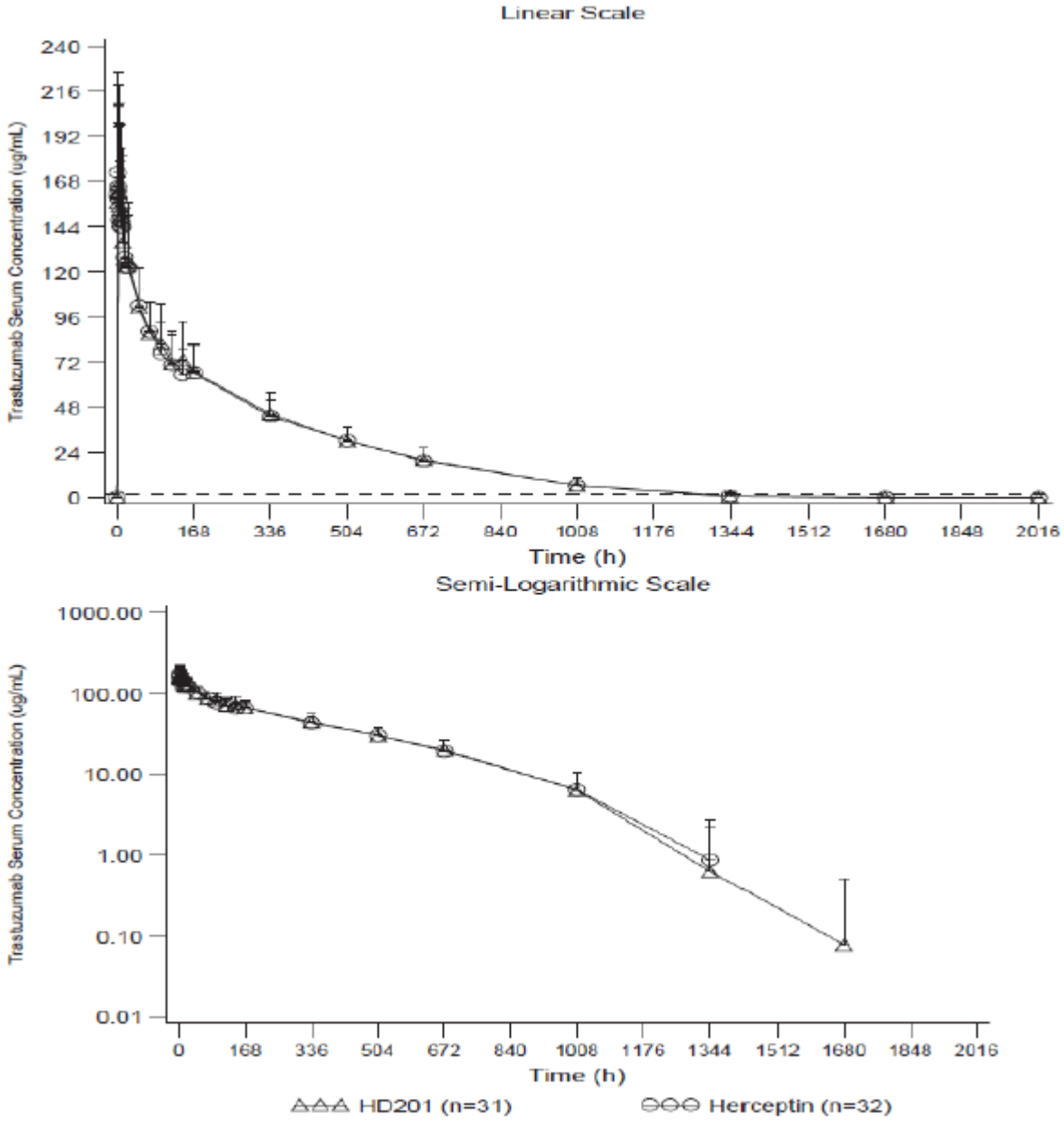
Table 9: Statistical analysis: PK properties of HD201, EU-Herceptin and US-Herceptin

	Geometric Mean [95% CI]	Ratio (%) [90% CI]
HD201 vs EU-Herceptin (EMA)		
$AUC_{0\text{-}inf}$ (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 (Reference Comparison for EMA Bridging)		
$AUC_{0\text{-}inf}$ (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]	94.17 [87.75 ; 101.05]
US-Herceptin (N = 31)	151.10 [142.16 ; 160.60]	
EU-/US-Herceptin		
HD201 vs. US-Herceptin (FDA)		
$AUC_{0\text{-}inf}$ (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 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.

EAGLE-I-12 (considered to be supportive PK data):

Mean (±SD) trastuzumab serum concentration-time profiles by treatment group are presented in Figure 7 below:



<LOQ = Below Lower Limit of Quantification for Trastuzumab (2 µg/mL).
Dotted line in linear plot represents LOQ.

Figure 7: Mean (+SD) trastuzumab serum concentration-time profiles

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 timepoints for both treatments.

Summary trastuzumab serum PK parameters by treatment group are presented in Table 10 below.

Table 10: Summary of the PK parameters for trastuzumab (PK population)

Pharmacokinetic Parameter (units)	Summary Statistic	HD201 N=32	Herceptin® N=32
$AUC_{0\text{-}inf}$ (µg.h/mL)	Mean	42304	41466
	SD	8904	8887
	%CV	21.0	21.4
C_{max} (µg/mL)	Mean	157	161
	SD	42.0	47.6
	%CV	26.8	29.5
$AUC_{0\text{-}t}$ (µg.h/mL)	Mean	40188	39449
	SD	8867	8808
	%CV	22.1	22.3
$t_{½}$ (h)	Mean	247	249
	SD	46.1	40.5
	%CV	18.7	16.2
CL (mL/h/kg)	Mean	0.149	0.151
	SD	0.0344	0.0314
	%CV	23.2	20.8
V_d (mL/kg)	Mean	52.0	53.4
	SD	12.2	10.7
	%CV	23.4	19.9

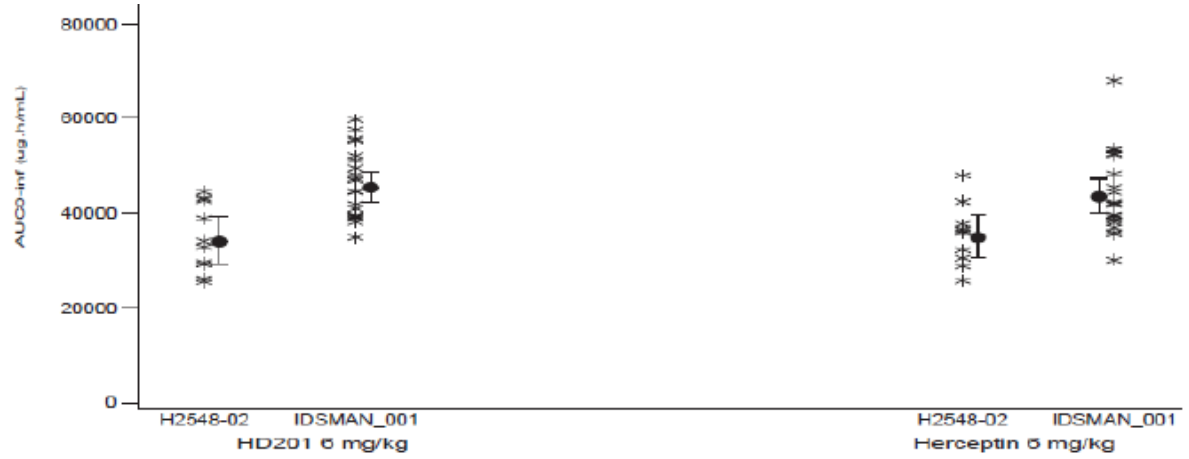
Abbreviations: $AUC_{0\text{-}inf}$ = area under the concentration time curve from 0 to infinity; $AUC_{0\text{-}t}$ = area under the concentration-time curve from time 0 to the last quantifiable concentration; C_{max} = maximum plasma concentration immediately prior to the end of the infusion; CL = total clearance; PK = pharmacokinetic; SD = standard deviation; $t_{½}$ = half-life; V_d = volume of distribution

For all subjects, after administration of both HD201 and Herceptin, the percentage of the $AUC_{0\text{-}inf}$ due to extrapolation was less than 17% demonstrating that the sampling schedule ensured the majority of AUC was captured and the range of times across which λz was estimated was greater than twice the resultant $t_{½}$. All summarised PK parameters were therefore considered to be reliably estimated.

Overall systemic exposure, based on $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$, and peak exposure, based on C_{max}, were similar after administration of HD201 and Herceptin, with mean values differing by less than 3% between the two treatments. The inter-subject variability based on $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} was moderate, with CV ranging from 21 to 30% across both treatments. The $t_{½}$ was long and consistent across treatments, being, on average, 247 h and 249 h after administration of HD201 and Herceptin, respectively. Clearance of trastuzumab was slow and consistent across treatments, being, on average, 0.149 and 0.151 mL/h/kg after administration of HD201 and Herceptin, respectively. The volume of distribution was small and consistent across treatments, being, on average, 52.0 and 53.4 mL/kg after administration of HD201 and Herceptin, respectively.

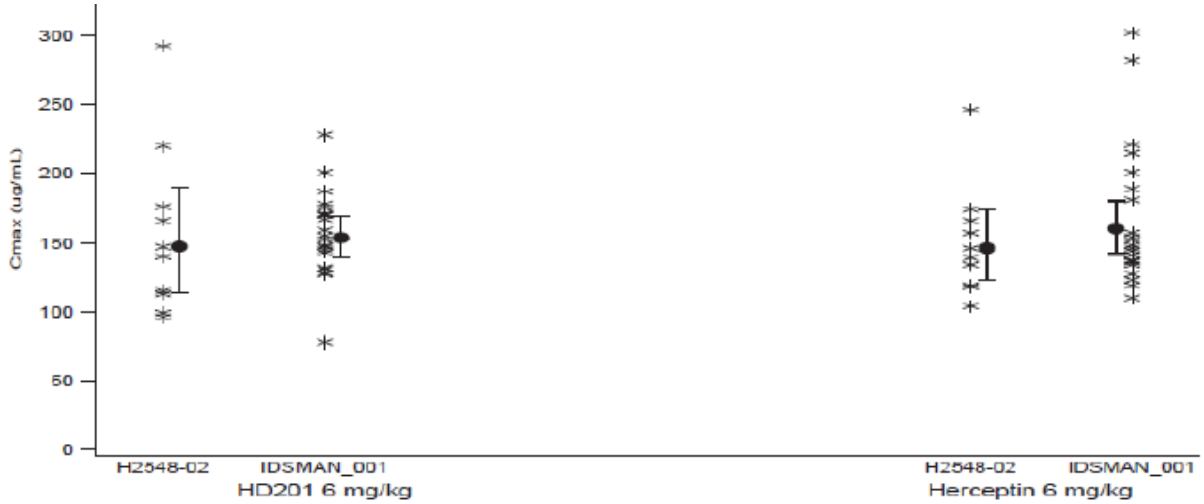
Scatter plots of $AUC_{0\text{-}inf}$ and C_{max} of trastuzumab comparing treatment group and site are presented in Figure 8 and Figure 9, respectively. For each site, the scatterplots of $AUC_{0\text{-}inf}$ and C_{max} indicate that $AUC_{0\text{-}inf}$ and C_{max} were consistent after administration of both HD201 and Herceptin. However, $AUC_{0\text{-}inf}$ appears

to be slightly lower at one study site (H2548-02) compared to the other (IDSMAN_001) for both treatments.



Stars represent individual values, filled circles represent geometric mean and error bars represent 95% CIs
N = 31 for HD201 group and N = 32 for Herceptin® group.
H2548-02 = BioKinetic study site; IDSMAN_001 = Manchester study site.

Figure 8: Scatterplot of trastuzumab $AUC_{0\text{-}inf}$ comparing treatments and sites



Stars represent individual values, filled circles represent geometric mean and error bars represent 95% CIs
N = 31 for HD201 group and N = 32 for Herceptin® group.
H2548-02 = BioKinetic CPU; IDSMAN_001 = Manchester CPU.

Figure 9: Scatterplot of trastuzumab C_{max} comparing treatments and sites

The results of the statistical analysis and sensitivity analysis of the equivalent PK properties of HD201 and Herceptin are presented in Table 11. For both the primary analysis and the sensitivity analysis, the 90% CI for the ratio of geometric means of HD201/Herceptin were contained within the acceptance interval of 0.8 to 1.25 for both AUC0-inf and C_{max} thus demonstrating equivalent PK properties of HD201 and Herceptin.

Table 11: Statistical analysis: Equivalent PK properties of HD201 and Herceptin

Pharmacokinetic Parameter (units)	n		LS Mean		Ratio (HD201/Herceptin®)	90% CI
	HD201	Herceptin®	HD201	Herceptin®		
Primary Analysis						
$AUC_{0\text{-}inf}$ (µg.h/mL)	31	32	39535	38697	1.0216	[0.9476, 1.1015]
C_{max} (µg/mL)	31	32	150	154	0.9743	[0.8723, 1.0883]
Sensitivity Analysis						
$AUC_{0\text{-}inf}$ (µg.h/mL)	34	35	39576	37824	1.0463	[0.9719, 1.1264]
C_{max} (µg/mL)	32	35	149	154	0.9691	[0.8718, 1.0772]

Abbreviations: $AUC_{0\text{-}inf}$ = area under the concentration-time curve from 0 to infinity; CI = confidence interval; C_{max} = maximum plasma concentration immediately prior to the end of the infusion; LS Mean = least square means; PK = pharmacokinetic

Model: Log(PK) = Treatment + Site + Subject (random effect) + Random Error

It is noted that C_{max} and AUC are generally somewhat lower in the TROIKA-1 study, compared to EAGLE-I-12, even if the study design is similar in both studies.

<u>TROIKA phase 3 study (data updated on day 121):</u>

Both at onset of Cycle 5 and Cycle 8, the 90% confidence interval on the mean relative difference of the steady-state trough level of the two treatments is contained within the interval [-20%; + 20%]. At cycles 10 and 14, on the other hand, this is not the case (Table 12).

Table 12: PK trough levels (ug/mL) at start of cycles 5, 8, 10 and 14 (PPS and mFAS)

Table 1 – PK C_{trough} levels (µg/mL) at start of Cycle 5, Cycle 8, Cycle 10 and Cycle 14 for PPS population (study TROIKA)

Statistics	Cycle 5		Cycle 8		Cycle 10		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	233	234	235	230	26	27	121	127
Mean (SD)	42.74 (20.47)	43.62 (27.66)	53.82 (21.48)	53.65 (24.15)	42.82 (21.94)	34.02 (13.19)	57.55 (25.95)	52.07 (21.56)
Median	41.20	38.80	51.70	50.75	34.60	30.70	55.70	47.20
Min; Max	1.0; 249.0	1.0; 268.0	1.0; 219.0	1.0; 230.0	18.8; 121.0	8.2; 69.9	1.0; 201.0	1.0; 160.0
C_{trough} < 20 µg/mL, n'/n (%)	15/233 (6.4%)	16/234 (6.8%)	6/235 (2.6%)	6/230 (2.6%)	1/26 (3.8%)	3/27(11.1%)	5/121 (4.1%)	2/127 (1.6%)
Mean difference (HD201-Herceptin), % [90% CI]	-2.0% [-10.5%; 6.5%]		0.3% [-6.2%; 6.8%]		25.9% [1.5%; 50.3%]		10.5% [0.9%; 20.1%]	

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

Table 2 – PK C_{trough} levels (µg/mL) at start of Cycle 5, Cycle 8, Cycle 10 and Cycle 14 for mFAS population (study TROIKA)

Statistics	Cycle 5		Cycle 8		Cycle 10		Cycle 14	
	HD201 N=250	Herceptin N=252	HD201 N=250	Herceptin N=252	HD201 N=250	Herceptin N=252	HD201 N=250	Herceptin N=252
n	240	245	241	238	28	29	124	131
Mean (SD)	42.30 (20.38)	43.30 (27.27)	53.83 (21.45)	53.90 (23.96)	40.83 (22.35)	33.90 (12.72)	57.06 (26.69)	51.83 (21.34)
Median	41.0	38.60	51.70	50.95	33.55	31.40	55.65	47.20
Min; Max	1.0; 249.0	1.0, 268.0	1.0; 219.0	1.0; 230.0	12.2; 121.0	8.2; 69.9	1.0; 201.0	1.0; 160.0
C_{trough} < 20 µg/mL, n'/n (%)	17/240 (7.1%)	17/245 (6.9%)	6/241 (2.5%)	6/238 (2.5%)	3/28 (10.7)	3/29 (10.3%)	7/124 (5.6%)	2/131 (1.5%)
Mean difference (HD201-Herceptin), % [90% CI]	-2.3% [-10.6%; 6.0%]		-0.1% [-6.5%; 6.2%]		20.4% [-3.2%; 44.1%]		10.1% [0.5%; 19.7%]	

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

2.5.2.2. Pharmacodynamics

No pharmacodynamic data were included in the programme as there are no specific, surrogate pharmacodynamic markers available that are considered relevant to predicting clinical outcomes for trastuzumab.

2.5.2.3. Discussion on clinical pharmacology

The evaluation of pharmacokinetic similarity is based on the phase I bioequivalence study TROIKA-1 in healthy male subjects and complementary data from the phase I study EAGLE-I-12 also in healthy male subjects in addition to the randomised phase III study TROIKA in patients with HER2+ early breast cancer.

The studies TROIKA-1 and EAGLE-I-12 were well designed.

No deficiencies in the conduct of the TROIKA-1 study have been identified, but the outcomes of the GCP inspections of the study site in Australia that performed the TROIKA-1 study has been requested as other concern **(OC)**. This issue has not been resolved**.**

In the EAGLE-I-12 study compliance with study protocol was an issue during study conduct (more than 500 protocol deviations were noticed). This led to questionable exclusions of subjects from PK population.

Initially, evaluation of C_{max} was not done properly and the results could not be accepted. The applicant set the concentration at the end of infusion (90 min) as C_{max}, however in most of cases the real C_{max} (maximal plasma levels of trastuzumab) were later and the evaluated and presented values for C_{max} do not represent real maximum plasma levels. The applicant recalculated the parameter C_{max} to represent the maximum plasma concentration and corrected the evaluation of parameters C_{max} and T_{max} to represent the maximum plasma concentration directly obtained from the plasma concertation/time curve.

The Median T_{max} values were 3.49 and 2.51 for test and reference product respectively.

The recalculated mean C_{max} was 187.56 µg/mL for the test and 191.16 for the reference product. The confidence intervals of the geometric means [90.48% to 110.94%] were within standard bioequivalence limits.

Moreover, in response to the use of two clinical sites and the indication of a slight site difference, site was incorporated into the statistical analysis model and equivalence between the two treatments was clearly demonstrated; hence site had no impact on the overall study conclusions as the site*treatment interaction term was not significant. This study was not formally designed to investigate for a site effect and with uneven subject numbers at each of the two sites, the differences in $AUC_{0\text{-}inf}$ indicated in this study should be viewed with caution.

It is noted that C_{max} and AUC are generally somewhat lower in the TROIKA-1 study, compared to EAGLE-I-12, even if the study design is similar in both studies. This issue is, however, not pursued, as the EAGLE-I-12 study is considered supportive only, and because there is no significant difference between the parameters determined for HD210 and Herceptin, respectively.

A major objection was raised on Day 120 due to the fact that the pivotal PK study was performed with an early phase version of the biosimilar product, and the applicant has not documented the comparability between this product's early version to the biosimilar product intended for commercialisation. Although, a new pivotal PK study was submitted on Day 121 (TROIKA-1), the same

concern applies, as the applicant has still not documented that product batches used in the second PK study (TROIKA-1) are comparable to the intended commercial biosimilar product. (MO)

Supportive PK data was provided from the efficacy study TROIKA in patients with HER2+ early breast cancer in the neoadjuvant setting. Although Several concerns related to the performed PK analysis were identified, these have been resolved, to the possible extent considering the available PK samples. The submitted data, including samples from cycles 10 and 14, as well as additional data from the earlier time-points, were eventually consistently discussed by the applicant in the CSR, clinical summary as well as in the clinical overview. In the clinical summary, it is discussed that the results obtained at Cycle 10 are unreliable due to small sample size (only 57 subjects in total). All in all, the results based on sampling at Cycle 5, 8 and 14 indicate PK similarity. However, due to the lack of bridging between clinical batches and commercial batches, no conclusion can be made.

However, although the results indicate PK similarity between HD201 and Herceptin, no conclusion can be made, due to uncertainty on the relevance of HD201 batches used in the clinical studies (Quality MO).

TROIKA:

Therefore, no conclusion can be made regarding the comparability at pharmacokinetics level of Tuznue (HD201) and Herceptin.

2.5.2.4. Conclusions on clinical pharmacology

The clinical development programme for the applied drug product was conducted in accordance with current EMA guidelines relevant for biosimilars, and in accordance with scientific advice received from the EMA except for the foreseen PK modelling. The applicant has explained why the foreseen PK modelling was not performed after all.

Bioanalytical methods for the determination of HD201/ trastuzumab (Herceptin) and antibodies were developed and validated. The bioanalytical methods including their validation are acceptable.

The pivotal phase I PK study in healthy volunteers, apparently demonstrated similarity of the pharmacokinetics of HD201 and Herceptin. However, the study was performed using HD201 batches that are not accepted as representative for the commercial Tuznue (HD201) drug product, and a conclusion on PK similarity can therefore not be made.

PK data obtained as secondary endpoints in the phase III TROIKA study, in part indicated similarity of the pharmacokinetics of HD201 and Herceptin. PK modelling, that could potentially have supported of the data, was not performed.

Considering the fundamental uncertainty regarding the comparability of the HD201 batches used in the pivotal PK study, and the commercial HD201 (Tuznue) batches, no conclusion can be made on the similarity of pharmacokinetics between Tuznue (HD201) and Herceptin.

2.6. Clinical efficacy

The clinical overview and summary of clinical efficacy presented in the initial submission did not contain the expected clinical information. Many of the specific requests for clarification and updates have been met, but a number of inconsistencies and false statements were identified in the Day 121 responses. It is acknowledged that the clinical overview and summary have been updated in the response to the first Day 180 LoOI. However, inconsistencies still remained; but, in light of the major problems regarding several quality issues for product HD201, these were not further pursued.

2.6.1. Dose response study(ies)

Not Applicable.

2.6.2. 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 programme 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***

Key inclusion criteria

- Females ≥ 18 years of age.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) < 2.
- Known hormone receptor (oestrogen receptor and progesterone receptor) status.
- HER2 overexpressed as assessed by:
    - Immunohistochemistry (IHC) or
    - Fluorescent in site hybridisation (FISH); FISH positive is defined as FISH amplification ratio ≥ 2.0 / number of HER2 gene copies per cell or
    - Chromogenic in situ hybridisation (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 also have a positive FISH/CISH/DISH test
- LVEF ≥ 50% or within the normal level of the institution, as assessed by echocardiography or MUGA scan.
- Non-metastatic, unilateral, newly diagnosed, operable early breast cancer (EBC) and locally advanced breast cancer (LABC) of clinical stage II and III including inflammatory breast cancer. Histologically confirmed primary invasive carcinoma of the breast.

Key exclusion criteria

- Metastatic (stage IV) with exception of supraclavicular nodes, bilateral breast cancer or multicentric breast cancer.
- History of any prior invasive breast carcinoma, except for subjects with a history of ductal carcinoma in situ (DCIS) treated with surgery.
- History of malignant neoplasms within five 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 are permitted if curatively treated with surgery only).
- Previous history of radiation therapy, anti-neoplastic immunotherapy, chemotherapy, or anti-neoplastic biotherapy (including prior HER2 directed therapy).
- Serious cardiac illness that would preclude the use of trastuzumab
- Serious pulmonary illness enough to cause dyspnoea at rest or requiring supplementary oxygen therapy.
- Known history of active hepatitis B virus (HBV) and active hepatitis C virus (HCV) infection and known HIV infection by patient declaration.
- Pre-existing peripheral sensory or motor neuropathy ≥ grade 2 (as defined by NCI-CTCAE v4.03).

- ***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 in a ratio of 1:1 ratio to the HD201 arm or the Herceptin arm. Subjects were assigned a unique subject number at Screening.

Subjects were stratified by:

• Geographical region

• Clinical stage (stage II vs. III)

• Oestrogen and/or progesterone receptor status (positive vs. negative)

This study was double-blinded. The HD201/Herceptin vials are slightly different in size, and the pharmacist preparing the infusion bags was therefore unblinded. The pharmacist prepared the infusion bags (labelled identically, identified by a treatment number, patient number and cycle number), and were responsible to ensure blinding of the investigator, the staff, and the patient. Patients, investigators, and the sponsor's trial team involved in analysing the trial, remained blinded about the randomised treatment assignments up to database lock for the primary analysis.

- ***Statistical methods***

Equivalence testing was done by comparing the exact 95% Santner-Snell CI on the difference between the two treatment groups with the interval [-0.15; +0.15].

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**

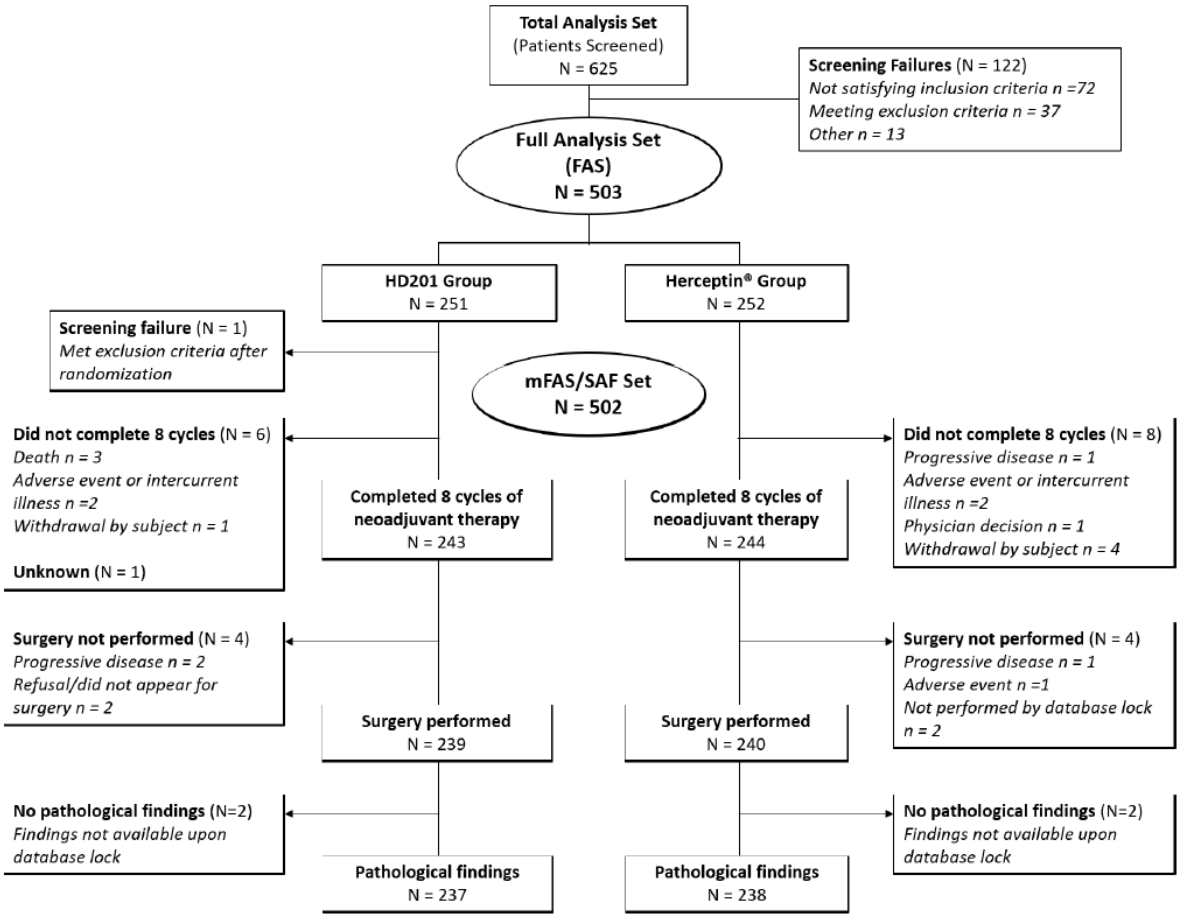


Figure 10: Disposition of subjects

Disposition of subjects are collected from the neoadjuvant period and at the time of surgery.

Patients were recruited from 70 centres across four geographical regions: Asia, Eastern Europe, Central Europe and Western Europe.

- **Recruitment**

Date First Patient Screened: 19 February 2018

Date Last Patient Completed: - Neoadjuvant period: 24 April 2019

- Adjuvant period: 21 January 2020

- Follow-up period: 13 January 2022

STUDY STATUS: Completed

- **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

GCP inspection of the sponsor and two of the CROs in Russia and Thailand were conducted (EudraCTnr: 2016-004019-11; EMA Inspection reference number: GCP/2019/022).

The GCP inspection for the phase III TROIKA study (EudraCTnr: 2016-004019-11; EMA Inspection reference number: GCP/2019/022) 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 (GCP/2021/004/1-3). However, the clinical sites where several critical and major findings were detected in the first GCP inspection, were not re-inspected.

Further to the GCP inspection integrated report (GCP/2021/004) for the phase III TROIKA study, a new clinical study report had to be issued excluding patients from clinical sites where there were critical findings.

- Protocol deviations

During the entire study, a total of 465 patients (92.6%) in the mFAS had at least one protocol deviation: 231 patients (92.4%) from the HD201 treatment group and 234 patients (92.9%) from the Herceptin treatment group.

13 patients (2.6%) had at least one major protocol deviation, 3 patients (1.2%) in the HD201 treatment group and 10 patients (4.0%) in the Herceptin treatment group:

o Inclusion and exclusion criteria: HD201 1 patient and Herceptin 7 patients

o Study treatment: HD201 1 patient

o Chemotherapy: Herceptin 1 patient

o Other: HD201 1 patient and Herceptin 2 patients

To comply with the guidance on the management of clinical trials during the COVID-19 pandemic, a separate analysis was performed to assess the effect of COVID-19 on efficacy outcomes. For this analysis, it was identified whether the protocol deviations were related to COVID-19. A total of 189 patient (37.6%) in the mFAS had at least one COVID-19 related protocol deviation: 89 patients (35.6%) in the HD201 treatment group and 100 patients (39.7%) in the Herceptin treatment group:

o Immunogenicity sample not taken: HD201 1 patient

o Safety evaluations not performed: HD201 5 patients and Herceptin 3 patients

o Safety visits out of schedule window: HD201 86 patients and Herceptin 97 patients

- **Baseline data**

Demographic characteristics

Table 13: **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 14: 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 15: 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 16: 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 17: 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.

- **Numbers analysed**

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 18: 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 19: 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 20: 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, 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 21: 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 22: 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 23: 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 24: 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.

Sensitivity analyses submitted in the CSR version 4.0

A sensitivity analysis to ascertain the reliability of the TROIKA study have been performed by the applicant. The analysis was performed on the final database of the study (locked on 02 February 2022) of the 2-year post-treatment follow-up period (including survival outcomes, EFS and OS at 3-years, and safety data of the post-treatment follow-up period) (see table below).

Table 25: Locally assessed tpCT for the PPS and relevant PPS subsets excluding sites inspected during the GCP inspections (study TROIKA)

	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]	
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 site in Thailand			
N, n'	234, 234	230, 230	-3.0% [-12.1; 6.3]
Responders, n (%)	107 (45.7)	112 (48.7)	
95% CI	[39.2%; 52.3%]	[42.1%; 55.4%]	
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 CRO in Spain			
N, n'	228, 228	228, 228	-3.9% [-13.3; 5.4]
Responders, n (%)	105 (46.1)	114 (50)	
95% CI	[39.5%; 52.8%]	[43.3%; 56.7%]	

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 responders (subjects with a positive assessment); PPS = per protocol set
Percentages were based on n' and are rounded to the nearest tenth of a percent

According to the applicant, for all analysis sets, PPS excluding one site in the Russian Federation, PPS excluding one site in Thailand, PPS excluding both sites in the Russian Federation and Thailand, and PPS excluding sites monitored by the CRO in Spain, the 95% CIs fell within the pre-defined equivalence margin of [-15%, 15%].

Summary of main study(ies)

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

Table 26: **Summary of efficacy for trial TROIKA**

Title: 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	
Study identifier	TROIKA, EudraCT number 2016-004019-11
Design	double-blind, randomised phase III, parallel group, multicentre study

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Neoadjuvant period: 8 cycles Adjuvant period (after surgery): up to 10 cycles not applicable not applicable
Hypothesis	Equivalence		
Treatments groups	HD201		Neoadjuvant Period: 8 mg/kg IV loading dose, then 7 cycles with 6 mg/kg IV combined with 4 cycles of docetaxel (cycle 1-4) followed by 4 cycles of Epirubicin and Cyclophosphamide Adjuvant Period: One cycle with 8 mg/kg IV followed by 8 cycles with 6 mg/kg IV Randomised subjects = 250
	Herceptin		Neoadjuvant Period: 8 mg/kg IV loading dose, then 7 cycles with 6 mg/kg IV combined with 4 cycles of docetaxel (cycle 1-4) followed by 4 cycles of Epirubicin and Cyclophosphamide Adjuvant Period: One cycle with 8 mg/kg followed by 8 cycles with 6 mg/kg Randomised subjects = 252
Endpoints and definitions	Primary endpoint	tpCR	Total pathological complete response (tpCR), defined as complete absence of cancer cells in the breast and in axillary lymph nodes at the time of surgery, after 8 cycles of neoadjuvant treatment completion.
	Secondary Endpoint	bpCR	Total breast pathological complete response (bpCR) is defined as complete disappearance of cancer cells in the breast at the time of surgery.
	Secondary Endpoint	ORR	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 and mammography and clinical examination prior to surgery.
Database lock	19 April 2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified full analysis set (mFAS) Per protocol set (PPS) After completion of 8 cycles of neoadjuvant therapy		
Descriptive statistics and estimate variability	Treatment group	HD201	Herceptin
	Number of subject	PPS: 238 mFAS: 250	PPS: 236 mFAS: 252
	tpCR (%) PPS	111 (46.6%)	109 (46.2%)
	tpCR (%) mFAS	112 (46.5%)	109 (45.0%)
Effect estimate per	Primary endpoint	Comparison groups	HD201 vs Herceptin

comparison	**tpCR (%)** PPS	difference	0.5%
		95% CI	-8.6%; 9.6%
	Primary endpoint **tpCR (%)** mFAS	Comparison groups	HD201 vs Herceptin
		difference	1.4%
		95% CI	-7.7%; 10.4%
Notes	Pre-defined equivalence margins were for risk difference ±15%		
Analysis description	**Secondary Analysis**		
Descriptive statistics and estimate variability	Treatment group	HD201	Herceptin
	Number of subject	PPS: 238 mFAS: 250	PPS: 236 mFAS: 252
	bpCR (%) PPS	131 (55.0%)	126 (53.4%)
	bpCR (%) mFAS	132 (54.8%)	127 (52.5%)
	ORR (%) PPS	216 (90.8%)	211 (89.4%)
	ORR (%) mFAS	219 (87.6%)	219 (86.9%)
Effect estimate per comparison	Secondary endpoint **bpCR (%)** PPS	Comparison groups	HD201 vs Herceptin
		difference	1.7%
		95% CI	7.5%; 10.7%
	Secondary endpoint **bpCR (%)** mFAS	Comparison groups	HD201 vs Herceptin
		difference	2.3%
		95% CI	-6.7%; 11.4%
	Secondary endpoint **ORR (%)** PPS	Comparison groups	HD201 vs Herceptin
		difference	1.3%
		95% CI	-7.5%; 10.5%
	Secondary endpoint **ORR (%)** mFAS	Comparison groups	HD201 vs Herceptin
		difference	0.7%
		95% CI	-8.1%; 9.3%

2.6.3. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.4. Clinical studies in special populations

Not applicable for biosimilars.

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

Not Applicable

2.6.6. Supportive study(ies)

Not Applicable.

2.6.7. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy and safety development programme to demonstrate equivalence between HD201 and the reference product EU-Herceptin consisted of a single double blind, randomised, phase 3 study (TROIKA) in women with histologically confirmed, newly diagnosed clinical Stage II-III, operable, HER2-positive breast cancer.

HD201 or Herceptin were administered in combination with chemotherapy in the neoadjuvant setting. After eight cycles of neoadjuvant treatment, surgery was performed and treatment was subsequently continued as monotherapy for up to 10 adjuvant cycles. The integrated CSR contains data from all subjects up to completed surgery and includes the primary efficacy analysis. This is acceptable in a biosimilar setting and from an efficacy point of view since it includes the primary endpoint.

The design of the TROIKA study including choice of the indication (early breast cancer), the primary endpoint and sample size has been endorsed in CHMP Scientific Advice. The chosen indication is considered sufficiently sensitive to enable the detection of clinical differences between HD201 and Herceptin.

The inclusion/exclusion criteria are generally based upon those for the reference product Herceptin for this indication and are overall acceptable. Information on HER2 detection is rather sparse in the protocol and information is missing on where testing were done (local/regional/national centres). The primary endpoint tpCR (total pathological complete response) is considered a sensitive endpoint to demonstrate biosimilarity.

The study was conducted in four geographic regions: Asia, Eastern Europe, Central Europe and Western Europe. The majority of subjects were enrolled at sites outside EU. 502 subjects were randomised to receive treatment; 250 in the HD201 treatment group and 252 in the Herceptin treatment group, of these 474 constituted the per protocol set (PPS). The sample size is acceptable, and a clinical rationale or justification behind the equivalence margins has been provided.

A total of 263 subjects (52.4%) had at least one protocol deviation, but the numbers were balanced across the two treatment groups. Only three patients were excluded from the primary analysis population due to major protocol deviations.

Eleven subjects (eight in the HD201 group and three from the Herceptin group) from the Italian sites were not fully entered and monitored. Therefore, an additional sensitivity analysis was performed on the primary endpoint excluding these patients. A detailed explanation was given for the deviations.

Further to several critical findings during GCP-inspections and re-inspections, the applicant submitted an updated clinical study report (CSR). In addition, the applicant presented sensitivity analyses

showing that the obtained results on efficacy were similar, also without data from affected patients. Therefore, the GCP issues are considered resolved.

Efficacy data and additional analyses

Baseline patient demographics and disease characteristics were balanced across treatment groups. The number of patients that completed the neoadjuvant phase and went through surgery was similar in the two treatment groups. Generally, the statistical methods are supported.

According to local laboratory assessment, 111 patients (46.6%) in the HD201 treatment group and 109 (46.2%) patients in the Herceptin treatment group achieved tpCR. The difference between the two groups was 0.5% [95% CI: of -8.6%; 9.6%], which is well contained within the pre-defined equivalence margin of ±15% and the primary endpoint as specified for this trial was met. Results from sensitive analyses and stratification subgroup analyses of tpCR reflected those of the primary efficacy outcome. Furthermore, the secondary endpoints bpCR and ORR showed similar efficacy outcomes between the two treatment groups and were consistent with the results from the primary analysis. For the stratification subgroup analyses a somewhat lower response in the Asia subpopulation compared to the other geographical regions, was seen for both the primary and the secondary bpCR and ORR subgroup analyses. In addition, a 10% higher response was reported in the breast cancer stage III for the HD201 treatment group as compared to the Herceptin treatment group in all stratification subgroup analyses (tpCR, bpCR, ORR).

The primary outcome is supported by sensitivity and stratification subgroup analyses in addition to the efficacy analyses for the secondary endpoints.

Further to several critical findings during GCP-inspections and re-inspections, the applicant presented an updated clinical study report. Therefore, the GCP issues are considered resolved.

Nevertheless, notwithstanding these efficacy outcomes, an earlier version of the drug product which is not considered comparable to the drug product intended for marketing ("Process 2-IV" = Process D) has been used in the TROIKA studies. Thus, clinical data from TROIKA cannot support the drug product applied for in the marketing authorisation application.

2.6.8. Conclusions on the clinical efficacy

Both, the pivotal phase 1 PK trial (TROIKA-1) and the phase 3 clinical trial (TROIKA) were entirely or largely conducted using HD201 Process B or Process C, whereas Process D is intended for marketing.

Comparability between the batches used in the clinical studies (Process B/C) and the product intended for marketing (Process D) has not been shown.

The CHMP considers that these issues preclude a conclusion on biosimilarity from an efficacy point of view.

2.7. Clinical safety

Due to poor presentation and incompleteness of safety data in the original dossier, the applicant was requested to re-submit module 2.5 Clinical Overview and module 2.7.4 Summary of Clinical Safety after performing critical review and revision of the data. The resubmitted documents additionally contained information about a third phase I PK trial, TROIKA-I which were not assessed initially. As the re-submitted documentation at day 121 also contained many deficiencies, it was again re-submitted at

day 181. Any inconsistencies and deficiencies in the clinical overview and summary of clinical safety are not pursued further.

In addition, as a result of the CAPA arising from the requested GCP inspection of the TROIKA study, neo-adjuvant subject data was 100% re-monitored and resubmitted, because substantial amounts of previously unreported safety data was discovered.

The safety profile of HD201 was investigated in three clinical trials comparing HD201 to the reference product, Herceptin (EU-sourced). Key safety information is derived from the Phase III trial in EBC (TROIKA), where 502 women with HER-2 positive breast cancer were randomised in a 1:1 ratio to receive either HD201 or Herceptin in a neoadjuvant setting for 8 cycles concurrently with chemotherapy, followed by surgery and a further 10 cycles of adjuvant HD201 or Herceptin for a total treatment duration of about 1 year. The TROIKA study has entered its 2- year follow-up phase, and all patients have completed 1-year trastuzumab-directed therapy (neoadjuvant and adjuvant treatment phases), clinical cut-off date 21 January 2020 (date of last subject EOT visit). Supportive safety data comes from two completed phase I single dose PK study in healthy volunteers (EAGLE-I-12 and TROIKA-1). The safety population consisted of subjects who received at least one dose of study drug.

Table 27: Tabular listing of all clinical studies

Type of study	Study number	Study design; objectives	Test products; dosage regimen; ROA	Duration of treatment	Number of subjects randomised	Total safety population
Phase 1 PK and safety study in healthy volunteers	TROIKA-1	Phase 1, randomized, double-blind, single-dose, 3-arm, parallel group study; PK similarity study of HD201 compared to US-Herceptin and EU-Herceptin	HD201 vs. US-Herceptin and EU-Herceptin; 6 mg/kg IV infusion for 90 minutes as a single dose	Single dose	105 (35 HD201, 35 US-Herceptin, 35 EU-Herceptin)	105 (35 HD201, 35 US-Herceptin, 35 EU-Herceptin)
Phase 1 PK and safety study in healthy volunteers	EAGLE-I-12	Phase 1, randomized, double-blind, single-dose, 2-arm, parallel group study; PK similarity study of HD201 compared to EU-Herceptin	HD201 vs. EU-Herceptin; 6 mg/kg IV infusion for 90 minutes as a single dose	Single dose	73 (37 HD201, 36 EU-Herceptin)	69 (34 HD201, 35 EU-Herceptin)
Phase 3 efficacy and safety study in patients with EBC	TROIKA	Phase 3, randomized, multicenter, double-blind, active controlled, 2-arm, parallel group study; Efficacy, safety and immunogenicity of HD201 comapred to EU-Herceptin	HD201 vs. EU-Herceptin; Initial loading dose of 8 mg/kg IV followed by maintenance doses of 6 mg/kg IV every 3 weeks	54 weeks of active treatment	503 (251 HD201, 252 EU-Herceptin)	Neoadjuvant: 502 (250 HD201, 252 EU-Herceptin) Adjuvant: 480 (238 HD201, 242 EU-Herceptin)

IV: Intravenous; PK: Pharmacokinetic; ROA: Route of administration

Table 28. Summary of safety population by study

Safety population, n	HD201	EU-Herceptin	US-Herceptin	Total
Healthy subject PK studies				
TROIKA-1	35	35	35	105
EAGLE-I-12	34	35	n/a	69
Controlled clinical studies pertinent to the claimed indication				
TROIKA	250	252	n/a	502
Neoadjuvant	250	252	n/a	502
Adjuvant	238	242	n/a	480

n: Number of subjects; n/a: Not applicable

2.7.1. Patient exposure

Phase III study TROIKA

Table 29: Exposure of patients (study 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 30: Summary of exposure to study drug for the entire study – safety set (Study TROIKA)

Variable		HD201 N=250	EU-Herceptin N=252
Total cumulative dose administered, 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
Total 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 category, 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%)
Number of cycle completion, 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 subjects within the treatment group; Q1: 1st quartile; Q3: 3rd quartile; SD: Standard deviation; n: number of patients within the category

Table 31: Summary of exposure to study drug in the neoadjuvant and adjuvant treatment phases (study TROIKA)

Variable		Neoadjuvant		Adjuvant	
		HD201 N=250	EU-Herceptin N=252	HD201 N=238	EU-Herceptin N=242
Total cumulative dose administered, mg/kg	Mean (SD)	49.46 (5.78)	49.58 (5.64)	60.86 (7.60)	60.78 (7.78)
	Median	50.10	50.15	62.10	62.20
	Q1, Q3	49.50, 50.80	49.70, 50.95	60.80, 63.60	60.40, 63.40
	Min, Max	8.0, 56.5	8.0, 56.1	14.4, 70.1	8.0, 68.7
Total treatment duration, weeks	Mean (SD)	24.07 (3.0)	24.14 (2.94)	29.38 (3.74)	29.46 (3.92)
	Median	24	24.14	30.00	30.00
	Q1, Q3	24, 24.86	24, 24.86	30.00, 30.29	30.00, 30.29
	Min, Max	3, 30.4	3, 31.0	5.9, 34.0	3.0, 37.4
Dose intensity, mg/kg/week	Mean (SD)	2.065 (0.102)	2.063 (0.101)	2.076 (0.083)	2.072 (0.107)
	Median	2.069	2.072	2.065	2.070
	Q1, Q3	2.016, 2.104	2.02, 2.10	2.027, 2.113	2.013, 2.110
	Min, Max	1.84, 2.70	1.79, 2.70	1.86, 2.46	1.66, 2.70
Relative dose intensity, %	Mean (SD)	99.12 (4.87)	99.01 (4.84)	100.46 (4.01)	100.28 (5.16)
	Median	99.33	99.47	99.94	100.16
	Q1, Q3	96.74, 101.0	96.94, 100.8	98.06, 102.26	97.42, 102.09
	Min, Max	88.2, 129.6	86.1, 129.6	90.2, 119.0	80.5, 130.6
Dose delay of more than 2 days, n (%)	Any delay	90 (36.4%)	91 (36.5%)	61 (25.6%)	67 (27.9%)
	Delay due to adverse event	60 (24.3%)	58 (23.3%)	9 (3.8%)	19 (7.9%)

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

Table 32: Summary of exposure to chemotherapy in the neoadjuvant treatment phase – safety set (study TROIKA)

Number of chemotherapy administrations		HD201 N=250	EU-Herceptin N=252
Number of docetaxel administrations, n (%)	0	0	0
	1	3 (1.2%)	3 (1.2%)
	2	2 (0.8%)	0
	3	0	2 (0.8%)
	4	245 (98.0%)	246 (97.6%)
	8	0	1 (0.4%)
Number of epirubicin administrations, n (%)	0	5 (2.0%)	7 (2.8%)
	1	0	3 (1.2%)
	2	1 (0.4%)	2 (0.8%)
	3	0	0
	4	244 (97.6%)	240 (95.2%)
Number of cyclophosphamide administrations, n (%)	0	5 (2.0%)	7 (2.8%)
	1	0	3 (1.2%)
	2	1 (0.4%)	2 (0.8%)
	3	0	0
	4	244 (97.6%)	240 (95.2%)
Number of subjects with the full dose administered as per package insert and scheduled in the protocol, n (%)		218 (87.2%)	218 (86.5%)

N: Number of patients within the treatment group; n = number of patients within the category

2.7.2. Adverse events

Phase I study EAGLE-I-12

Table 33: Summary of treatment-emergent adverse events – EAGLE-I-12 (safety population)

AE Category	HD201 N = 34 n (%) E	Herceptin® N = 35 n (%) E	Overall N = 69 n (%) E
Any TEAE	21 (61.8) 48	29 (82.9) 103	50 (72.5) 151
Intensity of TEAEs			
Mild	16 (47.1) 30	25 (71.4) 69	41 (59.4) 99
Moderate	9 (26.5) 18	11 (31.4) 33	20 (29.0) 51
Severe	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
TEAEs related to study drug	16 (47.1) 30	26 (74.3) 86	42 (60.9) 116
TEAEs leading to withdrawal	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Any SAE	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Any SAEs related to study drug	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1

Abbreviations: AE = adverse event; E = number of events; N = number of subjects; n = number of subjects exposed; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Table 34: Treatment-emergent adverse events by System Organ Class, Preferred Term, Treatment Group and Overall – EAGLE-I-12 (Safety Population)

System Organ Class Preferred Term	HD201 N = 34 n (%) E	Herceptin® N = 35 n (%) E	Overall N = 69 n (%) E
Subjects with any TEAE	**21 (61.8) 48**	**29 (82.9) 103**	**50 (72.5) 151**
Cardiac disorders	**1 (2.9) 1**	**3 (8.6) 3**	**4 (5.8) 4**
Extrasystoles	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Tachycardia	1 (2.9) 1	2 (5.7) 2	3 (4.3) 3
Ear and labyrinth disorders	**1 (2.9) 1**	**0 (0.0) 0**	**1 (1.4) 1**
Ear pain	1 (2.9) 1	0 (0.0) 0	1 (1.4) 1
Eye disorders	**0 (0.0) 0**	**1 (2.9) 1**	**1 (1.4) 1**
Conjunctivitis	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Gastrointestinal disorders	**5 (14.7) 10**	**9 (25.7) 9**	**14 (20.3) 19**
Abdominal pain	1 (2.9) 1	0 (0.0) 0	1 (1.4) 1
Constipation	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Diarrhoea	3 (8.8) 3	2 (5.7) 2	5 (7.2) 5
Dry mouth	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Dyspepsia	3 (8.8) 3	0 (0.0) 0	3 (4.3) 3
Grastrooesophageal reflux disease	1 (2.9) 1	0 (0.0) 0	1 (1.4) 1
Nausea	0 (0.0) 0	2 (5.7) 2	2 (2.9) 2
Toothache	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Vomiting	2 (5.9) 2	2 (5.7) 2	4 (5.8) 4
General disorders and administration site conditions	**2 (5.9) 2**	**13 (37.1) 26**	**15 (21.7) 28**
Catheter site bruise	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Chest pain	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Chills	0 (0.0) 0	5 (14.3) 7	5 (7.2) 7
Feeling cold	0 (0.0) 0	5 (14.3) 5	5 (7.2) 5
Feeling hot	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Malaise	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Pyrexia	2 (5.9) 2	9 (25.7) 9	11 (15.9) 11
Thirst	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Immune system disorders	**1 (2.9) 1**	**0 (0.0) 0**	**1 (1.4) 1**
Seasonal allergy	1 (2.9) 1	0 (0.0) 0	1 (1.4) 1

System Organ Class Preferred Term	HD201 N = 34 n (%) E	Herceptin® N = 35 n (%) E	Overall N = 69 n (%) E
Infections and infestations	**13 (38.2) 14**	**8 (22.9) 9**	**21 (30.4) 23**
Anal abscess	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Chlamydial infection	1 (2.9) 1	0 (0.0) 0	1 (1.4) 1
Nasopharyngitis	11 (32.4) 12	6 (17.1) 6	17 (24.6) 18
Upper respiratory tract infection	0 (0.0) 0	2 (5.7) 2	2 (2.9) 2
Viral upper respiratory tract infection	1 (2.9) 1	0 (0.0) 0	1 (1.4) 1
Injury, poisoning and procedural complications	**1 (2.9) 1**	**3 (8.6) 3**	**4 (5.8) 4**
Contusion	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Post procedural contusion	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Soft tissue injury	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Wound	1 (2.9) 1	0 (0.0) 0	1 (1.4) 1
Musculoskeletal and connective tissue disorders	**1 (2.9) 1**	**5 (14.3) 6**	**6 (8.7) 7**
Arthralgia	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Back pain	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Myalgia	1 (2.9) 1	1 (2.9) 1	2 (2.9) 2
Neck pain	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Pain in extremity	0 (0.0) 0	2 (5.7) 2	2 (2.9) 2
Nervous system disorders	**6 (17.6) 9**	**16 (45.7) 27**	**22 (31.9) 36**
Dizziness	0 (0.0) 0	5 (14.3) 5	5 (7.2) 5
Dysgeusia	1 (2.9) 1	0 (0.0) 0	1 (1.4) 1
Headache	4 (11.8) 7	11 (31.4) 16	15 (21.7) 23
Hypoaesthesia	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Presyncope	1 (2.9) 1	0 (0.0) 0	1 (1.4) 1
Syncope	0 (0.0) 0	2 (5.7) 3	2 (2.9) 3
Tremor	0 (0.0) 0	1 (2.9) 2	1 (1.4) 2
Respiratory, thoracic and mediastinal disorders	**4 (11.8) 5**	**8 (22.9) 14**	**12 (17.4) 19**
Cough	0 (0.0) 0	4 (11.4) 4	4 (5.8) 4
Dyspnoea	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Epistaxis	3 (8.8) 4	1 (2.9) 2	4 (5.8) 6
Nasal obstruction	0 (0.0) 0	2 (5.7) 3	2 (2.9) 3
Oropharyngeal discomfort	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Oropharyngeal pain	1 (2.9) 1	3 (8.6) 3	4 (5.8) 4

System Organ Class Preferred Term	HD201 N = 34 n (%) E	Herceptin® N = 35 n (%) E	Overall N = 69 n (%) E
Skin and subcutaneous tissue disorders	**2 (5.9) 2**	**3 (8.6) 3**	**5 (7.2) 5**
Hyperhidrosis	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1
Rash	2 (5.9) 2	2 (5.7) 2	4 (5.8) 4
Vascular disorders	**1 (2.9) 1**	**2 (5.7) 2**	**3 (4.3) 3**
Hot flush	1 (2.9) 1	1 (2.9) 1	2 (2.9) 2
Peripheral coldness	0 (0.0) 0	1 (2.9) 1	1 (1.4) 1

Abbreviations: E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects exposed; n = number of subjects

All AEs starting after the start of the infusion of study drug were considered treatment-emergent.

Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than one category were counted once in each of those categories.

MedDRA Version 16.1 used.

Phase I study TROIKA-1

Table 35: Summary of treatment-emergent adverse events – safety population (study TROIKA-1)

		HD201 N=35	EU-Herceptin N=35	US-Herceptin N=35	Total N=105
Any TEAE, n (%) nae		27 (77.1%) 62	30 (85.7%) 71	29 (82.9%) 73	86 (81.9%) 206
Treatment-related TEAE, n (%) nae		18 (51.4%) 37	23 (65.7%) 45	24 (68.6%) 42	65 (61.9%) 124
Intensity of any TEAE, n (%) nae					
	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
TEAE of special interest, n (%) nae		7 (20.0%) 10	12 (34.3%) 12	11 (31.4%) 11	30 (28.6%) 33
Serious TEAE, n (%) nae		0	1 (2.9%) 1	0	1 (1.0%) 1
Treatment-related serious TEAE, n (%) nae		0	0	0	0
TEAE leading to drug interruption/ withdrawal, n		1 (2.9%)	0	3 (8.6%)	4 (3.8%)
Death, n		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 36: Incidence of all TEAEs by SOC and PT reported in any treatment arm – safety population (study TROIKA-1)

SOC PT (MedDRA V 21.1)	HD201 N=35	EU-Herceptin N=35	US-Herceptin N=35	Total N=105
Nervous system disorders, n (%) nae	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
Injury, poisoning and procedural complications, n (%) nae	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 dislocation	0	1 (2.9%) 1	1 (2.9%) 1	2 (1.9%) 2
Contusion	0	0	1 (2.9%) 1	1 (1.0%) 1
Hand fracture	0	1 (2.9%) 1	0	1 (1.0%) 1
Joint injury	1 (2.9%) 1	0	0	1 (1.0%) 1
Ligament sprain	0	1 (2.9%) 1	0	1 (1.0%) 1

SOC PT (MedDRA V 21.1)	HD201 N=35	EU-Herceptin N=35	US-Herceptin N=35	Total N=105
Muscle strain	0	0	1 (2.9%) 1	1 (1.0%) 1
Infections and infestations, n (%) nae	6 (17.1%) 6	7 (20.0%) 7	12 (34.3%) 13	25 (23.8%) 26
Upper respiratory tract infection	0	2 (5.7%) 2	5 (14.3%) 5	7 (6.7%) 7
Rhinitis	1 (2.9%) 1	0	4 (11.4%) 5	5 (4.8%) 6
Influenza	0	1 (2.9%) 1	2 (5.7%) 2	3 (2.9%) 3
Viral upper respiratory tract infection	2 (5.7%) 2	1 (2.9%) 1	0	3 (2.9%) 3
Pharyngitis	1 (2.9%) 1	1 (2.9%) 1	0	2 (1.9%) 2
Folliculitis	1 (2.9%) 1	0	0	1 (1.0%) 1
Nasopharyngitis	0	1 (2.9%) 1	0	1 (1.0%) 1
Tonsillitis	0	0	1 (2.9%) 1	1 (1.0%) 1
Tooth infection	1 (2.9%) 1	0	0	1 (1.0%) 1
Urinary tract infection	0	1 (2.9%) 1	0	1 (1.0%) 1
General disorders and administration site conditions, n (%) nae	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
Catheter site pain	0	2 (5.7%) 2	0	2 (1.9%) 2
Influenza-like illness	2 (5.7%) 3	0	0	2 (1.9%) 3
Infusion site reaction	0	1 (2.9%) 1	1 (2.9%) 1	2 (1.9%) 2
Chills	0	0	1 (2.9%) 1	1 (1.0%) 1
Extravasation	1 (2.9%) 1	0	0	1 (1.0%) 1
Fatigue	0	1 (2.9%) 1	0	1 (1.0%) 1
Respiratory, thoracic and mediastinal disorders, n (%) nae	5 (14.3%) 7	7 (20.0%) 8	4 (11.4%) 5	16 (15.2%) 20
Cough	1 (2.9%) 1	4 (11.4%) 4	0	5 (4.8%) 5
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
Epistaxis	0	1 (2.9%) 1	2 (5.7%) 2	3 (2.9%) 3
Nasal congestion	1 (2.9%) 1	0	0	1 (1.0%) 1
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, n (%) nae	5 (14.3%) 7	3 (8.6%) 3	7 (20.0%) 7	15 (14.3%) 17
Back pain	1 (2.9%) 1	1 (2.9%) 1	3 (8.6%) 3	5 (4.8%) 5
Arthralgia	1 (2.9%) 2	0	1 (2.9%) 1	2 (1.9%) 3
Musculoskeletal pain	2 (5.7%) 3	0	0	2 (1.9%) 3
Myalgia	1 (2.9%) 1	1 (2.9%) 1	0	2 (1.9%) 2
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
Tendonitis	0	1 (2.9%) 1	0	1 (1.0%) 1
Skin and subcutaneous tissue disorders, n (%) nae	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	EU-Herceptin N=35	US-Herceptin N=35	Total N=105
Dermatitis acneiform	0	0	2 (5.7%) 2	2 (1.9%) 2
Erythema	1 (2.9%) 1	1 (2.9%) 1	0	2 (1.9%) 2
Rash	0	1 (2.9%) 1	1 (2.9%) 1	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
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 exfoliation	0	0	1 (2.9%) 1	1 (1.0%) 1
Gastrointestinal disorders, n (%) nae	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
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
Vomiting	1 (2.9%) 1	0	0	1 (1.0%) 1
Blood and lymphatic system disorders, n (%) nae	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
Eye disorders, n (%) nae	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
Investigations, n (%) nae	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 decrased	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, n (%) nae	1 (2.9%) 1	1 (2.9%) 1	1 (2.9%) 1	3 (2.9%) 3
Hypophosphataemia	0	1 (2.9%) 1	1 (2.9%) 1	2 (1.9%) 2
Dehydration	1 (2.9%) 1	0	0	1 (1.0%) 1
Psychiatric disorders, n (%) nae	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
Cardiac disorders, n (%) nae	2 (5.7%) 2	0	0	2 (1.9%) 2
Bundle brance block right	1 (2.9%) 1	0	0	1 (1.0%) 1
Tachycardia	1 (2.9%) 1	0	0	1 (1.0%) 1

Phase III study TROIKA

Table 37: Summary of treatment-emergent adverse events overall – safety set (study TROIKA)

Category	Neoadjuvant		Adjuvant		Overall	
	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 TEAE	246 (98.4%) 2188	243 (96.4%) 2133	164 (68.9%) 678	167 (69.0%) 625	250 (100%) 2859	247 (98.0%) 2755
Grade 3 or higher TEAE	76 (30.4%) 135	65 (25.8%) 114	15 (6.3%) 33	8 (3.3%) 12	86 (34.4%) 167	70 (27.8%) 126
Study treatment-related TEAEs	85 (34.0%) 310	90 (35.7%) 376	74 (31.1%) 233	72 (29.8%) 166	127 (50.8%) 541	136 (54.0%) 541
Chemotherapy treatment-related TEAEs	243 (97.2%) 1891	238 (94.4%) 1865	-	-	-	-
TEAEs leading to study treatment discontinuation	6 (2.4%) 7	3 (1.2%) 9	11 (4.6%) 28	9 (3.7%) 10	16 (6.4%) 34	12 (4.8%) 19
TEAEs leading to dose modification (delay) or study treatment discontinuation	69 (27.6%) 123	61 (24.2%) 118	21 (8.8%) 50	26 (10.7%) 42	83 (33.2%) 172	78 (31.0%) 160
Related to study treatment leading to dose modification (delay) or study treatment discontinuation	14 (5.6%) 22	10 (4.0%) 18	6 (2.5%) 13	7 (2.9%) 9	18 (7.2%) 35	16 (6.3%) 27
Any serious TEAE	16 (6.4%) 22	12 (4.8%) 17	8 (3.4%) 8	6 (2.5%) 7	24 (9.6%) 30	17 (6.7%) 24
Study treatment-related serious TEAEs	0 (0.0%) 0	1 (0.4%) 2	1 (0.4%) 1	2 (0.8%) 2	1 (0.4%) 1	3 (1.2%) 4
Chemotherapy-related serious TEAEs	11 (4.4%) 14	7 (2.8%) 11	-	-	-	-
Serious TEAEs leading to dose modification or study discontinuation	4 (1.6%) 4	5 (2.0%) 6	3 (1.3%) 3	3 (1.2%) 4	7 (2.8%) 7	7 (2.8%) 10
TEAEs of special interest	204 (81.6%) 900	197 (78.2%) 834	117 (49.2%) 269	110 (45.5%) 234	220 (88.0%) 1165	213 (84.5%) 1067
Deaths	3 (1.2%) 3	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	4 (1.6%) 4	0 (0%) 0

N = Number of patients within the treatment group, n = number of patients with an event, nae = number of events; TEAE: Treatment-emergent adverse events;

Table 38: 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) 1843 [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) 206 [83.2; 100.0]	17 (89.5) 159 [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]	9 (45.0) 42 [23.1; 68.5]	10 (52.6) 61 [28.9; 75.6]
Chemotherapy treatment-related TEAEs	211 (97.7) 1638 [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) 158 [68.3; 98.8]	16 (84.2) 133 [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	172 (79.6) 746 [73.6; 84.8]	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) 92 [75.1; 99.9]	15 (78.9) 69 [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 39: 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 (MeDRA V21.0)	Neoadjuvant HD201 N=250 n (%) nae	Neoadjuvant EU-Herceptin N=252 n (%) nae	Adjuvant HD201 N=238 n (%) nae	Adjuvant EU-Herceptin N=242 n (%) nae	Overall HD201 N=250 n (%) nae	Overall EU-Herceptin N=252 n (%) nae
Any TEAEs, n (%)	246 (98.4%) 2188	243 (96.4%) 2132	164 (68.9%) 678	167 (69.0%) 625	250 (100%) 2859	247 (98.0%) 2755
Skin and subcutaneous tissue disorders, n (%)	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%) 0	0 (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, n (%)	139 (55.6%) 363	135 (53.6%) 316	36 (15.1%) 66	39 (16.1%) 53	148 (59.2%) 429	153 (60.7%) 368
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	10 (4.1%) 16	62 (24.8%) 117	67 (26.6%) 102
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
Blood and lymphatic system disorders, n (%)	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
Gastrointestinal disorders, n (%)	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

Diarrhea	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%) 0	0 (0%) 0	19 (7.6%) 23	14 (5.6%) 22
Investigations, n (%)	78 (31.2%) 193	83 (32.9%) 213	60 (25.2%) 130	55 (22.7%) 126	104 (41.6%) 320	102 (40.5%) 338
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-glutamyltransferase 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
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	8 (3.2%) 8	12 (4.8%) 12	11 (4.6%) 11	7 (2.9%) 7	18 (7.2%) 18	18 (7.1%) 19
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
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
Musculoskeletal and connective tissue disorders, n (%)	62 (24.8%) 118	58 (23.0%) 121	30 (12.6%) 42	28 (11.6%) 44	80 (32.0%) 160	76 (30.2%) 165
Arthralgia	28 (11.2%) 49	23 (9.1%) 43	14 (5.9%) 17	11 (4.5%) 14	40 (16.0%) 66	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, n (%)	58 (23.2%) 75	57 (22.6%) 99	31 (13.0%) 51	19 (7.9%) 25	78 (31.2%) 126	73 (29.0%) 124
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
Peripheral sensory neuropathy	12 (4.8%) 12	13 (5.2%) 13	0 (0%) 0	0 (0%) 0	12 (4.8%) 12	13 (5.2%) 13
Cardiac disorders, n (%)	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
Infections and infestations, n (%)	47 (18.8%) 70	47 (18.7%) 66	22 (9.2%) 25	27 (11.2%) 32	61 (24.4%) 95	64 (25.4%) 98
Injury, poisoning and procedural complications, n (%)	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%) 0	0 (0%) 0	16 (6.7%) 16	16 (6.6%) 16	16 (6.4%) 16	16 (6.3%) 16
Metabolism and nutrition disorders, n (%)	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
Decreased appetite	13 (5.2%) 18	12 (4.8%) 21	1 (0.4%) 1	0 (0%) 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, n (%)	33 (13.2%) 42	25 (9.9%) 44	20 (8.4%) 36	16 (6.6%) 20	45 (18.0%) 78	39 (15.5%) 64
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
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
Neoplasms benign, malignant and unspecified	11 (4.4%) 14	7 (2.8%) 8	7 (2.9%) 7	7 (2.9%) 8	18 (7.2%) 21	14 (5.6%) 16

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

Table 40: Incidence of TEAEs related to study treatment by SOC and highest reported PT in any treatment arm for the entire study – safety set (study TROIKA)

Category	Neoadjuvant		Adjuvant		Overall	
	HD201 N = 250 n (%), nae	EU-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 related TEAE	85 (34.0%) 310	90 (35.7%) 375	74 (31.1%) 233	72 (29.8%) 166	127 (50.8%) 541	136 (54.0%) 541
Investigations	18 (7.2%) 33	23 (9.1%) 32	39 (16.4%) 77	27 (11.2%) 44	52 (20.8%) 109	46 (18.3%) 76
Ejection fraction decreased	7 (2.8%) 7	12 (4.8%) 12	10 (4.2%) 10	4 (1.7%) 4	17 (6.8%) 17	15 (6.0%) 16
Cardiac disorders	15 (6.0%) 21	18 (7.1%)	20 (8.4%) 30	24 (9.9%) 36	33 (13.2%) 50	39 (15.5%) 60
Mitral valve incompetence	1 (0.4%) 1	1 (0.4%) 1	3 (1.3%) 3	5 (2.1%) 5	4 (1.6%) 4	6 (2.4%) 6
Blood and lymphatic system disorders	18 (7.2%) 40	13 (5.2%) 32	16 (6.7%) 38	11 (4.5%) 17	30 (12.0%) 78	23 (9.1%) 49
Neutropenia	11 (4.4%) 21	8 (3.2%) 14	8 (3.4%) 11	2 (0.8%) 2	17 (6.8%) 32	9 (3.6%) 16
Gastrointestinal disorders	16 (6.4%) 38	30 (11.9%) 63	6 (2.5%) 8	1 (0.4%) 3	20 (8.0%) 46	31 (12.3%) 66
Nausea	7 (2.8%) 17	16 (6.3%) 30	0	1 (0.4%) 1	7 (2.8%) 17	17 (6.7%) 31
General disorders and administration site conditions	12 (4.8%) 30	24 (9.5%) 44	6 (2.5%) 20	8 (3.3%) 11	15 (6.0%) 50	29 (11.5%) 54
Fatigue	5 (2.0%) 11	11 (4.4%) 11	3 (1.3%) 15	3 (1.2%) 6	6 (2.4%) 26	13 (5.2%) 17
Musculoskeletal and connective tissue disorders	12 (4.8%) 21	15 (6.0%) 30	7 (2.9%) 12	6 (2.5%) 15	18 (7.2%) 33	18 (7.1%) 45
Arthralgia	8 (3.2%) 11	7 (2.8%) 16	5 (2.1%) 6	3 (1.2%) 5	12 (4.8%) 17	9 (3.6%) 21
Nervous system disorders	11 (4.4%) 17	13 (5.2%) 27	7 (2.9%) 9	6 (2.5%) 7	16 (6.4%) 26	18 (7.1%) 34
Headache	4 (1.6%) 5	4 (1.6%) 4	3 (1.3%) 3	3 (1.2%) 4	5 (2.0%) 8	7 (2.8%) 8
Respiratory, thoracic and mediastinal disorders	11 (4.4%) 14	8 (3.2%) 15	10 (4.2%) 13	2 (0.8%) 2	19 (7.6%) 27	10 (4.0%) 17
Dyspnoea	3 (1.2%) 4	3 (1.2%) 3	4 (1.7%) 4	0	6 (2.4%) 8	3 (1.2%) 3
Metabolism and nutrition disorders	6 (2.4%) 8	7 (2.8%) 13	9 (3.8%) 13	6 (2.5%) 9	15 (6.0%) 21	13 (5.2%) 22
Decreased appetite	6 (2.4%) 7	7 (2.8%) 13	0	0	6 (2.4%) 7	7 (2.8%) 13
Infections and infestations	8 (3.2%) 16	6 (2.4%) 13	1 (0.4%) 1	4 (1.7%) 4	8 (3.2%) 17	7 (2.8%) 17
Conjunctivitis	3 (1.2%) 6	1 (0.4%) 1	0	1 (0.4%) 1	3 (1.2%) 6	2 (0.8%) 2
Eye disorders	4 (1.6%) 6	6 (2.4%) 8	1 (0.4%) 1	1 (0.4%) 1	5 (2.0%) 7	7 (2.8%) 9
Lacrimation increased	4 (1.6%) 6	5 (2.0%) 6	1 (0.4%) 1	1 (0.4%) 1	5 (2.0%) 7	6 (2.4%) 7
Vascular disorders	1 (0.4%) 1	4 (1.6%) 8	4 (1.7%) 5	3 (1.2%) 5	5 (2.0%) 6	6 (2.4%) 13
Hypertension	1 (0.4%) 1	3 (1.2%) 6	2 (0.8%) 2		3 (1.2%) 3	3 (1.2%) 6
Injury, poisoning and procedural complications	1 (0.4%) 1	3 (1.2%) 3	0	1 (0.4%) 1	1 (0.4%) 1	4 (1.6%) 4
Infusion related reaction	1 (0.4%) 1	2 (0.8%) 2	0	0	1 (0.4%) 1	2 (0.8%) 2
Hepatobiliary disorders	1 (0.4%) 7	2 (0.8%) 2	0	1 (0.4%) 2	1 (0.4%) 7	3 (1.2%) 4
Hepatic pain	1 (0.4%) 7	2 (0.8%) 2	0	0	1 (0.4%) 7	2 (0.8%) 2
Psychiatric disorders	1 (0.4%) 1	2 (0.8%) 2	1 (0.4%) 2	0	2 (0.8%) 3	2 (0.8%) 2
Insomnia	1 (0.4%) 1	1 (0.4%) 1	1 (0.4%) 2	0	2 (0.8%) 3	1 (0.4%) 1
Reproductive system and breast disorders	1 (0.4%) 1	3 (1.2%) 3	0	0	1 (0.4%) 1	3 (1.2%) 3
Breast pain	1 (0.4%) 1	3 (1.2%) 3	0	0	1 (0.4%) 1	3 (1.2%) 3
Ear and labyrinth disorders	0	1 (0.4%) 1	0	1 (0.4%) 1	0	2 (0.8%) 2
Vertigo	0	1 (0.4%) 1	0	1 (0.4%) 1	0	2 (0.8%) 2
Immune system disorders	0	1 (0.4%) 1	0	0	0	1 (0.4%) 1
Hypersensitivity	0	1 (0.4%) 1	0	0	0	1 (0.4%) 1
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 41: Overview of TEAEs by severity by SOC occurring ≥5% in either treatment group - safety set (study TROIKA- modified by the assessor)

SOC	Neoadjuvant		Adjuvant		Overall	
	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%)
Mild	22 (8.8%)	24 (9.5%)	90 (37.8%)	93 (38.4%)	18 (7.2%)	25 (9.9%)
Moderate	148 (59.2%)	154 (61.1%)	59 (24.8%)	66 (27.3%)	146 (58.4%)	152 (60.3%)
Severe	58 (23.2%)	55 (21.8%)	13 (5.5%)	7 (2.9%)	66 (26.4%)	59 (23.4%)
Life-threatening	14 (5.6%)	10 (4.0%)	0 (0%)	1 (0.4%)	14 (5.6%)	11 (4.4%)
Fatal	4 (1.6%)	0 (0%)	2 (0.8%)	0 (0%)	6 (2.4%)	0 (0%)
Skin and subcutaneous tissue disorders	211 (84.4%)	210 (83.3%)	16 (6.7%)	13 (5.4%)	214 (85.6%)	210 (83.3%)
Mild	54 (21.6%)	46 (18.3%)	14 (5.9%)	10 (4.1%)	56 (22.4%)	46 (18.3%)
Moderate	147 (58.8%)	156 (61.9%)	2 (0.8%)	3 (1.2%)	148 (59.2%)	156 (61.9%)
Severe	10 (4.0%)	8 (3.2%)	0 (0%)	0 (0%)	10 (4.0%)	8 (3.2%)
Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
General disorders and administration site conditions	139 (55.6%)	135 (53.6%)	36 (15.1%)	39 (16.1%)	148 (59.2%)	153 (60.7%)
Mild	76 (30.4%)	76 (30.2%)	32 (13.4%)	34 (14.0%)	85 (34.0%)	90 (35.7%)
Moderate	60 (24.0%)	58 (23.0%)	3 (1.3%)	5 (2.1%)	59 (23.6%)	62 (24.6%)
Severe	2 (0.8%)	1 (0.4%)	1 (0.4%)	0 (0%)	3 (1.2%)	1 (0.4%)
Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatal	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (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	40 (16.0%)	35 (13.9%)	33 (13.9%)	30 (12.4%)	42 (16.8%)	44 (17.5%)
Moderate	43 (17.2%)	36 (14.3%)	14 (5.9%)	15 (6.2%)	49 (19.6%)	41 (16.3%)
Severe	32 (12.8%)	39 (15.5%)	2 (0.8%)	0 (0%)	33 (13.2%)	39 (15.5%)
Life-threatening	11 (4.4%)	10 (4.0%)	0 (0%)	0 (0%)	11 (4.4%)	10 (4.0%)
Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal disorders	131 (52.4%)	129 (51.2%)	15 (6.3%)	11 (4.5%)	137 (54.8%)	132 (52.4%)
Mild	88 (35.2%)	77 (30.6%)	9 (3.8%)	7 (2.9%)	92 (36.8%)	79 (31.3%)
Moderate	40 (16.0%)	48 (19.0%)	6 (2.5%)	4 (1.7%)	42 (16.8%)	49 (19.4%)
Severe	3 (1.2%)	4 (1.6%)	0 (0%)	0 (0%)	3 (1.2%)	4 (1.6%)
Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Investigations		78 (31.2%)	83 (32.9%)	60 (25.2%)	55 (22.7%)	104 (41.6%)	102 (40.5%)
	Mild	39 (15.6%)	39 (15.5%)	43 (18.1%)	34 (14.0%)	53 (21.2%)	46 (18.3%)
	Moderate	17 (6.8%)	38 (15.1%)	13 (5.5%)	20 (8.3%)	27 (10.8%)	49 (19.4%)
	Severe	20 (8.0%)	6 (2.4%)	4 (1.7%)	1 (0.4%)	22 (8.8%)	7 (2.8%)
	Life-threatening	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)	0 (0%)
	Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders		62 (24.8%)	58 (23.0%)	30 (12.6%)	28 (11.6%)	80 (32.0%)	76 (30.2%)
	Mild	38 (15.2%)	45 (17.9%)	21 (8.8%)	22 (9.1%)	50 (20.0%)	57 (22.6%)
	Moderate	24 (9.6%)	13 (5.2%)	9 (3.8%)	6 (2.5%)	30 (12.0%)	19 (7.5%)
	Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders		58 (23.2%)	57 (22.6%)	31 (13.0%)	19 (7.9%)	78 (31.2%)	73 (29.0%)
	Mild	47 (18.8%)	40 (15.9%)	22 (9.2%)	16 (6.6%)	60 (24.0%)	53 (21.0%)
	Moderate	11 (4.4%)	13 (5.2%)	5 (2.1%)	3 (1.2%)	14 (5.6%)	16 (6.3%)
	Severe	0 (0%)	4 (1.6%)	4 (1.7%)	0 (0%)	4 (1.6%)	4 (1.6%)
	Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cardiac disorders		44 (17.6%)	48 (19.0%)	33 (13.9%)	41 (16.9%)	61 (24.4%)	69 (27.4%)
	Mild	37 (14.8%)	37 (14.7%)	27 (11.3%)	35 (14.5%)	49 (19.6%)	54 (21.4%)
	Moderate	4 (1.6%)	10 (4.0%)	3 (1.3%)	5 (2.1%)	6 (2.4%)	13 (5.2%)
	Severe	1 (0.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)	3 (1.2%)	2 (0.8%)
	Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Fatal	2 (0.8%)	0 (0%)	1 (0.4%)	0 (0%)	3 (1.2%)	0 (0%)
Infections and infestations		47 (18.8%)	47 (18.7%)	22 (9.2%)	27 (11.2%)	61 (24.4%)	64 (25.4%)
	Mild	14 (5.6%)	17 (6.7%)	10 (4.2%)	10 (4.1%)	22 (8.8%)	25 (9.9%)
	Moderate	30 (12.0%)	26 (10.3%)	12 (5.0%)	16 (6.6%)	36 (14.4%)	35 (13.9%)
	Severe	3 (1.2%)	3 (1.2%)	0 (0%)	1 (0.4%)	3 (1.2%)	3 (1.2%)
	Life-threatening	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
	Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Injury, poisoning and procedural complications		34 (13.6%)	35 (13.9%)	26 (10.9%)	37 (15.3%)	55 (22.0%)	67 (26.6%)
	Mild	23 (9.2%)	20 (7.9%)	21 (8.8%)	33 (13.6%)	40 (16.0%)	49 (19.4%)
	Moderate	11 (4.4%)	14 (5.6%)	5 (2.1%)	4 (1.7%)	15 (6.0%)	17 (6.7%)
	Severe	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
	Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Metabolism and nutrition disorders	41 (16.4%)	36 (14.3%)	22 (9.2%)	20 (8.3%)	49 (19.6%)	44 (17.5%)
Mild	36 (14.4%)	30 (11.9%)	18 (7.6%)	16 (6.6%)	40 (16.0%)	34 (13.5%)
Moderate	1 (0.4%)	5 (2.0%)	4 (1.7%)	4 (1.7%)	5 (2.0%)	9 (3.6%)
Severe	4 (1.6%)	1 (0.4%)	0 (0%)	0 (0%)	4 (1.6%)	1 (0.4%)
Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	33 (13.2%)	25 (9.9%)	20 (8.4%)	16 (6.6%)	45 (18.0%)	39 (15.5%)
Mild	26 (10.4%)	20 (7.9%)	15 (6.3%)	12 (5.0%)	33 (13.2%)	31 (12.3%)
Moderate	7 (2.8%)	5 (2.0%)	5 (2.1%)	4 (1.7%)	12 (4.8%)	8 (3.2%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vascular disorders	27 (10.8%)	22 (8.7%)	14 (5.9%)	21 (8.7%)	40 (16.0%)	38 (15.1%)
Mild	22 (8.8%)	12 (4.8%)	9 (3.8%)	14 (5.8%)	30 (12.0%)	21 (8.3%)
Moderate	5 (2.0%)	8 (3.2%)	5 (2.1%)	4 (1.7%)	10 (4.0%)	12 (4.8%)
Severe	0 (0%)	2 (0.8%)	0 (0%)	3 (1.2%)	0 (0%)	5 (2.0%)
Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hepatobiliary disorders	16 (6.4%)	15 (6.0%)	3 (1.3%)	3 (1.2%)	17 (6.8%)	18 (7.1%)
Mild	12 (4.8%)	13 (5.2%)	1 (0.4%)	2 (0.8%)	12 (4.8%)	15 (6.0%)
Moderate	4 (1.6%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	4 (1.6%)	3 (1.2%)
Severe	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	1 (0.4%)	0 (0%)
Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (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	8 (3.2%)	6 (2.4%)	2 (0.8%)	10 (4.1%)	9 (3.6%)	16 (6.3%)
Moderate	2 (0.8%)	4 (1.6%)	1 (0.4%)	0 (0%)	3 (1.2%)	4 (1.6%)
Severe	1 (0.4%)	1 (0.4%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.4%)
Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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	7 (2.8%)	1 (0.4%)	4 (1.7%)	2 (0.8%)	11 (4.4%)	8 (3.2%)
Moderate	2 (0.8%)	6 (2.4%)	1 (0.4%)	2 (0.8%)	3 (1.2%)	3 (1.2%)
Severe	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (0.8%)	2 (0.8%)	2 (0.8%)
Life-threatening	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	1 (0.4%)
Fatal	1 (0.4%)	0 (0%)	1 (0.4%)	0 (0%)	2 (0.8%)	0 (0%)
Eye disorders	13 (5.2%)	10 (4.0%)	5 (2.1%)	3 (1.2%)	16 (6.4%)	13 (5.2%)
Mild	10 (4.0%)	8 (3.2%)	2 (0.8%)	3 (1.2%)	10 (4.0%)	11 (4.4%)
Moderate	3 (1.2%)	2 (0.8%)	2 (0.8%)	0 (0%)	5 (2.0%)	2 (0.8%)
Severe	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	1 (0.4%)	0 (0%)
Life-threatening	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fatal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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

Overall, the most common grade ⩾3 TEAEs were alopecia, neutropenia, leukopenia and rash. The most common life-threatening TEAE was neutropenia (4.0% of subjects in the HD201 group and 3.6% in the EU-Herceptin treatment). Fatal (Grade 5) TEAEs were reported in 4 patients in the HD201 group (1 sudden death, 2 cases of myocardial infarction, 1 cardio-respiratory arrest). In addition, there were 2 cases of metastasis to the central nervous system (refer to section on deaths below).

2.7.3. Serious adverse event/deaths/other significant events

Phase I study EAGLE-I-12

There was one SAE of perianal abscess in the Herceptin group, assessed as possibly related to the study drug, and none in the HD201 group. No TEAEs had a fatal outcome.

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 42: Summary of serious TEAEs during entire study – safety set (TROIKA)

	Neoadjuvant		Adjuvant		Overall	
	HD201 N = 250	EU-Herceptin N = 252	HD201 N = 238	EU-Herceptin N = 242	HD201 N = 250	EU-Herceptin N = 252
Number of subjects experiencing	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae	n (%) nae
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
Serious TEAE severity						
Grade 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	2 (0.8%) 2	0 (0%) 0	2 (0.8%) 2
Grade 2	1 (0.4%) 3	5 (2.0%) 7	3 (1.3%) 3	1 (0.4%) 1	4 (1.6%) 6	6 (2.4%) 8
Grade 3	10 (4%) 14	5 (2.0%) 6	4 (1.7%) 4	3 (1.2%) 4	14 (5.6%) 18	7 (2.8%) 10
Grade 4	2 (0.8%) 2	2 (0.8%) 4	0 (0%) 0	0 (0%) 0	2 (0.8%) 2	2 (0.8%) 4
Grade 5	3 (1.2%) 3	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	4 (1.6%) 4	0 (0%) 0
Serious TEAEs related with IP						
Related	0 (0%) 0	1 (0.4%) 2	1 (0.4%) 1	2 (0.8%) 2	1 (0.4%) 1	3 (1.2%) 4
Serious TEAEs related with chemotherapy						
Related	11 (4.4%) 14	7 (2.8%) 11	0 (0%) 0	0 (0%) 0	11 (4.4%) 14	7 (2.8%) 11
Serious TEAE outcome						
Recovered/Resolved	13 (5.2%)19	10 (4.0%) 15	5 (2.0%) 5	3 (1.2%) 3	18 (7.2%) 24	13 (5.2%) 18
Recovered/Resolved with sequelae	0 (0%) 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	0 (0%) 0	0 (0%) 0	0 (0%) 0	0 (0%) 0
Fatal	3 (1.2%) 3	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	4 (1.6%) 4	0 (0%) 0
Unknown	0 (0%) 0	0 (0%) 0	0 (0%) 0	0 (0%) 0	0 (0%) 0	0 (0%) 0

N: Number of subjects, n: Number of subjects with an event; TEAE: Treatment-emergent adverse event

Table 43: Serious TEAEs by SOC and PT for the entire study – safety set (study TROIKA)

SOC PT (MeDRA V21.0)	Neoadjuvant		Adjuvant		Overall	
	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 serious TEAE, n (%)	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%) 0	0 (0%) 0	8 (3.2%) 9	5 (2.0%) 5
Febrile neutropenia	6 (2.4%) 6	4 (1.6%) 4	0 (0%) 0	0 (0%) 0	6 (2.4%) 6	4 (1.6%) 4
Anaemia	2 (0.8%) 2	0 (0%) 0	0 (0%) 0	0 (0%) 0	2 (0.8%) 2	0 (0%) 0
Neutropenia	1 (0.4%) 1	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	1 (0.4%) 1
Infections and infestations, n (%)	3 (1.2%) 3	4 (1.6%) 5	1 (0.4%) 1	2 (0.8%) 2	4 (1.6%) 4	5 (2.0%) 7
Pneumonia	0 (0%) 0	3 (1.2%) 3	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	3 (1.2%) 4
Bronchitis	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Influenza	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1
Mastitis	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Septic shock	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1
Urinary tract infection	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Erysipelas	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1
Opisthorchiasis	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Cardiac disorders, n (%)	2 (0.8%) 2	1 (0.4%) 1	2 (0.8%) 2	1 (0.4%) 1	4 (1.6%) 4	2 (0.8%) 2
Cardio-respiratory arrest	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Myocardial infarction	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	2 (0.8%) 2	0 (0%) 0
Supraventricular tachycardia	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1
Cardiac failure chronic	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Cytotoxic cardiomyopathy	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1
Nervous system disorders, n (%)	0 (0%) 0	2 (0.8%) 3	2 (0.8%) 2	0 (0%) 0	2 (0.8%) 2	2 (0.8%) 3
Hemorrhagic stroke	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1
Seizure	0 (0%) 0	1 (0.4%) 2	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 2
Cerebrovascular accident	0 (0%) 0	0 (0%) 0	2 (0.8%) 2	0 (0%) 0	2 (0.8%) 2	0 (0%) 0
Immune system disorders, n (%)	2 (0.8%) 2	1 (0.4%) 2	0 (0%) 0	0 (0%) 0	2 (0.8%) 2	1 (0.4%) 2
Hypersensitivity	2 (0.8%) 2	1 (0.4%) 2	0 (0%) 0	0 (0%) 0	2 (0.8%) 2	1 (0.4%) 2
Gastrointestinal disorders, n (%)	2 (0.8%) 2	0 (0%) 0	0 (0%) 0	0 (0%) 0	2 (0.8%) 2	0 (0%) 0
Diarrhoea	2 (0.8%) 2	0 (0%) 0	0 (0%) 0	0 (0%) 0	2 (0.8%) 2	0 (0%) 0
Injury, poisoning and procedural complications, n (%)	0 (0%) 0	1 (0.4%) 1	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1	1 (0.4%) 1
Post procedural haematoma	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1
Post procedural inflammation	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
General disorders and administration site conditions, n (%)	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Sudden death	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Investigations, n (%)	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Liver function test abnormal	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Metabolism and nutrition disorders, n (%)	1 (0.4%) 2	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 2	0 (0%) 0
Hyperglycaemia	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Hyponatraemia	1 (0.4%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Reproductive system and breast disorders	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	1 (0.4%) 1	1 (0.4%) 1	1 (0.4%) 1
Colpocele	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1
Uterine polyp	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Vascular disorders	0 (0%) 0	0 (0%) 0	0 (0%) 0	2 (0.8%) 2	0 (0%) 0	2 (0.8%) 2
Essential hypertension	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1
Hypertensive crisis	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1
Eye disorders	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Open angle glaucoma	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1	0 (0%) 0
Neoplasms benign, malignant and unspecified	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1
Uterine leiomyoma	0 (0%) 0	0 (0%) 0	0 (0%) 0	1 (0.4%) 1	0 (0%) 0	1 (0.4%) 1

N: Number of subjects within the treatment group; n: Number of subjects with an event; nae: Number of adverse events; TEAE: Treatment-emergent adverse event; SOC: System organ class; PT: Preferred term

A total of six deaths occurred in TROIKA, all 6 occurring in the HD201 treatment arm. Four deaths were reported during the neoadjuvant treatment period and 2 deaths were reported during the adjuvant treatment period. Three deaths in the neoadjuvant period (sudden death, myocardial infarction and cardio-respiratory arrest) and 1 death in the adjuvant period (myocardial infarction) were outcomes of reported serious AEs. One death each in the neoadjuvant and adjuvant treatment period was due to disease progression and not reported as serious TEAE. None of the 4 deaths from TEAEs were considered by the investigators to be related to the study drug.

Table 44: Summary of deaths by SOC and PT for the entire study – safety set (study TROIKA)

SOC PT	Neoadjuvant (SAF) HD201 N=250 n (%)	 EU-Herceptin N=252 n (%)	Adjuvant (aSAF) HD201 N=238 n (%)	 EU-Herceptin N=242 n (%)	Entire period (SAF) HD201 N=250 n (%)	 EU-Herceptin N=252 n (%)
Any death	**4 (1.6)**	**0**	**2 (0.8)**	**0**	**6 (2.4)**	**0**
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**	**1 (0.4)**	**0**	**2 (0.8)**	**0**
Metastases to central nervous system	1 (0.4)	0	1 (0.4)	0	2 (0.8)	0

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

Details of each case are briefly described below.

A 53-year-old Caucasian female patient was randomised to receive HD201. The patient's medical history includes anaemia since 1996 and grade 1 hypertension. Her past medical history includes, diffuse hepatic and pancreatic abnormalities, grade 1 chronic pyelonephritis, grade 1 nonspecific change in myocardium, aortic fibrosis, mitral valve insufficiency, grade 1 asynergy of interventricular septum, grade 1 pulmonary hypertension and grade 2 acute cerebrovascular event. On 4 June 2018, she received the 2nd cycle of the study drug at a dose of 6 mg/kg via intravenous infusion (neoadjuvant treatment period). She also received a cycle of docetaxel. On 18 June 2018, Day 14 of cycle 2, the patient presented with dizziness and fell. Her daughter reported her blood pressure as 60/40. The patient died prior to the arrival of the ambulance. Cause of death was reported as sudden death. This event was considered by investigator as unrelated to the study drug.

A 51-year-old Caucasian female patient was assigned to HD201 treatment arm. The patient had no significant medical history. On 29 June 2018, she received the first cycle of the study drug at a dose of 8 mg/kg via intravenous infusion (neoadjuvant treatment period). She also received a cycle of docetaxel on the same day. On 5 July 2018, 7 days after the first dose of the study drug, she reported over the phone that she experienced a heart attack. She was taken to the hospital where she passed away on the same day. The cause of death was reported as myocardial infarction. This event was considered by the investigator to be unrelated to the study drug.

A 53-year-old Caucasian female patient was randomised to receive HD201. The patient's medical history includes hypertension, depressive syndrome, dyslipidaemia, gout of the right foot, and grade 2 anaemia. The patient had a history of central venous catheter thrombosis treated with one month of subcutaneous heparin. On 14 January 2019, she received the 6th cycle of the study drug at a dose of 6 mg/kg via intravenous infusion (neoadjuvant treatment period). She also received a cycle of epirubicin and cyclophosphamide on the same day. On 30 January 2019, on Day 16 of cycle 6, she presented with progressive grade 3 dyspnoea and was taken to the emergency department where she received

treatment for cardiac arrest. Despite cardiopulmonary resuscitation attempts, she was pronounced dead due to cardiorespiratory arrest likely provoked by a massive pulmonary embolism. The event was considered by the investigators as unlikely related to drug.

A 63-year-old Caucasian female patient was randomised to receive HD201. The patient's medical history includes chronic cardiac failure (NYHA stage 2) since 2017, ischemic heart disease since 2017 and grade 1 hypertension since 2016. On 4 July 2019, she received the 14th cycle of study drug at a dose of 6 mg/kg via intravenous infusion (adjuvant treatment period). It was reported by her husband that on 6 July 2019 (Day 2 of cycle 14), patient presented with heart pain and died prior to the arrival of the ambulance. An autopsy revealed the cause of death as myocardial infarction and heart tamponade and deemed unrelated to the study drug.

Adverse events of special interest

EAGLE-I-12

Neither the study protocol nor the summary of clinical safety contained any information about adverse events of special interest in the Phase I study EAGLE-I-12.

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 45: TEAEs of special interest by SOC and PT (study 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
Subjects with TEAEs of special interest	7 (20.0%) 10	12 (34.3%) 12	11 (31.4%) 11	30 (28.6%) 33
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
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
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
Nervous system disorders	2 (5.7%) 2	0	0	2 (1.9%) 2
Headache	2 (5.7%) 2	0	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

The study protocol of the TROIKA study did not contain any information about adverse events of special interest. TEAEs of special interest were derived based on the mechanism of action and clinical data available in product labelling for trastuzumab. The AEs of special interest were identified by searching through TROIKA TEAE database using MedDRA SOC, MedDRA PTs and Standardised MedDRA

queries to identify potential cases of interest as defined in statistical analysis plan for safety. The TEAEs of special interest for this study included cardiotoxicity, infusion-site reactions and hypersensitivity, haematotoxicity, pulmonary disorders, infections and oligohydramnios.

Table 46: Overall summary of treatment-emergent adverse events of special interest- safety set (study TROKA)

	Neoadjuvant		Adjuvant		Overall	
	HD201 n (%) nae	EU-Herceptin n (%) nae	HD201 n (%) nae	EU-Herceptin n (%) nae	HD201 n (%) nae	EU-Herceptin n (%) nae
Any TEAE of special interest	204 (81.6%) 900	197 (78.2%) 834	117 (49.2%) 269	111 (45.5%) 234	220 (88.0%) 1165	213 (84.5%) 1067
Types of TEAEs of special interest						
Cardiotoxicity	65 (26.0%) 105	60 (23.8%) 99	53 (22.3%) 84	50 (20.7%) 72	92 (36.8%) 187	87 (34.5%) 171
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
Hematotoxicity	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
Oligohydramnios	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%)

N: Number of patients within the treatment group, n: Number of patients with an event, nae: Number of adverse events; SOC: System Organ class; PT: Prefered term; TEAE: Treatment-emergent adverse event

Cardiotoxicity

Table 47: Incidence of cardiotoxic TEAEs occurring in ≥2% of patients by PT reported in any treatment arm for the entire study – safety set (study TROIKA)

Preferred Term	HD201 N=250		EU-Herceptin N=252	
	Any	Related to study treatment	Any	Related to study treatment
Any cardiotoxic TEAE of special interest n (%)	92 (36.8%)	53 (21.2%)	87 (34.5%)	55 (21.8%)
Ejection fraction decreased	18 (7.2%)	17 (6.8%)	18 (7.1%)	15 (6.0%)
Sinus tachycardia	16 (6.4%)	2 (0.8%)	16 (6.3%)	6 (2.4%)
Oedema peripheral	17 (6.8%)	1 (0.4%)	14 (5.6%)	4 (1.6%)
Electrocardiogram abnormal	16 (6.4%)	7 (2.8%)	9 (3.6%)	3 (1.2%)
Dyspnoea	9 (3.6%)	6 (2.4%)	7 (2.8%)	3 (1.2%)
Electrocardiogram repolarisation abnormality	6 (2.4%)	5 (2.0%)	9 (3.6%)	5 (2.0%)
Left ventricular hypertrophy	4 (1.6%)	2 (0.8%)	8 (3.2%)	2 (0.8%)
Tachycardia	5 (2.0%)	4 (1.6%)	7 (2.8%)	5 (2.0%)
Bundle branch block right	6 (2.4%)	3 (1.2%)	5 (2.0%)	4 (1.6%)
Left ventricular dysfunction	8 (3.2%)	5 (2.0%)	3 (1.2%)	2 (0.8%)
Ventricular dyssynchrony	4 (1.6%)	2 (0.8%)	7 (2.8%)	1 (0.4%)
Supraventricular extrasystoles	2 (0.8%)	0 (0%)	6 (2.4%)	3 (1.2%)
Atrial enlargement	2 (0.8%)	1 (0.4%)	5 (2.0%)	1 (0.4%)
Sinus bradycardia	5 (2.0%)	3 (1.2%)	2 (0.8%)	0 (0%)

N: Number of subjects; TEAE: Treatment-emergent adverse event

ECG

12-Lead ECG was performed at screening, before cycle 5, before surgery, before cycles 12, 16 and EOT visit and will be followed up at 6 and 12 months after completion of trastuzumab treatment.

Heart Failure

In the HD201 treatment group, 1 (0.4%) patient had cardiac failure (related to investigational medicinal product (IP)) and 1 (0.4%) patient had cardiac failure chronic (related to IP). Both these related events were severe. In the EU-Herceptin arm, 1 (0.4%) patient had cardiac failure chronic (severe, non-IP related).

Infusion site reactions and hypersensitivity

Table 48: Incidence 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 – safety set (study TROIKA)

Preferred Term	HD201 N=250		EU-Herceptin N=252	
	Any	Related to study treatment	Any	Related to study treatment
Any IRR and hypersensitivity TEAEs, n (%)	127 (50.8%)	48 (19.2%)	121 (48.0%)	43 (17.1%)
Nausea	86 (34.4%)	7 (2.8%)	93 (36.9%)	17 (6.7%)
Headache	26 (10.4%)	5 (2.0%)	22 (8.7%)	7 (2.8%)
Rash	26 (10.4%)	17 (6.8%)	17 (6.7%)	9 (3.6%)
Vomiting	21 (8.4%)	2 (0.8%)	18 (7.1%)	5 (2.0%)
Stomatitis	19 (7.6%)	1 (0.4%)	14 (5.6%)	3 (1.2%)
Pyrexia	17 (6.8%)	2 (0.8%)	13 (5.2%)	1 (0.4%)
Dyspnoea	9 (3.6%)	6 (2.4%)	7 (2.8%)	3 (1.2%)
Pruritus	6 (2.4%)	2 (0.8%)	7 (2.8%)	3 (1.2%)
Tachycardia	5 (2.0%)	4 (1.6%)	7 (2.8%)	5 (2.0%)
Erythema	5 (2.0%)	1 (0.4%)	6 (2.4%)	5 (2.0%)
Conjunctivitis	5 (2.0%)	3 (1.2%)	4 (1.6%)	2 (0.8%)

N: Number of subjects; TEAE: Treatment-emergent adverse event

Haematotoxicity

Table 49: Incidence of Haematotoxic TEAEs of special interest occurring in ⩾2% of patients by PT reported in any treatment arm for the entire study – safety set (study TROIKA)

Preferred Term	HD201 N=250		EU-Herceptin N=252	
	Any	Related to study treatment	Any	Related to study treatment
Any haematotoxic TEAEs, n(%)	144 (57.6%)	32 (12.8%)	142 (56.3%)	26 (10.3%)
Hematopoietic leukopenia	110 (44.0%)	23 (9.2%)	107 (42.5%)	16 (6.3%)
Neutropenia	77 (30.8%)	17 (6.8%)	78 (31.0%)	9 (3.6%)
Leukopenia	44 (17.6%)	9 (3.6%)	51 (20.2%)	10 (4.0%)
Neutrophil count decreased	15 (6.0%)	3 (1.2%)	8 (3.2%)	3 (1.2%)
Febrile neutropenia	8 (3.2%)	0 (0%)	7 (2.8%)	0 (0%)
White blood cell count decreased	10 (4.0%)	4 (1.6%)	4 (1.6%)	2 (0.8%)
Lymphopenia	3 (1.2%)	0 (0%)	5 (2.0%)	0 (0%)
Hematopoitic erythropenia	72 (28.8%)	11 (4.4%)	61 (24.2%)	8 (3.2%)
Anaemia	72 (28.8%)	11 (4.4%)	61 (24.2%)	7 (2.8%)
Hematopoietic thrombocytopenia	20 (8.0%)	7 (2.8%)	13 (5.2%)	7 (2.8%)
Thrombocytopenia	13 (5.2%)	4 (1.6%)	10 (4.0%)	5 (2.0%)
Platelet count decreased	7 (2.8%)	3 (1.2%)	3 (1.2%)	2 (0.8%)

N: Number of subjects; TEAE: Treatment-emergent adverse event

Pulmonary disorders

Table 50: Incidence of pulmonary TEAEs of special interest occurring in ⩾ 2% of patients by PT reported in any treatment arm for the entire study – safety set (study TROIKA)

Preferred Term	HD201 N=250		EU-Herceptin N=252	
	Any	Related to study treatment	Any	Related to study treatment
Any pulmonary TEAEs, n (%)	29 (11.6%)	12 (4.8%)	23 (9.1%)	7 (2.8%)
Pulmonary hypertension	10 (4.0%)	3 (1.2%)	9 (3.6%)	2 (0.8%)
Dyspnoea	9 (3.6%)	6 (2.4%)	7 (2.8%)	3 (1.2%)
Atrial enlargement	2 (0.8%)	1 (0.4%)	5 (2.0%)	1 (0.4%)

N: Number of subjects; TEAE: Treatment-emergent adverse event

Infections

Table 51: Incidence of TEAEs of special interest related to infections occurring in ⩾ 2% of patients by PT reported in any treatment arm for the entire study – safety set (study TROIKA)

Preferred Term	HD201 N=250		EU-Herceptin N=252	
	Any	Related to study treatment	Any	Related to study treatment
Any infection TEAEs, n (%)	61 (24.4%)	8 (3.2%)	64 (25.4%)	7 (2.8%)
Bronchitis	4 (1.6%)	0 (0%)	11 (4.4%)	0 (0%)
Nasopharyngitis	5 (2.0%)	1 (0.4%)	9 (3.6%)	0 (0%)
Upper respiratory tract infection	11 (4.4%)	0 (0%)	4 (1.6%)	0 (0%)
Respiratory tract infection viral	6 (2.4%)	0 (0%)	7 (2.8%)	0 (0%)
Respiratory tract infection	6 (2.4%)	0 (0%)	5 (2.0%)	0 (0%)
Rhinitis	4 (1.6%)	1 (0.4%)	7 (2.8%)	4 (1.6%)
Conjunctivitis	5 (2.0%)	3 (1.2%)	4 (1.6%)	2 (0.8%)
Pharyngitis	2 (0.8%)	0 (0%)	6 (2.4%)	0 (0%)
Tracheitis	6 (2.4%)	0 (0%)	1 (0.4%)	0 (0%)

N: Number of subjects; TEAE: Treatment-emergent adverse event

2.7.4. Laboratory findings

Phase I study EAGLE-I-12

Electrocardiograms, echocardiography, physical examination findings and clinical laboratory analyses including haematology, biochemistry and urine analyses did not show any significant changes over time and were in general similar between treatment groups.

The mean change from baseline in pulse rate was higher for the Herceptin group than for the HD201 group between day 1, 1.25 hrs post dose (3.7 beats/min vs 1.6 beats/min) and 11.5 hrs post dose

(12.9 beats/min vs 6.4 beats/min). The applicant did not report any other obvious differences in vital signs between the treatment groups.

Six subjects had clinically significant oral temperature values. It is unclear which treatment they received.

Phase I study TROIKA-1

There were no notable differences in laboratory parameters between HD201, EU-Herceptin and US-Herceptin in clinical laboratory evaluations in healthy volunteers. A slight decrease in average values for haemoglobin and haematocrit was observed in all three treatment groups. A minor decrease in erythrocytes, slightly more pronounced in the HD201 group, was also noted. All abnormal haemoglobin and haematocrit values below the lower limit of normal range were assessed as Grade I CTCAE abnormalities. For all other haematological parameters, results were similar across the three treatment groups. For biochemistry parameters, results were similar across the three treatment groups. Urine tests performed at site were not integrated into the database, but the investigator confirmed that all urine tests were normal with no clinically significant abnormalities.

Phase III study TROIKA

There was no notable difference between the treatment groups with regards to haematology and biochemistry (ALP, ALT, AST, Tbili, sCr, albumin, Na, K, GGT) laboratory parameters based on treatment received in the neoadjuvant/adjuvant phases. More details are provided below.

The pattern of laboratory abnormalities of haematology parameters (haemoglobin, neutrophil count, platelet count, leukocytes and lymphocytes) observed was similar between HD201 and EU-Herceptin treatment arm during the entire study period.

Neoadjuvant period

In both arms, commonly (incidence > 5% in either treatment group) reported haematology related TEAEs in the neoadjuvant treatment period were: neutropenia (120 events were reported in 69 [27.6%] patients in HD201, and 123 events in 72 [28.6%] patients in EU-Herceptin arm), anaemia (93 events were reported in 68 [27.2%] patients in HD201, and 74 events in 56 [22.2.%] patients in EU-Herceptin arm) and leukopenia (55 events were reported in 36 [14.4%] patients in HD201, and 62 events in 38 [15.1%] patients in EU-Herceptin arm.

Adjuvant period

In both arms, commonly (incidence > 5% in either treatment group) reported haematology related TEAEs in the adjuvant treatment period were: neutropenia (23 events were reported in 15 [6.3%] patients in HD201, and 15 events in 14 [5.8%] patients in EU-Herceptin arm), anaemia (22 events were reported in 19 [8.0%] patients in HD201, and 18 events in 15 [6.2%] patients in EU-Herceptin arm) and leukopenia (27 events were reported in 19 [8.0%] patients in HD201, and 18 events in 15 [6.2%] patients in EU-Herceptin arm).

Cardiac assessments

Left ventricular ejection fraction was assessed by echocardiography or MUGA scan at screening, before cycle 5, before surgery, before cycle 12, 16 and EOT visit, and will be followed up at 6 and 12 months after completion of trastuzumab treatment.

Table 52: LVEF (%) at each assessment time and change from baseline – safety set (study TROIKA)

Timepoint		HD201 (N=250)	EU-Herceptin (N=252)
Baseline	n	n = 250	n = 252
	Mean (SD)	65.1 (5.5)	65.8 (5.8)
	Median	65.5	66.0
	Min; Max	52; 77	51; 80
	Change in mean LVEF from Neo-Adjuvant baseline	NA	NA
Cycle 5	n	n = 245	n = 247
	Mean (SD)	64.3 (5.3)	64.8 (5.5)
	Median	65.0	65.0
	Min; Max	53; 78	52; 78
	Change in mean LVEF from Neo-Adjuvant baseline	-0.9	-1.1
Before Surgery	n	n = 242	n = 242
	Mean (SD)	63.6 (5.6)	64.4 (5.4)
	Median	64.0	65.0
	Min; Max	39; 77	46; 79
	Change in mean LVEF from Neo-Adjuvant baseline	-1.6	-1.5
Cycle 12	n	n = 232	n = 237
	Mean (SD)	63.0 (5.7)	63.7 (5.3)
	Median	63.0	64.0
	Min; Max	46; 78	47; 76
	Change in mean LVEF from Neo-Adjuvant baseline	-2.3	-2.3
Cycle 16	n	n = 223	n = 231
	Mean (SD)	63.5 (5.6)	63.4 (5.3)
	Median	64.0	64.0
	Min; Max	51; 79	50; 78
	Change in mean LVEF from Neo-Adjuvant baseline	-1.8	-2.6
End of Treatment	n	n = 228	n = 242
	Mean (SD)	63.6 (5.8)	63.1 (5.6)
	Median	64.0	63.0
	Min; Max	43; 82	50; 84
	Change in mean LVEF from Neo-Adjuvant baseline	-1.6	-2.7
LVEF < 50% any time after baseline		9 (3.7%)	3 (1.2%)
Decrease in LVEF > 10% any time after baseline		30 (12.2%)	32 (12.8%)

N = Number of patients within the group, n = Number of patients within the category; Percentages are calculated with respect to the number of patients with an available assessment within the group

Table 53: Abnormal or clinically significant 12-lead ECGs readings – safety set (study TROIKA)

12-Lead ECG (Abnormal, clinically significant)	HD201 (N = 250) n (%)	EU-Herceptin (N = 252) n (%)
Baseline	1 (0.4%)	0 (0.0%)
Cycle 5	14 (5.7%)	13 (5.3%)
Before Surgery	18 (7.4%)	17 (7.0%)
Cycle 12	21 (9.0%)	19 (8.0%)
Cycle 16	20 (8.9%)	21 (9.2%)
End of Treatment	17 (7.5%)	17 (7.0%)

N = Number of patients within the group, n = Number of patients within the category; Percentages are calculated with respect to the number of patients with an available assessment within the group

2.7.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.7.6. Safety in special populations

In accordance with regulatory guidance, safety studies in special groups and situations are not required for biosimilar products and were not conducted.

2.7.7. Immunological events

Immunogenicity of the study drug, HD201, a humanised antibody, was evaluated in three clinical trials. A phase I clinical study, EAGLE-I-12, now presented as supportive, a new pivotal phase 1 PK study TROIKA 1 and TROIKA, a phase 3 clinical study which was ongoing at the time of assessment.

Two immunoassays for the detection of anti-drug antibodies (ADA) in human serum are described and found acceptable. The first was for the determination of HD201 or trastuzumab reference ADA using electrochemiluminescent methodology and rabbit anti-trastuzumab antibody as a positive control. The second was detection of anti-trastuzumab antibodies in human female serum which used a human anti-trastuzumab antibody.

Individual immunogenicity results from both methods (ALM-323 and ALM-425) were presented in TROIKA 1. The final results were based on the re-validated method (ALM-425) (table below).

Table 54: Summary of anti-drug antibody results (safety population)

	HD201 N= 35		EU-Herceptin N= 35		US-Herceptin N= 35	
	n	%	n	%	n	%
Day 1 (Baseline)	–	–	1	2.9	–	–
Day 15	–	–	–	–	–	–
Day 29	–	–	–	–	–	–
Day 43	–	–	–	–	–	–
Day 54/End of Study	–	–	–	–	–	–

N = number of subjects in the group; n = number of subjects with positive ADA test; % is calculated based the number of non-missing values.

According to scientific advice (EMA/CHMP/SAWP/719944/2017), the impact of ADA on PK and outcomes should be systematically investigated in the clinical studies.

The EAGLE-1-12 study design had few time points for ADA detection and only two time points coincided with PK measurements. No participant showed positive ADA post-administration, although one participant in the HD201 group had pre-existing ADA.

In the TROIKA 1 study there were five time points for sampling of ADAs, all coinciding with PK sampling (pre-dose, Day 15, Day29, Day 43 and at study exit (Day 54). Only one subject from the EU-Herceptin group presented with ADAs (at baseline), the rest were negative.

Subject 169 (EU-Herceptin) tested positive on Day 1, and not at any time after injection. Therefore, no test for neutralising antibodies was performed as the positive ADA response observed during pre-dose (baseline) was not treatment induced, according to the applicant.

For the TROIKA study, new data (reanalysed by the ALM-425 method) were submitted covering also the adjuvant phase. Corresponding patient listings have also been submitted, Therefore, the new tabulated data is adequately verified.

From the ALM-425 data the overall incidence of ADAs to trastuzumab also appeared to be low in the HD201 and the Herceptin treatment groups at each time point. At baseline positive ADAs to trastuzumab was found for only 2 subjects of the HD201 treatment group (0.8%) which is a reduction of nine subject from the previous analysis by ALM-323 and for one subject of the Herceptin treatment group (0.4%%), which is also a significant reduction compared to the first ADA-analysis. Following administration of HD201 or Herceptin, positive ADAs to trastuzumab was found for a total of eight subjects both in the HD201 treatment group and the Herceptin treatment group.

Table 55: Summary of anti-drug antibody results (safety population) in TROIKA

Timepoint	HD201 N=250		Herceptin N=252	
	n'	n (%)	n'	n (%)
Screening	249	2 (0.8)	251	1 (0.4)
Before surgery	240	1 (0.4)	241	1 (0.4)
Before cycle 10	28	0	29	0
Before cycle 14	124	1 (0.8)	131	2 (1.5)
EOT	220	6 (2.7)	237	5 (2.1)

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

The overall incidence of ADAs was low in both the HD201 and Herceptin treatment groups in the TROIKA study. Therefore, based on the data available, the relationship between immunogenicity and treatment efficacy cannot not be statistically analysed.

The protocol foresaw that for immunogenicity assessment, anti-drug positive samples were to be tested for neutralising antibodies. At database lock the results of the testing for neutralising antibodies were not yet available and could therefore not be analysed. Data on neutralising antibodies have since then been provided, and none of the ADA samples tested, showed neutralising activity.

The additional PK data referred to in the response to OC166 have now been presented, in addition to updating of the CSR for TROIKA with new ADA-results coming from the ALM-425 method.

However, PK-sampling time points were not aligned with ADA-sampling in the TROIKA study, and therefore it was not possible for the applicant to present proper data correlating ADA- with PK -measurements.

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

Not applicable

2.7.9. Discontinuation due to adverse events

Phase I study EAGLE-I-12

One subject in the Herceptin treatment group had their infusion stopped due to moderate TEAEs of feeling cold, pyrexia and chills considered definitely related to study drug.

Three subjects were not dosed due to pre-dose AEs of due to pre-dose AEs fainting or feeling faint.

Phase I study TROIKA-1

There were no AEs leading to dose discontinuation of withdrawal from the TROIKA-1 study.

Phase III study TROIKA

Overall, 172 TEAEs in 83 patients (33.2%) in the HD201 treatment group and 160 TEAEs in 78 patients (31.0%) in the EU-Herceptin group led to the dose modification or discontinuation of study treatment during the entire study period.

2.7.10. Post marketing experience

No post-marketing data exists, as the product is not marketed in any country.

2.7.11. Discussion on clinical safety

The applicant has provided safety data from three clinical studies comparing HD201 to the reference product Herceptin: two completed randomised phase I single-dose PK trials (EAGLE-I-12 and TROIKA-1) in healthy male volunteers, and one ongoing randomised phase III trial in women with early breast cancer (TROIKA).

Phase I study EAGLE-I-12
This study randomised 73 subjects to receive a single dose of HD201 (n=34) or Herceptin (n=35). Safety findings from this trial revealed a lower proportion of patients in the HD201 treatment group who experienced a TEAE compared to the Herceptin group (62% vs 83%, respectively). The total number of TEAEs experienced in the HD201 group was 48, compared to 103 in the Herceptin group. In the Herceptin treatment group, the most subjects experienced TEAEs in the SOC Nervous system disorders (46%, vs. 18% in the HD201 group), general disorders and administration site conditions (37%, vs 6% in the HD201 group) and gastrointestinal disorders (26%, vs 15% in the HD201 group). In the HD201 treatment group, the most frequently experienced TEAEs were in the SOC infections and infestations (38%, vs 23% in the Herceptin group), nervous system disorders (18%, vs. 46% in the

Herceptin group), and respiratory, thoracic and mediastinal disorders (12% vs 23% in the Herceptin group).

The most frequently reported TEAEs were headache, nasopharyngitis and pyrexia, reported in 9%, 6% and 17% of subjects in the Herceptin group, and 6%, 15% and 6% of subjects in the HD201 group, respectively. Subjects in the Herceptin group also experienced larger mean changes in pulse rate between Day 1, 1.25 hours post-dose and Day 1, 11.5 hours post-dose compared to subjects in the HD201 treatment group (3.7 beats/min versus 1.6 beats/min at 1.25 hours post-dose, respectively and 12.9 beats/min versus 6.4 beats/min 11.5 hours post-dose, respectively). The pulse rate findings were considered to be sporadic variations and not treatment-related.

Most TEAEs were mild or moderate in intensity. Of TEAEs reported with moderate intensity, the most frequent by PT were pyrexia, experienced by 6% of patients in the HD201 group and 17% of patients in the Herceptin group; nasopharyngitis (15% vs 6%, respectively); and headache (6% and 9%, respectively). There was one SAE in the trial: perianal abscess in the Herceptin treatment arm, assessed as related to study drug by the investigator. One subject in the Herceptin treatment group had their infusion stopped due to moderate TEAEs of feeling cold, pyrexia and chills considered definitely related to study drug.

The observed differences in safety results seen between treatments in the EAGLE-I-12 study could be due to chance findings (relatively small sample size) or due to real differences between the products administered.

Phase I study TROIKA-1

TROIKA-1 was a Phase 1, double-blind, randomised, single dose, 3-arm, parallel group study conducted to demonstrate equivalent PK properties of HD201, EU-Herceptin and US-Herceptin in healthy male subjects. A total of 105 healthy male subjects were randomised (1:1:1) to receive a single dose of HD201 (n = 35), EU-Herceptin (n = 35) or US-Herceptin (n = 35) at 6 mg/kg by 90-minute IV infusion.

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. The total number of TEAEs reported in each of the three arms was 62 in HD201, 71 in EU-Herceptin, 73 in US-Herceptin. In the overall 3 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-Hercetpin, 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). TEAEs of moderate intensity occurred in 1 subject (2.9%) in the HD201 treatment arm, while higher number of moderate intensity TEAEs were reported in the EU-Herceptin and US-Herceptin treatment arms (25.7% with 12 TEAEs, and 17.1% with 9 TEAEs, respectively). A slightly lower proportion of subjects reported TEAEs of special interest (prospectively defined as infusion-related reactions (IRR), cutaneous, respiratory, cardiovascular and gastrointestinal symptoms) in the HD201 treatment arm (20.0%) compared to the other treatment groups (EU-Herceptin 34.3%; US-Herceptin, 31.4% with 11 TEAEs of special interest, but the number of TEAEs of special interest was similar in all three treatment groups (10 in HD201; 12 in EU-Herceptin; 11 in US-Herceptin arm). There was one serious adverse event of thumb fracture in a subject in the EU-Herceptin arm (unrelated). There were no AEs leading to dose discontinuation of

withdrawal from the TROIKA-1 study. In conclusion, safety results overall appeared balanced between the three treatment arms in the TROIKA-1 study.

Phase III study TROIKA

The safety set from the ongoing phase III study is comprised of 502 patients, of which 250 received at least one dose of HD201, and 252 patients received at least one dose of EU-Herceptin. As of the clinical cut-off date 21 January 2020, the last patient has completed the EOT visit. The total mean exposure duration (56.48 weeks with HD201, and 56.88 weeks with Herceptin), and the number of cycles completed were similar between both treatment groups (88.8% and 90.5% completed the prescribed 18 cycles of treatment with HD201 and Herceptin, respectively). In the neoadjuvant treatment period, a total of 87.2% in the HD201 treatment arm and 86.5% in the Herceptin treatment arm received 8 cycles of chemotherapy, as scheduled in the protocol. The exposure in the adjuvant (monotherapy) phase of the trial was also comparable between the treatment groups, with 93.3% of patients completing adjuvant treatment with HD201, and 93.8% with Herceptin. Total cumulative dose administered was similar in the two treatment groups, both overall and for the neoadjuvant and adjuvant treatment phase.

Overall, during the entire treatment period, the number of all-causality treatment-emergent adverse events (TEAEs) was slightly higher in the HD201 group (nae = 2859) compared to the Herceptin group (nae = 2755). The proportion of subjects reporting any TEAE of any grade was comparable; 100% and 98.0% of subjects in the HD201 and Herceptin treatment groups, respectively. The most commonly reported TEAEs were in the SOC skin and subcutaneous tissue disorders (85.6% in the HD201 treatment group vs. 83.3% in the EU-Herceptin treatment group), general disorders and administration site conditions (59.2% vs. 60.7%, respectively) and blood and lymphatic system disorders (54.0% vs. 53.2%, respectively). The incidence of severe (Grade ≥ 3) TEAEs during overall study period was slightly higher in the HD201 treatment group (34.4%) compared to the Herceptin group (27.8%). The most common grade ≥3 TEAEs were alopecia, neutropenia, leukopenia and rash. Life threatening (Grade 4) TEAEs were reported in 14 (5.6%) patients in the HD201 group and 11 (4.4%) patients in the EU-Herceptin group. The most common life-threatening TEAE was neutropenia (4.0% of subjects in the HD201 group and 3.6% in the EU-Herceptin treatment group). An imbalance in the frequency of grade ≥3 TEAEs in the SOC investigations was noted (9.6% in the HD201 group vs 2.8% in Herceptin). A similar trend was seen when evaluating two individual PT, neutrophil count decreased and white blood cell count decreased. The presence of contributing factors including chemotherapy and baseline conditions/ comorbidities is acknowledged. The majority of the events were not assigned to study drug and all of them were resolved without sequalae. Moreover, only limited number of patients experienced the same issues in adjuvant phase implying their transiency. The proportion of subjects reporting TEAEs assessed as related to study treatment was slightly higher in the Herceptin group (54%) compared to the HD201 group (50.8%). The largest difference between treatment groups was observed in the SOCs Respiratory, thoracic and mediastinal disorders (HD201: 7.6% vs. Herceptin: 4.0%), Blood and lymphatic system disorders (HD201: 12.0% vs. Herceptin: 9.1%) and Investigations (HD201: 20.8% vs. Herceptin: 18.3%). Number of reported events in the SOC Respiratory, thoracic and mediastinal disorders was 27 in the HD201 arm and 17 in the Herceptin arm. In the SOC Blood and lymphatic system disorders, there were 78 events in the HD201 arm and 49 events in the Herceptin arm. In the SOC Investigations, there were 109 events in the HD201 arm vs. 76 events in the Herceptin arm. Related TEAEs of grade 2 and 3 were slightly more frequent in the HD201 treatment group compared to the Herceptin group. A slightly larger proportion of subjects in the HD201 group experienced any serious adverse event (9.6%) compared to the Herceptin group (6.7%). Except for reported deaths, all other SAE were resolved without further sequelae for HD201. The PT Febrile neutropenia was the most frequently reported serious TEAE (6 patients [2.4%] reported

6 serious TEAEs in the HD201 arm and 4 patients [1.6%] reported 4 serious TEAEs in the EU-Herceptin arm) followed by PT Hypersensitivity (2 events were reported in 2 patients [0.8%] in the HD201 arm and 1 patient (0.4%) in the EU-Herceptin group). Six deaths have occurred so far, all of them in the HD201 treatment group. Four of the deaths were from TEAEs (sudden death, 2 x myocardial infarction, cardiorespiratory arrest), and two were from disease progression. None of the deaths were assessed as related to the study treatment. No remarkable differences in pattern of laboratory abnormalities of haematology or biochemistry parameters between the HD201 and the Herceptin treatment groups were noted. A slightly larger proportion of subjects in the HD201 group experienced any serious adverse event (9.6%) compared the Herceptin group (6.7%). Except for reported deaths, all other SAE were resolved without further sequelae for HD201. The PT Febrile neutropenia was the most frequently reported serious TEAE (6 patients [2.4%] reported 6 serious TEAEs in the HD201 arm and 4 patients [1.6%] reported 4 serious TEAEs in the EU-Herceptin arm) followed by PT Hypersensitivity (2 events were reported in 2 patients [0.8%] in the HD201 arm and 1 patient (0.4%) in the EU-Herceptin group).

Some imbalances were noted across geographic regions, for example particularly large differences in across most of the TEAE categories between the treatment groups in Western Europe which were less pronounced in subjects recruited in Eastern Europe (where most of the subjects were recruited) for the overall treatment period. Taking into account the low number of subjects included in the safety population in Western Europe (n=28), these observed imbalances are likely to be due to chance findings.

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 (nae=2188 and 2133, respectively). In the HD201 treatment arm, 34.0% of subjects had 310 TEAEs related to study drug and 97.2% had 1891 TEAEs related to chemotherapy, whereas 35.7% of subjects in the Herceptin arm had 375 TEAEs related to study treatment and 94.4% had 1865 TEAEs related to chemotherapy. The most frequently reported all-causality TEAEs by PT in both treatment groups were alopecia (80.8% of subjects in the HD201 group and 79.4% of subjects in the Herceptin group); nausea (34.4% of subjects in the HD201 group and 36.9% of subjects in the EU-Herceptin group); neutropenia (27.6% of subjects in the HD201 group and 28.6% of subjects in the Herceptin group); asthenia (26.0% of patients in the HD201 group and 23.4% of subjects in the EU-Herceptin group) and anaemia (27.2% of subjects in the HD201 group and 22.2% of subjects in the Herceptin group. The number of patients who experienced any SAE was slightly higher in patients taking HD201 ((16 (6.4%) and 12 (4.8%) patients in the HD201 and EU-Herceptin had 22 and 17 SAEs)). The overall higher incidence of SAEs in neoadjuvant period was probably related to the concomitantly administered 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 (nae=678) compared to the Herceptin group (nae=625). The most frequently affected SOCs were investigations (25.2% in the HD201 treatment group vs. 22.7% in the Herceptin treatment group), blood and lymphatic system disorders (20.6% vs. 18.6%, respectively), general disorders and administration site conditions (15.1% vs. 16.1%, respectively) and cardiac disorders (13.9% vs. 16.9%, respectively. The most frequently reported TEAEs by PT in both treatment groups were leukopenia (8.0% of subjects in the HD201 group and 8.7% in the EU-Herceptin group), headache (8.0% of subjects in the HD201 group and 4.5% in the EU-Herceptin group), neutropenia (6.3% of subjects in the HD201 group and 5.8% in the EU-Herceptin group), aspartate aminotransferase increased (8.0% of subjects in the HD201 group and 6.6% in the EU-

Herceptin group) and anaemia (8.0% of subjects in the HD201group and 5.8% in the EU-Herceptin group. The proportion of subjects who experienced grade ≥3 TEAEs in the 2 treatment groups was 6.3% in the HD-201 group and 3.3% in the Herceptin group, with no clear pattern of distribution of events. The number of patients who experienced any SAE was slightly higher, but still comparable between the treatment groups in the adjuvant phase (8 (3.4%) patients in the HD201 arm and 6 (2.5%) patients in the EU-Herceptin arm had 8 and 7 serious TEAEs)). Although slight imbalances were noted in the total number of TEAEs reported and for some SOCs and PTs in the adjuvant treatment period, no clear pattern was evident that would suggest a different safety profile between the treatments. In the adjuvant phase, 8 SAEs and 7 SAEs were reported in HD201 and Herceptin group, respectively. None of the events were considered attributed to HD201, whereas two patients experienced Herceptin-related SAEs. The incidence of SAEs and individual reported cases did not reveal any new safety issues in the adjuvant phase of the study.

The applicant identified cardiotoxicity, infusion-site reactions and hypersensitivity, haematotoxicity, pulmonary toxicity, infections and oligohydramnios as TEAEs of special interest based on the established safety profile of trastuzumab. According to the applicant, AESI were prespecified and identified by searching the TROIKA TEAE database using MedDRA Preferred terms (PTs) and pre-defined Standardised MedDRA queries (SMQs). However, no information about AESI was included in the original protocol for the TROIKA study, and the AESI were apparently decided and defined post-hoc: AESI definitions were not included in the original SAP, but included in a revised SAP, dated October 2020 which was submitted with the responses to the first CHMP list of questions. As such, they cannot be considered pre-defined and this may cast doubt on the integrity of this part of the study.

Review of the AESI data revealed slightly more subjects in the HD201 group experiencing AESIs overall (88.0%) and slightly more total number of AESI reported (nae=1165) compared to the Herceptin group, (84.5%; nae=1067). This slight imbalance was apparent across the AESI categories, (except AESI of infections and oligohydamnios, where no imbalance was noted between treatment arms), and was distributed as follows (HD201 arm vs Herceptin arm): 81 vs. 77 events for cardiotoxicy, 99 vs. 114 events for infusion-site reactions and hypersensitivity, 87 vs. 57 events for haematotoxicity, 14 vs. 8 events for pulmonary disorders and 17 vs. 17 events for infections. The imbalances noted do not raise cause for concern regarding any difference in AESI between the two treatment arms.

There were no notable differences between the treatment groups with regards to haematology and chemistry, laboratory parameters based on treatment received in the neoadjuvant phase or treatment received in the neoadjuvant/adjuvant phases. A similar proportion of patients in each treatment group had a significant decrease in LVEF of ≥ 10% points from baseline (12.2% of subjects in the HD201 group and 12.8% of subjects in the EU-Herceptin treatment arm). Few patients had drop in LVEF < 50% any time after baseline (3.7% of subjects in the HD201 treatment arm and 1.2% of subjects in the EU Herceptin treatment group).

Overall, 172 TEAEs in 83 patients (33.2%) in the HD201 treatment group and 160 TEAEs in 78 patients (31.0%) in the EU-Herceptin group led to the dose modification or discontinuation of study treatment during the entire study period.

Immunogenicity

Immunogenicity was shown to be low in all studies and comparable to Herceptin. However, PK sampling time points were not aligned with ADA-sampling in the TROIKA study, and therefore it was not possible for the applicant to present proper data correlating ADA- with PK-measurements.

Reliability of clinical data

Further to several critical findings during GCP-inspections and re-inspections, the applicant presented an updated clinical study report. Therefore, the GCP issues are considered.

Furthermore, an earlier version of the drug product which is not considered comparable to the drug product intended for marketing ("Process 2-IV") has been used in the clinical studies. Thus, the clinical safety data presented do not support the drug product applied for in the marketing authorisation application.

2.7.12. Conclusions on the clinical safety

The safety data presented for the Phase I study TROIKA-1 and the phase 3 study TROIKA do not appear to show dissimilar safety results for the two products *per se*. However, batches used in the pivotal and supportive phase I studies as well as the phase III study, are not considered representative for the product intended for the commercial process.

The CHMP considers that these issues preclude a conclusion on biosimilarity from a safety point of view.

2.8. Risk Management Plan

Given the negative outcome on the demonstration of biosimilarity of Tuznue to EU-Herceptin precluding the conclusion of a benefit/risk balance comparable to the reference product, an RMP could not have been agreed.

2.9. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

Not applicable.

2.10. Product information

2.10.1. User consultation

The applicant was asked to submit a user consultation or if possible, a bridging report with the D 120 response as the applicant initial wish to omit the user consultation was not accepted. The applicant submitted a full user consultation with the D 120 response.

A thorough user consultation have been done and the submitted user consultation is acceptable. Some aspects were commented on during the user consultation and changes have been made to the PL respectively. This is a biosimilar application and the package leaflet (PL) should therefore be copy-paste of the PL to the reference product. The proposed changes are acceptable since they are related to layout and spelling mistakes.

2.10.2. Labelling exemptions

Not applicable

2.10.3. Quick Response (QR) code

Not applicable.

2.10.4. Additional monitoring

Not applicable

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

HD201 is being developed as a biosimilar to the reference product Herceptin. The administration, posology, and indications are according to the reference product, as described in the Herceptin SmPC.

HD201 is claimed for the following indications:

- treatment of adult patients with HER2 positive metastatic breast cancer (MBC):
- treatment of adult patients with HER2 positive early breast cancer (EBC):
- in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Summary of analytical comparability (quality data)

The applicant presents a biosimilarity exercise of HD201 AS and FP batches produced using the commercial manufacturing process. To establish the analytical similarity between HD201 and EU-Herceptin, a 3 tier approach was used which is generally acceptable. All qualitative attributes were assessed using descriptive raw data and / or graphical comparison to Herceptin regardless of their criticality scoring. Only graphical presentations or data summaries are presented, limiting assessment of the data. All the analytical methods were shown to be suitable for its intended purpose. The validation reports are presented. The analytical tests were performed on HD201 FP, originating from different active substance batches, to assess their performance against lots of EU-Herceptin for similarity evaluation. Clinically relevant HD201 lots were included, and the included EU-Herceptin lots included are considered suitable.

Significant concerns are raised with regards to the comparability exercise bridging material used to generate the clinical biosimilarity data to material from the proposed commercial manufacturing process.

Several quality attributes with high criticality directly impacting mode of action or which can influence efficacy, safety demonstrate significant variation between the manufacturing processes used during clinical development and the proposed commercial manufacturing process. The applicant's approach to addressing the issues raised by continuous re-analysis of the data is not endorsed. Therefore, the material used to generate the clinical biosimilarity data is not considered representative of the proposed commercial material.

For the claim of biosimilarity with Herceptin, significant concerns were identified in the biosimilarity data. This includes a poor structure function relationship between ADCC activity, Fc binding and glycosylation, indicating that the assays are not sufficiently sensitive to reliably detect any differences.

Throughout the procedure the applicant has sought to exclude or retract data following concerns raised by the Rapporteurs on the presented quality profile. This approach is not supported as the withdrawal of results may introduce a bias in the data.

In addition, the presented quality profile of the reference medicinal product is not considered to be representative of the known quality profile of Herceptin with respect to the ranges observed for several quality attributes of high criticality that can impact on efficacy and safety. This raises significant concern on the reliability of the data presented and the overall analytical biosimilarity exercise.

In conclusion, significant concerns are raised on the representativeness and quality of the presented data. The presented biosimilarity exercise with the EU-reference product, is therefore not considered sufficient to support the approval of HD201 as a biosimilar to its reference product Herceptin.

Summary of non-clinical data

The HD201 non-clinical programme consists of two pharmacodynamics studies in mice xenograft models, a tissue cross-reactivity study with normal human tissue, single dose pharmacokinetic studies in mice and Cynomolgus monkeys, and a 4-week repeat-dose toxicity study in Cynomolgus monkeys. All studies were done in comparison with Herceptin.

As indicated in EMA/CHMP/BMWP/403543/2010, a stepwise approach should be applied when evaluating non-clinical biosimilarity. Step 1 comprises a number of comparative in vitro studies considered paramount for non-clinical similarity assessment. The non-clinical in vivo studies provided by the applicant are not sufficient to overcome the unresolved MOs concerning the in vitro biocomparability exercise, indicating that HD201 is not similar to Herceptin.

Summary of clinical comparability data

The design of the phase 1 and phase 3 clinical trials has been discussed in a CHMP SA from September 2011 (EMA/CHMP/SAWP/868018/2011) and June 2017 (EMA/CHMP/SAWP/719944/2017). From a PK, efficacy and safety point of view, the applicant mostly followed the CHMP scientific advice.

The pharmacokinetic development programme to demonstrate equivalence between HD201 and the reference product Herceptin consisted of a pivotal phase I double-blind, randomised, parallel group study to demonstrate the equivalent pharmacokinetic properties of a single intravenous dose of HD201 versus EU-Herceptin and US-Herceptin in healthy male subjects. 105 subjects were randomised into the study. Another phase 1 (initially presented as pivotal) is supportive.

The clinical efficacy and safety development programme to demonstrate equivalence between HD201 and the reference product EU-Herceptin consisted of a single double blind, randomised, phase 3 study in women with histologically confirmed, newly diagnosed clinical Stage II-III, operable, HER2-positive breast cancer (TROIKA).

3.2. Results supporting biosimilarity

Quality data

The biosimilarity exercise gives some indications of analytical similarity between HD201 and the quality profile established by the applicant for the reference medicinal product.

Nonclinical data

In general, similar PD, PK and toxicity findings have been observed in the in vivo studies conducted with EU-Herceptin and early Phase I lots of HD201.

Clinical data

Pharmacokinetics

The 90% confidence intervals obtained in the pivotal phase I study for the ratio of geometric means of HD201/Herceptin were contained within the acceptance interval of 0.80 to 1.25 for both $AUC_{0\text{-}inf}$ and C_{max} thus demonstrating equivalent PK properties of HD201 and Herceptin: 90% CI for $AUC_{0\text{-}inf}$ [0,9595, 1.0940] and C_{max} [0.9755, 1.122].

In the phase III study, similar results were obtained for the modified full analysis set (mFAS) with mean difference between treatment groups of -3.0% [-11.4%; 5.3%] at Cycle 5, -2.7% [-3.3%; 8.7%] at Cycle 8 and 10.6% [0.8%; 20.3%] at Cycle 14. However, at cycle 10, the mean difference was 20.4% [-3.2%; 44.1%]. The results at Cycle 10 are based on a small sample size, and the estimate is less reliable.

Efficacy

Similar outcomes in the two treatment groups were reported for the primary efficacy analysis. 111 patients (46.6%) in the HD201 treatment group and 109 (46.2%) patients in the Herceptin treatment group achieved tpCR. The risk difference between the two groups was 0.5% [95% CI: -8.6%; 9.6%], which is contained within the pre-defined equivalence margin of ±15%.

Sensitivity analyses and stratification subgroup analysis supported the outcomes from the primary endpoint.

The secondary endpoint bpCR rate was in the HD201 and Herceptin treatment groups 55.0% (95% CI: 48.4%; 61.5%) and 53.4% (95% CI: 46.8%; 59.9%), respectively in the PPS population. There was no statistically significant difference (1.7% [-7.5%; 10.7%]) between the two groups.

For the secondary endpoint ORR, comparable results between the two treatment groups (90.8% and 89.4%, in the HD201 and Herceptin group, respectively) with a measured difference of 1.3% [-7.5%; 10.5%], was reported.

After re-monitoring of neoadjuvant data, analysis of tpCR and bpCR, minor changes for these parameters were noted for both treatment groups and there was no impact on the response outcome.

Sensitivity analyses and stratification subgroup analyses for both bpCR and ORR supported the outcomes from the primary endpoint.

Safety

In the ongoing Phase III study, the results submitted showed similar frequencies of patients experiencing TEAEs overall and in the neoadjuvant and adjuvant treatment period. There were no obvious differences noted between the treatment groups in the frequencies of patients experiencing TEAEs within reported SOCs or PTs, or grade ≥ 3 TEAEs or TEAEs assessed as related to investigational product, or AESIs. Likewise, laboratory findings and cardiac assessments (LVEF and ECG) appeared balanced between the treatment groups.

Immunogenicity

In the phase I PK studies (TROIKA -1 and EAGLE-I-12), no ADAs were detected post-administration of HD201 or Herceptin. One participant had pre-existing ADAs (in each study).

The overall incidence of ADA was low in both HD201 and Herceptin treatment groups in the TROIKA study.

Following re-analysis of ADA using the ALM-425 method in the ongoing phase III study (TROIKA), pre-existing ADAs were identified at screening for 2 (0.8%) subjects of the HD201 treatment group (and one subject (0.4%) in the Herceptin treatment group. Following administration of HD201 or Herceptin, positive ADA to trastuzumab was found for a total of eight subjects of the HD201 treatment group and eight subjects of the Herceptin treatment group. None of the ADAs were found to be neutralising.

3.3. Uncertainties and limitations about biosimilarity

Overarching uncertainty

Several apparent and obvious errors, inconsistencies, lack of update in the clinical study reports, as well as poorly described and presented data, have been discovered in the MAA, both in the initial submission and in the documents submitted on Day 121, and also in response to the several Day 180 LoOIs. During GCP (re-)inspections, several errors were discovered.

Furthermore, an earlier version of the drug product which is not considered comparable to the drug product intended for marketing ("Process 2-IV") has been used in the TROIKA studies. Thus, clinical data from TROIKA-1 and TROIKA cannot support the drug product applied for in the marketing authorisation application (see section on quality aspects).

Quality data

Several manufacturing processes were used during the clinical development programme, and the comparability exercise indicates significant differences in quality attributes of concern between the respective manufacturing processes.

The clinical trial material from Process C display increased HER2 binding affinity, compared to lots from the proposed commercial process. In addition, lots manufactured in the proposed commercial process display lower rate of HER2 binding kinetics than clinical trial material upon heat stress. As HER2 is the target receptor for trastuzumab binding, the data indicate a potentially different efficacy profile of Process C material compared to the proposed commercial process. Highly variable results for FcγRIIIa (V variant) and FcγRIIIa (F variant) do not support the overall comparability claim. A drift towards stronger FcγRIIIa binding affinity was identified for process C and D. Process A and B material cannot be concluded as comparable to representative commercial material for these attributes. This variability in results is further substantiated in relative ADCC activity where results for V variant show approximately 50-200% potency range regardless of the differences in glycan structure, and results for F variants show that process B material is not comparable to C and proposed commercial process. This also relates to the observed major differences in glycosylation profile (afucosylation, high mannose content and galactosylation). Process C material also displays higher afucosylation, while Process B material displays lower afucosylation, than the proposed commercial material. Considering the strong correlation between afucosylation and effector function of trastuzumab, the differences are likely to have an impact on other quality attributes and the clinical profile compared to the proposed commercial process. Process C material also displays reduced binding affinity to FcγRIIa, a receptor involved in antibody dependent cellular phagocytosis (ADCP) that contribute to trastuzumab-mediated cytotoxicity, and which could negatively impact efficacy. Reduced affinity to the inhibitory receptor FcγRIIb is also seen, which could further impact the efficacy profile of the Process C material compared to the proposed commercial process material. Process C material also displays higher afucosylation, while Process B material displays lower afucosylation, than the proposed commercial process. In conclusion, the analytical comparability data on key quality attributes (i.e. afucosylation, high mannose content, galactosylation, binding to FcγRIIIa, FcγRIIa and FcγRIIb) indicates that clinical trial material is not considered to be comparable to the proposed commercial material.

In the biosimilarity exercise the quality target profile established for reference medicinal product Herceptin displays an uncharacteristically high variability. In addition, there is a poor structure function relationship between afucosylation and ADCC effector function, as well as negative relationship to FcgRIIIa (F) binding which is contrary to the established literature. In addition, there is an established historical quality drift in afucosylation and effector function seen in the reference product, which is not reproduced in the applicant's data. The poor structure function relationship and absence of historic quality drift in the applicant's data raises additional concerns with respect to the representativeness of the presented data. Given the unexplained variability, the presented data is considered to be of questionable value in terms of demonstrating analytical similarity and supporting a biosimilarity claim. In summary, there are significant uncertainties in the data presented and the biosimilarity exercise.

Nonclinical data

As indicated in the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), a stepwise approach should be applied when evaluating non-clinical biosimilarity. Step 1 comprises a number of comparative in vitro studies considered paramount for non-clinical similarity assessment. The non-clinical in vivo studies provided by the applicant are however not sufficient to overcome the unresolved MOs concerning the in vitro comparability and biosimilarity exercises, indicating that HD201 is not similar to Herceptin.

Clinical data

Pharmacokinetics and efficacy

Although the PK data presented indicate some similarity between HD201 and Herceptin, a major concern is the performance of the pivotal PK as well as clinical study with a version of the biosimilar product not demonstrated to be comparable to the commercial biosimilar product.

Therefore, no conclusion can be made regarding pharmacokinetics nor efficacy of HD201 intended for commercialisation compared to trastuzumab EU-reference.

Even if the discrepancies and lack of updating of reports had been partly sorted out, uncertainties remained regarding biosimilarity, due to concern regarding critical findings from the GCP inspections and re-inspections of the TROIKA study. But since the applicant presented sensitivity analyses showing that the obtained results on efficacy were similar, also without affected patients, this issue is considered resolved.

However, a GCP report from the clinical site in Brisbane supporting TROIKA-1 is still pending (OC).

Safety

The reason for the difference in observed safety profile in the Phase I single dose PK study EAGLE-I-12 between HD201 and Herceptin could be due to chance findings, given the small sample size of the study, but they could also be due to real differences between the two products.

The immunogenicity sampling time-points for both the TROIKA-1 and the phase III TROIKA study were not aligned and did not allow for an adequate determination of the effect of ADAs on PK or efficacy. However, considering the low ADA results observed for both HD201 and Herceptin and the similarity between arms, the issue is not pursued further.

3.4. Discussion on biosimilarity

From a quality perspective

The analytical tests were performed on a total of 12 lots of HD201 finished product, originating from different active substance batches, to assess their performance against between 10 and 28 lots of EU-Herceptin for similarity evaluation. The biosimilarity exercise addressed primary structure, higher order structure, size and molecular variants, charge variants, glycosylation, biological activity and immunochemical properties. Concerns are raised on structural difference identified and the absence of established structure function relationships in the presented data. Concerns are also raised on the representativeness of the presented Herceptin quality profile. As presented, HD201 is not considered to be similar to EU-licensed Herceptin with respect to the presented biological and physicochemical biosimilarity data.

From a non-clinical perspective

Following assessment of the applicant's response to D180 LoQ, there are remaining MOs concerning the in vitro comparability and biosimilarity exercises. The non-clinical in vivo studies provided by the applicant are however not sufficient to overcome the unresolved MOs indicating that HD201 cannot be considered biosimilar to Herceptin.

Taken together, a conclusion with regard to non-clinical similarity cannot be drawn.

From a clinical perspective

No conclusion can be made on the similarity of pharmacokinetics between the intended commercial product (HD201) and Herceptin, due to the fundamental uncertainty regarding comparability of the HD201 batches used in the pivotal PK study, and the intended commercial HD201 (Tuznue) batches.

The imbalance in safety results observed in the Phase I trial EAGLE-I-12 were apparently not replicated in the Phase I trial TROIKA-I or the Phase III trial, where safety results were more balanced. Batch variation is one possible explanation for the apparent between-trial difference in comparability, although other explanations, such as small sample size in the Phase I trial, and differences in study population also have to be considered. In the pivotal phase 1 study TROIKA-I, HD201 process B was administered.

Overall, the submitted safety results from the Phase III study appear to support a similar safety profile of the two products evaluated in the study. An imbalance in the number of deaths is noted (6 in the HD201 group vs none in the Herceptin group). This is likely due to chance findings as most of or all the events were assessed to be unrelated to HD201.

No ADAs were evident post-dosing in the phase I study (TROIKA-1), although pre-existing ADAs were evident in one patient in the HD201 group. However, it is not known if these antibodies were neutralising. Due to the lack of ADA-monitoring post-dosing, the impact of ADA on HD201 pharmacokinetics or effect could not be determined. Low level ADAs were evident in both the HD201 and Herceptin groups in the phase 3 TROIKA study. None of these were neutralising, but their potential impact on PK and effect remains to be determined.

Overall, the phase 3 efficacy and safety study seems adequately designed with regard to patient populations and endpoints. The outcomes of both primary and secondary efficacy analyses per se are supportive of similarity between HD201 and EU-Herceptin, in spite of several critical findings during GCP-inspections and re-inspections. In addition, the applicant presented sensitivity analyses showing that the obtained results on efficacy were not impacted when data associated with critical findings during the GCP inspections were removed from the analyses. Therefore, the GCP issues are considered resolved.

The lack of comparability of clinical batches with the product intended for marketing authorisation still remains.

Discussion from clinical perspective following Oral Explanation

No significant new information was provided. The fundamental issue from a clinical perspective is the lack of demonstration of comparability between the clinical batches and the intended commercial product. Reference is made to the discussion from the quality perspective above. During the oral explanation, the applicant indicated the proportion of various HD201 variants vials (Process B, C and D) during the TROIKA phase 3 study. The applicant stated that vials with the product intended for marketing (Process D) represented approximately one fourth of grand total of vials used in the trial but no correlation with the corresponding proportion of the study population was provided.

To further justify the claim of quality consistency between the different processes, the applicant stated that no clinical difference between the three processes had been observed; However, as part of this statement, the applicant referred to ~70 patients' worth of data that had since been removed from the study report due to critical GCP findings. Besides, the applicant did not present any data analysis to support such claim. Lastly, the TROIKA study was not powered for or designed to investigate any impact on similarity between the products produced by different manufacturing processes. Consequently, such a post-hoc analysis would not be considered appropriate.

In conclusion, the clinical major objection is not resolved.

From a biosimilarity point of view, comparisons at the quality and functional levels, as well as similarity regarding pharmacokinetic profiles, are the pivotal exercises, whereas results from efficacy studies mainly are considered supportive. The biosimilarity concept is clear in that if highly similarity has been shown at the quality and functional levels, the clinical properties of those products would be the same. However, a product cannot be proven similar primarily based on a clinical efficacy trial if uncertainties remain at the quality and functional levels. Therefore, since the presented biological and physicochemical biosimilarity data are not considered adequate, HD201 cannot be claimed as biosimilar to EU-licensed Herceptin.

3.5. Extrapolation of safety and efficacy

The indications granted for the reference product EU-Herceptin are all claimed for the trastuzumab biosimilar HD201. These include HER2 positive metastatic breast cancer, HER2 positive early breast cancer and HER2 positive metastatic breast cancer.

The mechanism of action of trastuzumab is the same in all three indications. The dosage is also similar for all three indications, and trastuzumab is administered via the same route in all indications mentioned. Based on these points, extrapolation of all originator indications can be supported given that robust evidence from the quality characterisation, functional assays, clinical pharmacokinetics, efficacy and safety including immunogenicity is demonstrated. However, due to the Major Objections precluding an approval of the marketing authorisation application, extrapolation to all Herceptin-EU approved indications is not relevant.

3.6. Additional considerations

- Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on review of the submitted data, biosimilarity of Tuznue to EU-Herceptin is not considered to be demonstrated. Therefore, a benefit/risk balance comparable to the reference product cannot be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Tuznue in the treatment of

- adult patients with HER2 positive metastatic breast cancer (MBC),
- adult patients with HER2 positive early breast cancer (EBC),
- in combination with capecitabine or 5-fluorouracil and cisplatin, 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,

the CHMP considers by consensus decision that biosimilarity of the above-mentioned medicinal product to the reference product is not properly demonstrated, and therefore recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product.

Due to the aforementioned concerns, a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as previously outlined in the list of outstanding issues cannot be agreed at this stage.

List of grounds for refusal

The CHMP considers that the product is non approvable on the following grounds:

Quality aspects

- Significant concerns have been identified in relation to the presented biosimilarity exercise which preclude a conclusion of biosimilarity between Tuznue/Hervelous and EU-sourced Herceptin. The poor structure-function relationship between ADCC activity, Fc binding and glycosylation, is raising significant concerns on the data presented. In addition, the data indicates decreased stability for the proposed biosimilar in comparison to Herceptin. Some of the data presented outside the validated parameter range of the respective assays have been withdrawn, with questionable exclusion of batches to justify the data. This is creating uncertainty around the credibility of the results presented and the integrity of the data. Furthermore, the presented quality profile of the reference medicinal product is not considered to be representative of the known quality profile of the reference medicinal product. This raises further significant concern on the reliability of the data presented and the overall analytical biosimilarity exercise. Thus, the credibility of the presented analytical biosimilarity assessment is highly questioned and based on the data provided biosimilarity to the reference product cannot be considered established.

Multidisciplinary aspects:

- Multiple quality attributes with high criticality directly impacting the mode of action or which can have an effect on efficacy and safety demonstrate significant variation between the manufacturing processes used during clinical development and the proposed commercial manufacturing process. The underlying differences in the data are not resolved by the applicant's continuous re-analysis of the data. Therefore, considering the extent of differences seen in the batch data for multiple quality attributes of high criticality, the batches from the manufacturing processes used to generate clinical material cannot be considered comparable to the commercial process material. In conclusion, the clinical trial material is not considered representative of the proposed commercial material. This renders the clinical data unreliable.

Therefore biosimilarity cannot be concluded between Tuznue and Herceptin.