28 May 2020
EMA/327248/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zercepac

International non-proprietary name: trastuzumab

Procedure No. EMEA/H/C/005209/0000

Note

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

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List of abbreviations

AC	Affinity chromatography
ADCC	Antibody-dependent cell-mediated cytotoxicity
AEX	Anion exchange chromatography
CAS	Chemical Abstracts Service
CDC	Complement dependent cytotoxicity
CE-SDS	Capillary electrophoresis sodium dodecyl sulphate
CEX	Cation exchange chromatography
cGMP	Current Good Manufacturing Practice
CI	Confidence interval
cIEF	Capillary isoelectric focusing
CHO	Chinese Hamster Ovary
CPPs	Critical process parameters
CQAs	Critical quality attributes
CV	Coefficient of variation
DLS	Dynamic light scattering
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucle ic acid
DO	Dissolved oxygen
DP	Drug product
DS	Drug substance
EAC	Equivalence acceptance criterion
ELISA	Enzyme-linked immunosorbent assay
EOPC	End of production cells
EU	Endotoxin unit
EU	European Union
FBS	Fetal bovine serum
FLR	Fluorescence spectroscopy
FTIR	Fourier transform infrared spectroscopy
GFP	Green fluorescent protein

GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HC	Heavy chain
HCP	Host cell protein
HER2	Human epidermal growth factor receptor 2
HLX02	Product code for Trastuzumab biosimilar
HMW	High molecular weight
HMWS	High molecular weight substances
HPLC	High-performance liquid chromatography
HVAC	Heating, ventilation and air-conditioning
icIEF	Imaged capillary isoelectric-focusing
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISF	Impurity safety factor
INN	International Non-proprietary Name
LC	Light chain
LC-MS	Liquid chromatography–mass spectrometry
LMWS	Low molecular weight substances
MCB	Master cell bank
MFI	Micro-flow-imaging
MoA	Mechanism of action
NAb	Neutralising antibody
N/A	Not applicable
NGHC	Non-glycosylated heavy chain
OCB	Original research cell bank
OOS	Out of specification
PAGE	Polyacrylamide gel electrophoresis
PC	Process characterisation
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PPQ	Process performance qualification

PTM	Posttranslational modification
QbD	Quality by design
qPCR	Quantitative polymerase chain reaction
RCB	Research cell bank
RMP	Reference medicinal product
RSD	Relative standard deviation
SEC	Size exclusion chromatography
SOP	Standard operating procedure
SPR	Surface plasma resonance
tBHP	tert-butyl hydroperoxide
UF/DF	Ultrafiltration / diafiltration
UHPLC	Ultra-high-pressure liquid chromatography
UPB	Unprocessed bulk
UPLC	Ultra-performance liquid chromatography
USP	United States Pharmacopeia
VCD	Viable cell density
VF	Virus removal filtration
WCB	Working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 29 May 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Zercepac, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Metastatic breast cancer

Zercepac 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

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

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

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

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

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

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

Metastatic gastric cancer

Zercepac 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.

Zercepac should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2

overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see SmPC sections 4.4 and 5.1).

The legal basis for this application refers to:

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

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

The chosen reference product is:

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 GmbH
- 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 GmbH
- 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 GmbH
- Date of authorisation: 28-08-2000
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/00/145/001

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant received Scientific Advice on 21 July 2016 (EMEA/H/SA/3366/1/2016/III) for the development programme relevant to the present application. The Scientific Advice pertained to the following quality, preclinical and clinical aspects of the dossier:

- Quality:
    - Testing plans for the Master Cell Bank, Working Cell Bank and End of Production Cells.
    - Appropriateness of the study protocol to compare different drug substance manufacturing process (versions 2, 3 and 4).
    - Analytical Methods Panel to use in support of the demonstration of analytical similarity between the biosimilar and the Reference Medicinal Product.
- Preclinical: *In vitro* study plan to provide non-clinical evidence of similarity; Waiver of *in vivo* studies.
- The main clinical aspects under consideration were:
    - The design of the PK study in healthy volunteer to demonstrate similarity in PK profiles of Zercepac, EU sourced Herceptin, and China-sourced (US manufactured) Herceptin.
    - The design of the efficacy and safety trial in patients with untreated HER2-overexpressing metastatic breast cancer including population selected and the primary endpoint, proposed margins and statistical assumptions, duration and safety database.
    - Extrapolation of the clinical results in metastatic breast cancer to support registration in the other indications approved for the Reference Medicinal Product.

Date	Reference	SAWP Co-ordinators
21 July 2016	EMEA/H/SA/3366/1/2016/III	*Dr Juha Kolehmainen, Dr Helgi Helgason*

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sol Ruiz Co-Rapporteur: Koenraad Norga

The application was received by the EMA on	29 May 2019
The procedure started on	20 June 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 September 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	13 September 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	23 September 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 October 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 January 2020
The following GMP and GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A routine GCP inspection at one investigator site in the Philippines, one investigator site in China and the Contract Research Organisation (CRO) in China to which a number of sponsor activities were delegated, took place between 14 October 2019 and 17 January 2020. The outcome of the inspection carried out was issued on:	5 February 2020
– A GMP inspection at 2 manufacturing sites in China between 9 and 10 December 2019. The outcome of the inspections carried out was issued on	2 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	04 March 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 March 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 March 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 May 2020
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	22 May 2020

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zercepac on	28 May 2020

2. Scientific discussion

2.1. Problem statement

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is observed in 20 %-30 % of primary breast cancers. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8 % to 34.0 % for IHC and 7.1 % to 42.6 % for FISH. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. The extracellular domain of the receptor (ECD, p105) can be shed into the blood stream and measured in serum samples.

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

Zercepac (HLX02) has been developed as a biosimilar to the reference product Herceptin. The proposed indications of HLX02 are the same as those currently authorised for the reference medicinal product Herceptin (see section 1.1):

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

The posology and method of administration are the same as the ones approved for Herceptin 150 mg powder for concentrate for solution for infusion. The applicant did not claim subcutaneous use.

Zercepac intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only. It contains 150 mg powder for concentrate for solution for infusion.

2.2. Quality aspects

2.2.1. Introduction

Zercepac (company code HLX02) is developed as a similar biological medicinal product (biosimilar) to the Reference Medicinal Product (RMP) Herceptin.

The finished product is presented as a sterile lyophilised powder for concentrate for solution for infusion containing 150 mg of trastuzumab as active substance. The reconstituted Zercepac solution contains 21 mg/mL of trastuzumab. Other ingredients are L-histidine hydrochloride monohydrate, L-histidine, α, α-trehalose dihydrate and polysorbate 20.

The product is available in a 20 mL clear glass type I vial with bromobutyl rubber stopper.

2.2.2. Active Substance

General Information

HLX02 is a humanised recombinant anti-HER2 monoclonal antibody produced using Chinese Hamster Ovary (CHO) cells. It is comprised of the constant region of human IgG1 kappa and the humanised variable region of murine anti-HER2 antibody. HLX02 is a disulphide bond-linked tetramer consisting of two identical 450-aa glycosylated heavy chains (HC) and two identical 214-aa kappa light chains (LC), with a molecular weight around 145 kDa before N-linked glycosylation. The antibody contains 4 pairs of interchain and 12 pairs of intrachain disulfide bonds, and 1 N-linked glycosylation site at N_{300} of each HC.

Trastuzumab binds to Human Epidermal growth factor Receptor 2 protein (HER2) that is overexpressed in breast cancer cells. The mechanism of action of trastuzumab is known to be its inhibition of proliferation of human tumor cells that overexpress HER2.

The antibody presents high affinity and specificity binding activity to sub-domain IV of HER2´s extracellular domain, anti-proliferation activity against HER2-positive carcinoma cells and antibody-dependent cell-mediated cytotoxicity (ADCC) against HER2-positive carcinoma cells.

Manufacture, process controls and characterisation

The active substance is manufactured at Shanghai Henlius Biopharmaceutical Co. Ltd, Shanghai, China.

Description of manufacturing process and process controls

The manufacturing process for the active substance uses a recombinant CHO cell line that contains the DNA coding sequence for trastuzumab. The active substance manufacturing process includes 1) an upstream cell culture process, consisting on cell expansions and a final cell culture in a Bioreactor a downstream purification process, consisting on several chromatographic steps and filtrations. The active substance manufacturing process is well described in the dossier, including flow charts summarizing all process steps.

Information regarding media compositions, buffers and reagents used in cell cultures is presented, as well as composition of resins for the chromatographic columns and filters characteristics. Information on the storage conditions and lifetime of the different columns used during purification has been provided.

In-process controls (IPCs) are established at all steps of manufacture

Control of materials

The Applicant has listed the raw materials used during the manufacturing of HLX02 active substance. Certificates of analysis for raw materials are provided and quality controls of materials not conforming to Ph. Eur. grade are presented in the dossier.

Materials of animal origin were used only during early stages of cell line development and a TSE risk assessment has been provided. Information on the qualitative composition media used has been provided.

The Applicant has provided complete information on the bioreactors and bioreactor bags used for active substance manufacture. In addition, extractable studies on the bags have been conducted and the results confirm a low risk.

Regarding generation of the producer cell line, the Applicant has provided information on the amino acid sequences used to express the HLX02 monoclonal antibody. Information concerning the parental cell line source is provided. Expression vectors, cloning strategy, transfection method and development of the producer cell line are adequately described in the dossier. Clone selection steps are described and data demonstrating the clonality of the cell bank are presented.

Cell bank preparation and establishment are adequately described in the dossier. Characterisation of the Master Cell Bank (MCB) and the Working Cell Bank (WCB) has been performed. An End of production cell bank (EOPC) has been established to evaluate the stability of the producer cell line and to determine the limit of the *in vitro* cell age. EOPC has been adequately characterized and several tests have been performed to analyse cell substrate stability.

Finally, any future WCB will be established according to the description of the current WCB. Regarding the characterisation, a future WCB will be tested similarly as the current WCB for the parameters identity, viability, sterility and bacteriostasis/fungistasis, Mycoplasma, *in vitro* adventitious viruses and *in vivo* assay for viral contaminants.

Control of critical steps and intermediates

The Applicant has determined critical steps and key parameters to control the robustness and reproducibility of the active substance manufacture. Specifications and their acceptance criteria for in-process controls (IPCs)/intermediates have been established. A description of the analytical methods used for IPCs testing and their validation reports are presented in the dossier.

Process validation and/or evaluation

A prospective process validation with a sufficient number of consecutive batches has been performed. To accomplish process validation, a panel of controls have been used, including manufacturing process parameters, in-process monitoring and active substance batch release.

In general, the analysis performed and data provided support that the process is well established and robust enough to yield a consistent product. Impurities clearance has also been validated and, after purification, impurity levels for the validation batches met acceptance criteria for the active substance. Furthermore, hold times and hold conditions for process intermediates in the purification process have been adequately justified.

Lifetime studies for the three chromatographic resins and UF/DF filter have been carried out at small scale and the proposed lifetimes for commercial manufacturing are considered acceptable. The proposed lifetimes will be

verified during the continued process verification. A protocol for the qualification of the proposed lifetimes at manufacturing scale has been provided.

Manufacturing Process Development

From the initial non-clinical to the clinical material manufactured for the Phase III study and finally to the commercial material, the Applicant states continuous efforts have been made to improve product quality, especially biosimilarity and process performance. Several manufacturing processes have been defined for the manufacturing process development.

The comparability studies performed between the materials manufactured with the different manufacturing processes are considered adequate.

Critical quality attributes (CQAs) were identified. The Applicant has provided satisfactory information related to the approach to define the CQAs. Impact and uncertainty definitions and scores for QAs have been justified based on the impact on biological function, PK and immunogenicity and safety. Scores assigned to CQAs have been based on regulatory requirements, product experience and previous knowledge.

Anticipated ranges for CQAs to meet biosimilarity requirements were established based on a combination of clinical experience, non-clinical studies, laboratory studies, prior knowledge and regulatory requirements.

A study has been performed to evaluate the impact of process parameter variations (critical process parameters (CPPs) and key process parameters (KPPs)) on the quality attributes and ensure the control strategy is appropriate to achieve the intended quality of the active substance. A risk assessment has been performed to identify key performance attributes and CQAs.

Based on the clinical and pharmacokinetic as well as the physicochemical characteristics of trastuzumab, a quality target product profile (QTPP) was defined. A major objection was raised as frozen samples had been used to establish the QTPP. To demonstrate that the reconstitution and frozen storage at -80°C does not impact the quality of the samples additional data was provided and the major objection was adequately addressed.

Characterisation

A comprehensive characterisation study has been performed.

Characterisation studies include the assessment of several quality attributes classified into two categories: physicochemical characterisation and functional assays. The physicochemical characterisation includes tests to determine the primary structure (amino acid sequence, molecular weight, disulphide linkages, glycosylation site, post-translational modifications and free thiols), higher order structure, charge variants and isoelectric point, glycosylation and size variants. The functional assays include tests to determine the immunochemical properties and bioactivity (anti-proliferation, ADCC, and apoptosis by cell-based assay and HER2 target binding by ELISA and SPR).

Process-related impurities include Protein A, insulin, host cell protein (HCP), and deoxyribonucleic acid (DNA). They are controlled in the active substance release specification and their removal has been successfully demonstrated on the process validation batches.

In addition, the removal of other impurities was also studied during the active substance process validation. A safety evaluation of these impurities was carried out based on the impurity safety factor (ISF).

In conclusion, the information provided in characterisation is considered acceptable and described in sufficient detail.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The specifications have been set in accordance with ICH Q6B and cover tests for identity, appearance, general tests, quantitation, purity, potency, impurities and microbial contamination.

Analytical methods

The active substance is tested using a combination of non-compendial and compendial methods. For non-compendial test methods, descriptions of the test procedures including samples preparation, procedures and system suitability criteria are provided. For the compendial test methods relevant pharmacopoeial references are given.

Analytical methods developed in house were appropriately validated according to ICH Q2, and pharmacopoeial methods were verified based on the Ph. Eur. monographs. Validation reports are provided.

Biological activity is measured through the analysis of its anti-proliferation activity in a human breast cancer cell line over expressing HER2. The Applicant has added also a HER2 binding assay to the active substance release specification. The proposed acceptance limits are deemed acceptable.

Batch analysis

Batch analysis data submitted comply with the active substance specification and confirm consistency of the manufacturing process.

Reference materials

The reference standards have been characterised with respect to primary and higher order structures, post-translational modifications, protein content, potency, immune characteristics, purity, physical/chemical characteristics and impurities/pollutants. The analytical procedures are described.

A requalification strategy of reference materials is defined.

Container closure system

The active substance is stored in single-use Mobius storage bags. Extractable and leachable studies were conducted and analytical results were provided. A safety assessment based on the study results was performed to evaluate the potential health risk for patients. All extractables and leachables were present in concentrations below their derived permitted daily exposures (PDEs). Therefore, it is agreed that the risk for patients is negligible. Suitability of the proposed container closure system for the active substance has been appropriately demonstrated.

Stability

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

Stability studies were conducted in accordance with ICH guidelines and analytical methods were stability indicating.

Stability studies were performed with samples stored in containers representative of the proposed container for active substance storage.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is supplied as a sterile, white to pale yellow, preservative-free, lyophilized powder for concentrate for solution for infusion in a dosage strength of 150 mg. Before use, the lyophilized finished product is reconstituted with 7.2 ml of sterile water for injections yielding a colourless to pale yellow, clear to slightly opalescent solution containing 21 mg/ml at pH 6.0. The reconstituted solution is further diluted with sterile 0.9% sodium chloride for administration by intravenous infusion. The finished product is supplied in a 20 mL Type I borosilicate clear glass vial sealed with a 20 mm bromobutyl rubber lyophilisation stopper and a 20 mm aluminium seal with flip-off plastic cap.

The composition of HLX02 finished product contains L-histidine hydrochloride monohydrate, L-histidine, α, α-Trehalose dihydrate and polysorbate 20 as excipients All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The finished product has the same dosage form and formulation components as the reference medicinal product (RMP), EU Herceptin. No further formulation development was performed. The formulation is appropriate to ensure the stability of HLX02 protein, according to stability data.

The finished product contains a 5% overfill that ensures that the labelled dose of 150 mg can be withdrawn from each vial, but no overage was included.

The Applicant has provided a description of the process development. The finished product manufacturing process evolved through different processes to increase robustness and production capacity, and to meet the needs of future commercial production. The formulation composition has remained the same throughout development.

The Applicant performed comparability studies between finished product lots used in the phase III clinical study and lots from the proposed commercial process. All results obtained were highly similar thereby confirming comparability. The information on the process development is sufficiently detailed.

The Applicant has provided detailed information on the container closure system. The primary packaging consists of type I glass vials with rubber stoppers. The glass vials comply with Ph. Eur. 3.2.1, whereas the bromobutyl rubber stoppers comply with Ph. Eur. 3.2.9. They have been shown to be suitable for storage of the finished product, providing a good integrity to reduce the entry of water vapour, oxygen and other contamination during the long-term storage, and ensuring the quality of the finished product. Suitability of the container closure system has been appropriately demonstrated through a number of studies including extractables, leachables, integrity and compatibility with diluent and components used for the preparation of product for intravenous administration.

Manufacture of the product and process controls

During the procedure a major objection was raised in relation to the lack of valid GMP certificates for the active substance/finished product manufacturing site, one QC site and one importation/batch release site. The requested GMP certificates were provided for the manufacturing site and the QC site. The batch release and importation site was withdrawn from the application as a valid GMP certificate could not be provided in a timely manner. The major objection was thereby considered resolved.

As the active substance is already formulated, there is no formulation step in the finished product manufacturing process. The finished product manufacturing process consists of active substance thawing, mixing, sterile filtration, filling and partial stoppering, lyophilisation and full stoppering, capping, visual inspection, labelling and packaging.

Reprocessing is not allowed. No holding times have been proposed.

An overview of the CPPs and intermediates has been provided. The proposed CPPs, process monitoring parameters and IPCs are deemed sufficient to control the finished product manufacturing process.

The Applicant states that the manufacturing process has undergone continuous improvement and optimisation in order to increase production capacity and meet the needs for commercial production with only one major revision being a change in lyophiliser during the scale up prior to the phase III clinical trials.

The acceptable range for total operation time has been justified and maximum times for thawing, mixing, sterilising filtration, filling and lyophilisation were specified.

The manufacturing process has been validated with a sufficient number of consecutive validation batches following ICH Q8 (R2). In addition, an enhanced in-process monitoring has been conducted for a comprehensive study of product quality and process performance attributes during process validation. Several studies have been performed to demonstrate stability of the active substance before and after mixing and homogeneity of active substance after mixing.

Several validation procedures have been successfully performed including lyophilisation process (position effect), aseptic filling (media fill simulation studies), sterilisation processes (vials and stoppers), filtration (bacteria retention, filter compatibility and product bubble point ratio) and shipping (summer and winter scenarios).

Product specification, analytical procedures, batch analysis

Finished product specifications for release and shelf-life include tests for identity, appearance, reconstitution time, visible particles, sub-visible particles, pH after reconstitution, mass variation, osmolality, water content, protein content, purity, potency, bacterial endotoxin and sterility.

For some parameters the same specifications (with identical acceptance limits) are applied for active substance and finished product. For quantitative parameters, ranges were set based on mean +/- 3SD of historical data.

The finished product specifications for release and shelf-life are considered appropriate since they cover all the important features of the product and comply with ICH Q6B requirements.

Analytical methods

The analytical test methods were appropriately described and non-compendial methods have been validated. Analytical procedures common for the active substance and finished product are described in the active

substance part of the dossier. Analytical procedures specific for the finished product are compendial and have been properly verified.

Method transfer protocols have been provided for all analytical methods. In addition, for the anti-proliferation assay, the Applicant has confirmed the successful transfer to the EU lab and provided validation results. This is considered acceptable.

Batch analysis

An overview of all finished product batches manufactured, and full release testing data were provided. This includes process validation batches manufactured according to the final commercial process. The batches were in compliance with the specifications and confirm consistency of the manufacturing process.

No additional impurities are introduced by the finished product manufacturing process. The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

Reference standards

The reference standard used for analysis of the finished product is the same as that used for the active substance.

Stability of the product

A shelf life of 36 months at 2°C - 8°C is claimed for the finished product. The stability program was designed to follow ICH guidelines Q1A (R2) and Q5C.

Data for up to 36 months under long term storage conditions (2°C - 8°C) are available for lots of finished product. The available data shows that the quality attributes remain in conformance with the commercial acceptance criteria and supports a shelf life of 36 months at 2°C - 8°C.

The shelf-life specifications are identical to those applied for release, with the addition of a complementary identity and purity test for shelf-life testing.

A forced degradation study was performed as part of the analytical similarity assessment. The photostability study showed that the finished product is sensitive to light. Therefore, the finished product should be stored protected from light.

The in-use stability results demonstrated that the reconstituted solution is stable for 48 hours at 2°C - 8°C, and the solution for intravenous infusion (finished product diluted in 0.9% sodium chloride) is stable for 7 days at 2°C - 8°C and subsequently for 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and Zercepac infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, unless reconstitution have taken place under controlled and validated aseptic conditions.

Biosimilarity

A biosimilarity study has been performed including several batches of HLX02 and EU approved Herceptin.

Samples used in the generation of the QTPP and the biosimilarity analysis were stored frozen before analysis. This raised doubts on whether the quality profile was representative of product stored under approved conditions. The Applicant was requested to present further justification to demonstrate that the material used could be considered representative of the quality of product stored under approved conditions. This was raised as a major objection. Based on additional data provided by the applicant, the major objection was considered adequately addressed. Consequently, the results obtained in the biosimilarity exercise can be considered as valid.

The quality attributes included in the biosimilarity study in order to provide a full and comprehensive package of information have been classified under the following categories: physicochemical characterisation, functional assays, process related impurities (HCP and protein A by ELISA and DNA by qPCR), particles (sub-visible particles by MFI and submicron particles by DLS) and forced degradation study (high temperature, illumination, acidity, alkalinity, oxidation and shaking). All analytical methods were properly qualified and are deemed suitable for the intended purposes.

Attributes/assays were assigned to one of three 3 tiers based on the potential relevance of each attribute to safety and efficacy. The quality attributes were ranked based on the risk assessment principles set out in the ICH Quality Guidelines Q8 and Q9.

The data from the analytical similarity assessment indicate that HLX02 is highly similar to the reference product (see Table 1, Table 2 and Table 3 below). The amino acid sequence is identical, and primary and higher order structures including secondary, tertiary structure are similar. The purity and heterogeneities between HLX02 and the reference product assessed by SEC, CE-SDS, CEX, icIEF and UPLC-FLR glycan profiling are highly similar, with similar profiles of size and charge variants and glycan moieties. Minor differences in relative abundance of charge variants and glycan moieties were observed and have been appropriately justified.

The extinction coefficient (used for protein determination) has been adequately substantiated, in order to assure that the absolute amount of protein is correctly determined and the biosimilar contains the amount of protein stated on the label claim.

The forced degradation studies involving high temperature, illumination, acidity, alkalinity, oxidation and shaking showed that HLX02 and EU Herceptin had similar degradation behaviours and degradation trends.

A series of functional assays relevant to the mechanism of action, efficacy and safety were conducted to evaluate the biological activity. However, from the description of the ADCC assay it appeared that ADCC had been only analysed using an ADCC reporter assay. It was acknowledged that such reporter assays are more reproducible compared to classical ADCC assays. However, it was unclear to which extent these ADCC reporter assays are representative for ADCC activity *in vivo*. Therefore, the ADCC reporter assay alone was not considered sufficient to conclude on biosimilarity as regards ADCC activity.

In addition, the sensitivity of the current ADCC assay as performed by the Applicant was questioned. Taken together, the issues identified in relation to the ADCC assay were raised as a major objection.

In response to the major objection, the Applicant provided results from additional ADCC assays. Several lots of HLX02 and EU Herceptin were included in these analyses. High similarity in ADCC activity was shown between HLX02 and EU Herceptin. The classic ADCC assay used also appeared to be more suitable than the reporter ADCC assay to distinguish between Herceptin lots with higher/lower afucosylation levels.

Taken together, the data provided in response to the major objection are deemed sufficient to confirm that HLX02 can be considered as similar to EU Herceptin as regards ADCC activity.

It is noted that the Applicant has provided extensive biosimilarity data for both EU-sourced and China-sourced Herceptin. Whereas the data from China-sourced Herceptin have been taken into consideration, these are considered as supportive data only.

In conclusion, an extensive comparability exercise has been performed between HLX02 and EU Herceptin and the results confirm a high level of similarity from a quality point of view.

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

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Primary structure	Amino acid sequence	Peptide mapping by reduced LC-MS/MS	1) 100% amino acid sequence coverage; 2) Identical primary sequence
	Molecular weight	Intact, reduced and papain digested by LC-MS	Similar masses for each species
	Disulfide linkage	Peptide mapping by non-reduced LC-MS/MS	Identical disulfide bridging patterns
	Free thiols	Free thiol fluorescent detection kit	Similar low level of free thiol
	Glycosylation site	Peptide mapping with and without deglycosylation	Identical glycosylation site to the RMP (HC: N300)
	Post translation modifications (PTMs)	Peptide mapping by reduced LC-MS/MS	Identical sites of PTMs, and Similar levels for each PTM
Higher order structure	Secondary and tertiary structure	Differential scanning calorimetry (DSC)	Transition temperatures consistent to EU sourced Herceptin
		Circular dichroism (CD)	Similar secondary and tertiary structures
		Fluorescence Spectroscopy (FLR)	FLR profiles and emission wavelength comparable between all batches
		Fourier transform infrared spectroscopy (FTIR)	FTIR profiles comparable between all batches
		Protein nuclear magnetic resonance (NMR)	NMR profiles comparable between the batches
Glycan	Glycation profile	Hydrophilic interaction ultrahigh pressure liquid chromatography -Fluorescence analysis (HILIC UPLC-FLD)	Highly similar levels of afucosylation, high mannose and galactosylation, similar G0F, but a slightly higher sialylation content for HLX02, which is not clinically meaningful
	Sialic Acids	HPLC-FLD	1) Same NANA sialic acid present; 2) Slightly higher level in HLX02 than the RMP, which is not clinically meaningful
Charge variants	Charged variant profile	Cation exchange chromatography (CEX)	1) Highly similar levels of acidic and basic species; 2) Slightly higher main peak for HLX02 and is not clinically meaningful

Molecular parameter	Attribute	Methods for control and characterization	Key findings
			3) HLX02 has slightly less peak 4 than Herceptin which is not clinically meaningful based on the small magnitude of the difference
		Imaged capillary isoelectric focusing (icIEF)	1) Highly similar levels of acidic and basic species; 2) Slightly higher main peak for HLX02 and is not clinically meaningful
Purity and Size Variants	Aggregates and Fragments	SEC-HPLC	Similar level of monomer, and less HMWS
		SV-AUC	
	Intact IgG	CE-SDS (non-reduced)	Similar level of intact IgG
	Heavy Chain+ Light Chain	CE-SDS (reduced)	Similar level of HC+LC
	NGHC	CE-SDS (reduced)	HLX02 has less NGHC than Herceptin
Process-related impurities	HCP	Enzyme-linked immunosorbent assay (ELISA)	No relevant difference
	Protein A		No relevant difference
	Residual DNA	qPCR	No relevant difference
Particles	Submicron particles	DLS	No relevant difference
	Sub-visible particles	MFI	No relevant difference

Table 2: Biological analytical similarity assessment between Zercepac and EU Herceptin

Test		Method / cell line	Key findings
Bioactivity	HER2 binding assay	Enzyme-linked immunosorbent assay (ELISA)	Similar binding to HER2
	Binding kinetics to HER2 assay	Surface plasmon resonance (SPR)	Similar binding to HER2
	Anti-proliferation assay	Cell-based assay	Similar anti-proliferation activity
	ADCC assay	Reporter gene assay	Similar ADCC activity
	ADCC assay	NK cell assay	Similar ADCC activity
	ADCP assay	Cell-based assay	Similar ADCP activity
	Apoptosis assay	Cell-based assay	Similar apoptosis activity
	CDC assay	Cell-based assay	Similarly lack of CDC activity
Immuno-chemical properties	FcγRIa binding assay	Surface plasmon resonance (SPR)	Similar binding to FcγRIa
	FcγRIIa-R binding assay		Similar binding to FcγRIIa-R
	FcγRIIa-H binding assay		Similar binding to FcγRIIa-H

	FcγRIIb/c binding assay		Similar binding to FcγRIIb/c
	FcγRIIIa-V binding assay		Similar binding to FcγRIIIa-V
	FcγRIIIa-F binding assay		Similar binding to FcγRIIIa-F
	FcγRIIIb binding assay		Similar binding to FcγRIIIb
	FcRn binding assay		Similar binding to FcRn
	C1q binding assay	Enzyme-linked immunosorbent assay (ELISA)	Similar binding to C1q

Table 3: Forced degradation study and similarity assessment between Zercepac and EU Herceptin

	Stress conditions	**Methods**	**Key findinds**
Forced degradation Study	High temperature	CEX, SEC, CE-SDS, LC-MS and antigen-antibody binding activity,	Similar to RMP
	Illumination	CEX, SEC, CE-SDS, LC-MS	Similar to RMP
	Acidity	CEX, SEC, CE-SDS, LC-MS	Similar to RMP
	Alkalinity	CEX, SEC, CE-SDS, LC-MS	Similar to RMP
	Oxidation	CEX, SEC, CE-SDS, LC-MS	Similar to RMP
	Shaking	CEX, SEC, CE-SDS, LC-MS and antigen-antibody binding	Similar to RMP

Adventitious agents

No materials from human or animal origin are used in the manufacturing process except two materials which were used in the first stages during the development of the suspension-adapted CHO cell line. A certificate of analysis is presented for these two materials. A TSE certificate is not presented but this is supported by an appropriate justification.

Viral testing results of all cell banks (Research Cell Bank, MCB, WCB and EOPC) and of three batches of unprocessed bulk are presented in tabulated form.

Hepatitis E virus was not tested and could, potentially, have been introduced in the cells from the Trypsin-EDTA used in the first stages of the cell line development. However, the Applicant presented a risk assessment to conclude that the risk for the presence of this virus is negligible. This conclusion is endorsed.

The effectiveness of the manufacturing process to inactivate/remove viruses has been demonstrated in spike-recovery studies of 4 model viruses, Xenotropic Murine Leukemia Virus (MuLV), Pseudorabies Virus (PRV), Reovirus type 3 (Reo-3), and Minute Virus of Mice (MVM). The effectiveness of inactivation/removal of viruses was tested on scaled-down purification steps (Protein A Affinity Chromatography (AC), Low pH Inactivation, Cation Exchange Chromatography (CEX), Multimodal Anion Exchange Chromatography (AEX) and Viral Filtration (VF)) validated to be representative of the full scale process. Overall, high clearance/inactivation factors were observed for all 4 model viruses.
In conclusion appropriate data has been presented to give reassurance on viral/TSE safety.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure three major objections were raised. The first one related to the lack of valid GMP certificates for the active substance/finished product manufacturing site, one QC site and one importation/batch release site. The requested GMP certificates were provided for the manufacturing site and the QC site. The batch release and importation site was withdrawn from the application as a valid GMP certificate could not be provided in a timely manner. Since batch release and importation activities are also covered by other sites registered in the dossier (and for which valid GMP certificates are available) the major objection could thereby be considered resolved.

A second major objection related to the use of data in the comparability exercise and for the establishment of the QTPP from samples that had been stored frozen. To demonstrate that this does not impact the quality of the samples additional data was provided and the major objection was considered adequately addressed.

The third major objection was in relation to the suitability of the ADCC reporter assay used. In response to the major objection, the Applicant provided results from additional ADCC assays. The data provided in response to the major objection were deemed appropriate to confirm high similarity between HLX02 and EU Herceptin with regard to ADCC activity.

Overall, an extensive comparability exercise has been performed between HLX02 and EU Herceptin and the results confirm a high level of similarity from a quality point of view.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

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

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical data package consisted in *in vitro* pharmacology studies and an array of *in vivo* pharmacology and toxicology studies. Animal toxicology studies (single and repeat dose), an *ex vivo* erythrocyte haemolysis study and a behavioural safety pharmacology assay were conducted in accordance with the OECD principles of GLP according to the applicant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

A summary of the *in vitro* functionality and binding assays is provided below.

Table 4: Summary of the functional similarity assays

Assay		Tier	Method	Reason of Tier
Biological Activity	Soluble HER2 Binding	1	ELISA	Primary MoA
			SPR	
	Anti-proliferation	1	Cell-based assay	Primary MoA
	ADCC	1		
	Apoptosis	2		Secondary MoA
	ADCP	2		Secondary MoA
	CDC	3		Not MoA
Immunochemical properties	C1q binding	3	ELISA	Not MOA
	FcRn binding	2	Surface Plasma Resonance (SPR)	Impact PK
	FcγRIa binding	2		Impact effector functions
	FcγRIIa binding	2		
	FcγRIIb/c binding	2		
	FcγRIIIa (F) binding	2		
	FcγRIIIa (V) binding	2		
	FcγRIIIb binding	2		

In vitro studies were carried out comparing frozen batches of trastuzumab including several batches of HLX02 against several batches of Herceptin-EU (Herceptin). Data from several China-sourced Herceptin (Herceptin-CN) lots were also analysed. HLX02 batches were manufactured from two different manufacturing processes.

HER2 binding by ELISA

Soluble HER2 binding was first assessed by using an ELISA assay. Recombinant human soluble HER2 was coated onto the wells of a microtiter ELISA plate, a dose titration of HLX02 was applied as a test sample, and binding was detected using an anti-human IgG conjugated to horseradish peroxidase. Relative receptor binding activities were calculated based on the ratio of EC50 values (the effective dose at which 50% inhibition is observed) of the reference standard curve relative to the test sample.

Table 5: Statistical analysis results of soluble HER2 binding by ELISA for HLX02 and Herceptin-EU

Assay	Standard Deviation (N=26)	Similarity interval	90% CI of HLX02 (N=10) and Herceptin-EU measurements	Equivalent
HER2 binding-ELISA	8%	(-12.0%, 12.0%)	(-7.0%, 2.6%)	Yes

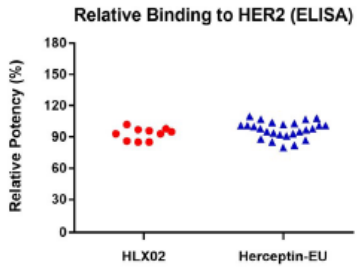


Figure 1: Soluble HER2 binding and statistical analysis results for HLX02 and Herceptin-EU

Binding kinetics to Soluble HER2 by SPR

The aim of the assay was to determine the potency using a suitable HER2 protein in a SPR Assay with 1:1 binding evaluation model. In the study, it was performed a measurement and comparison of the kinetic parameters of the Sample HER2-affinity with that of the Reference HER2-affinity by measurement of the binding capacity with HER2 of IgG bases on Surface Plasmon Resonance (SPR).

Table 6: Statistical analysis results of soluble HER2 binding by SPR for HLX02 and Herceptin-EU

Assay	Standard Deviation (N=26)	Similarity interval	90% CI of HLX02 (N=10) and Herceptin-EU measurements	Equivalent
SPR	21.1%	(-31.7%, 31.7%)	(-8.6%, 15.1%)	Yes

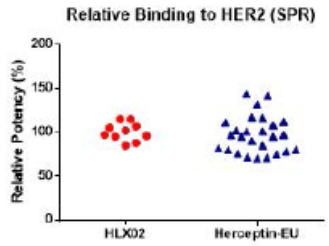


Figure 2: Soluble HER2 binding by SPR and statistical analysis results for HLX02 and Herceptin-EU

Anti-proliferation (cell-based assay)

Overexpression of the HER2 receptor promotes cell growth, proliferation, survival, and migration. Binding to HER2 and has a direct inhibitory effect on proliferation of HER2-overexpressing cells through multiple pathways. Evaluation of functional activity was measured *in vitro* for HLX02/Herceptin using the HER2- overexpressing BT-474 cell line. Relative Anti-proliferation activities are calculated based on the ratio of EC_{50} values.

Table 7: Statistical analysis results of Anti-proliferation for HLX02 and Herceptin-EU

Assay	Standard Deviation (N=26)	Similarity interval	90% CI of HLX02 (N=10) and Herceptin-EU measurements	Equivalent
Anti-proliferation	8%	(-12.0%, 12.0%)	(0.4%, 10.5%)	Yes

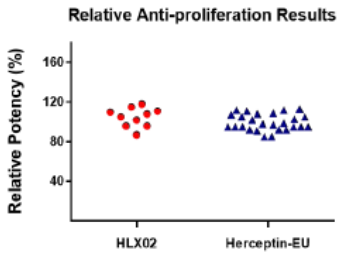


Figure 3: Anti-proliferation and statistical analysis results for HLX02 and Herceptin-EU

Antibody-dependent cell-mediated cytotoxicity (ADCC)

Two different ADCC assays were conducted. The first approach employed a human breast cancer cell line overexpressing HER2 (BT-474) as target cells and CD16a cells (engineered Jurkat effector cells), stably transfected with human FcγRIIIa (158V), as effector cells. Relative ADCC activities were calculated based on the ratio of EC_{50} values.

The second assay, a classic assay based on NK cells, was conducted with BT-474 as target cells and NK92-CD16 as effector cells, expressing FcγRIIIa V/F. Activities were calculated as mentioned above.

Table 8: Statistical analysis results of ADCC (with NFAT_CD16a Jurkat cells) for HLX02 and Herceptin-EU

Assay	Standard Deviation(N=26)	Similarity interval	90% CI of HLX02 (N=10) and Herceptin-EU measurements	Equivalent
ADCC	13%	(-19.5%, 19.5%)	(-8.2%, 6.4%)	Yes

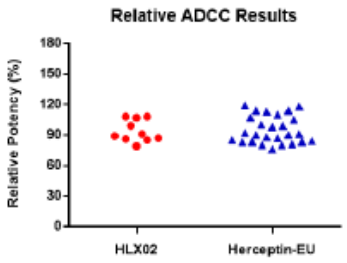


Figure 4: ADCC (Jurkat cells) and statistical analysis results for HLX02 and Herceptin-EU

Table 9: Statistical analysis results of ADCC (with NK92-CD16 cells) for HLX02 and Herceptin-EU

Assay	Standard Deviation (N=26)	Similarity interval	90% CI of HLX02 (N=10) and Herceptin-EU measurements	Equivalent
ADCC by NK cell	18%	(-26.8%, 26.8%)	(-14.08%, 1.16%)	Yes

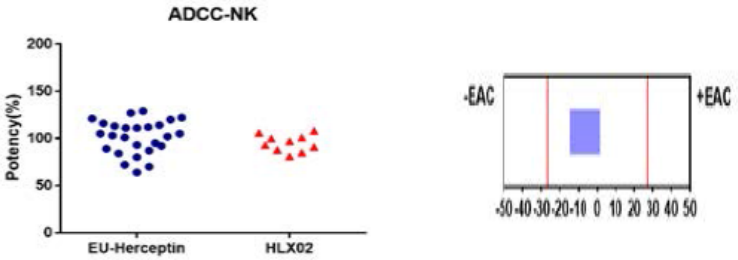


Figure 5: ADCC (NK cells) and statistical analysis results for HLX02 and Herceptin-EU

Antibody-dependent Cellular Phagocytosis (ADCP)

An assay was conducted to analyse whether HLX02/Herceptin have ADCP activity on BT-474 cells by using as effector cells the NFAT_FcγRIIa-H_Jurkat transgenic cells. Measurements were based on the EC_{50} values.

Table 10: Statistical analysis results of ADCP for HLX02 and Herceptin-EU

Assay	Range of RMP (n=26)	Average of RMP (n=26)	Standard Deviation	Similarity interval	HLX02 measured interval (n=10)
ADCP	77%-125%	99%	14%	57%-141%	96%-119%

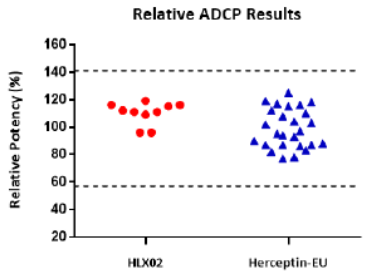


Figure 5: ADCP results for HLX02 and Herceptin-EU

Apoptosis

The apoptosis assay, a secondary mechanism of action, was performed using a cell-based assay that employed a human breast cancer cell line overexpressing HER2 (BT-474) as target cells, and a dose titration of HLX02 is applied as a test sample. After the apoptotic cells are stained, it was calculated the median effective concentration of reference material and sample based on their fluorescence and then the cell apoptosis activity of HLX02 by comparing the median effective concentration of reference material and sample. Relative apoptosis activities were calculated based on the ratio of EC_{50} values.

Table 11: Apoptosis similarity assessment results of HLX02 and Herceptin-EU

Assay	Range of RMP (n=26)	Average of RMP (n=26)	Standard Deviation	Similarity interval*	HLX02 measured interval (n=10)
Apoptosis	82%-123%	105%	10%	75%-135%	91%-109%

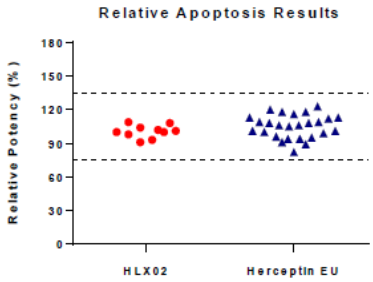


Figure 6: Apoptosis similarity assessment results of HLX02 and Herceptin-EU

Complement-dependent cytotoxicity (CDC)

Herceptin-EU lots and Herceptin-CN lots were tested using a human breast cancer cell line overexpressing HER2 (BT-474). HLX02 and Herceptin-EU CDC activity was not observed.

FcγR Receptor-affinity Assay

SPR analysis was used to determine the association and dissociation rate constants and dissociation equilibrium binding constant (KD) for FcγR (FcγRIa, FcγRIIa (R and H), FcγRIIb/c, FcγRIIIa(V), FcγRIIIa(F) and FcγRIIIb). Relative FcγR binding activities are calculated based on the ratio of KD values.

Table 12: FcγR binding similarity assessment results of HLX02 and Herceptin-EU

FcγR	Range of RMP (N=26)	Average of RMP (N=26)	Standard Deviation	Similarity interval*	HLX02 measured interval (N=10)
FcγRIa	64%-117%	99%	14%	57%-141%	90%-105%

FcγR	Range of RMP (N=26)	Average of RMP (N=26)	Standard Deviation	Similarity interval*	HLX02 measured interval (N=10)
FcγRIIa-R	87%-109%	98%	4%	86%-110%	98%-107%
FcγRIIa-H	88%-104%	95%	5%	80%-110%	90%-103%
FcγRIIb/c	87%-113%	101%	7%	80%-122%	94%-110%
FcγRIIIa-V	64%-113%	93%	12%	57%-129%	84%-109%
FcγRIIIa-F	62%-115%	93%	17%	42%-144%	84%-113%
FcγRIIIb	58%-117%	93%	17%	42%-144%	86%-106%

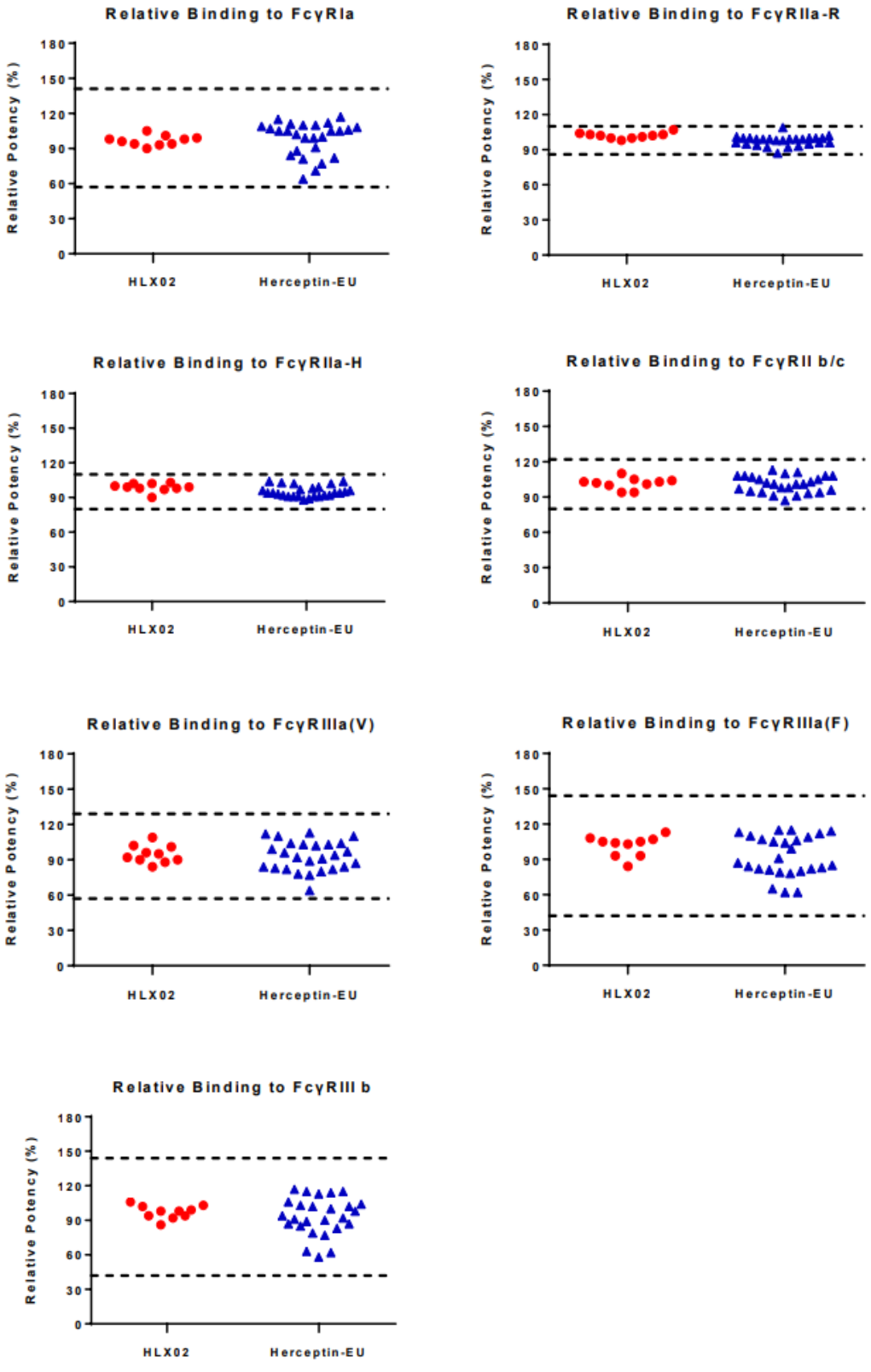


Figure 7: FcγR binding similarity assessment results of HLX02 and Herceptin-EU

FcRn Receptor-affinity Assay

SPR-based analysis was used and relative FcRn binding activities were calculated based on the ratio of KD values.

Table 13: FcRn binding similarity assessment results of HLX02 and Herceptin-EU

FcγR	Range of RMP (n=26)	Average of RMP (n=26)	Standard Deviation	Similarity interval*	HLX02 measured interval (n=10)
FcRn	92%-132%	110%	12%	74%-146%	76%-113%

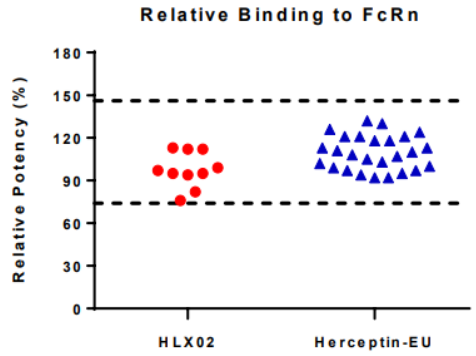


Figure 8: FcRn binding similarity assessment results of HLX02 and Herceptin-EU

C1q binding by ELISA

Binding to C1q was measured using ELISA. A dose titration of test samples were coated onto the wells of a microtiter ELISA plate as test sample, recombinant human soluble C1q is applied, and binding was detected using an goat anti-human C1q conjugated to horseradish peroxidase.

ELISA-based analysis was used and relative C1q binding activities are calculated based on the ratio of EC_{50} values.

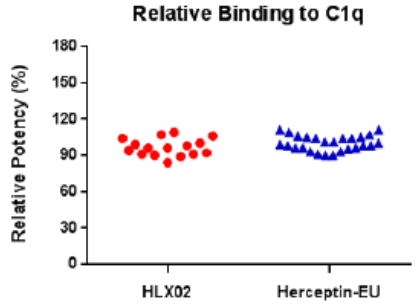


Figure 9: C1q binding similarity assessment results of HLX02 and Herceptin-EU

Additional analyses

Herceptin batches with expiry dates between August 2018 and December 2019 were reported with a marked downward shift in %Afucose, FcγRⅢa binding affinity and ADCC activity (Kim 2017). To investigate whether such findings were present in the products tested in HLX02 biosimilarity assessment, the FcγRⅢa binding and ADCC activity were summarized and compared among 39 Herceptin batches with different expiry dates.

Results are presented below. Consistent with the Samsung Bioepis's report (Kim 2017), among the 39 Herceptin batches, all the 5 batches with expiry dates before February 2018 showed normal levels for the %Afucose, %Galactose and FcγRIIIa affinity, all the 23 Herceptin batches with expiry dates between February 2018 and May 2020 had the %Afucose, %Galactose and FcγRIIIa affinity down drifted, and all the 11 Herceptin batches with expiry dates after May 2020 returned to the original levels (Figure 10).

As a result, Herceptin batches analysed in the study were divided into two groups: low FcγRIIIa binding affinity with expiry dates between February 2018 and May 2020; and high FcγRIIIa binding affinity with expiry dates before February 2018 or after May 2020. In addition, the binding affinity to other FcγRs, FcRn and C1q, as well as proliferation inhibition activity, CDC and apoptosis, were similar among the Herceptin batches investigated in the study. Comparison of FcγRIIIa binding and ADCC (reporter gene) activities for HLX02 and the Herceptin with low affinity and with high affinity, respectively is shown in Figure 11.

For the additional data of ADCC assays using NK cells, the relevance between ADCC activity (NK cell based) and the expiry dates of Herceptin were also analysed (Figure 12). The results showed that, similar to the observation from the data of ADCC reporter assay, the ADCC activity in Herceptin-EU batches expiring after May 2020 returned to a relatively high levels when compared with Herceptin-EU batches expiring between February 2018 and May 2020.

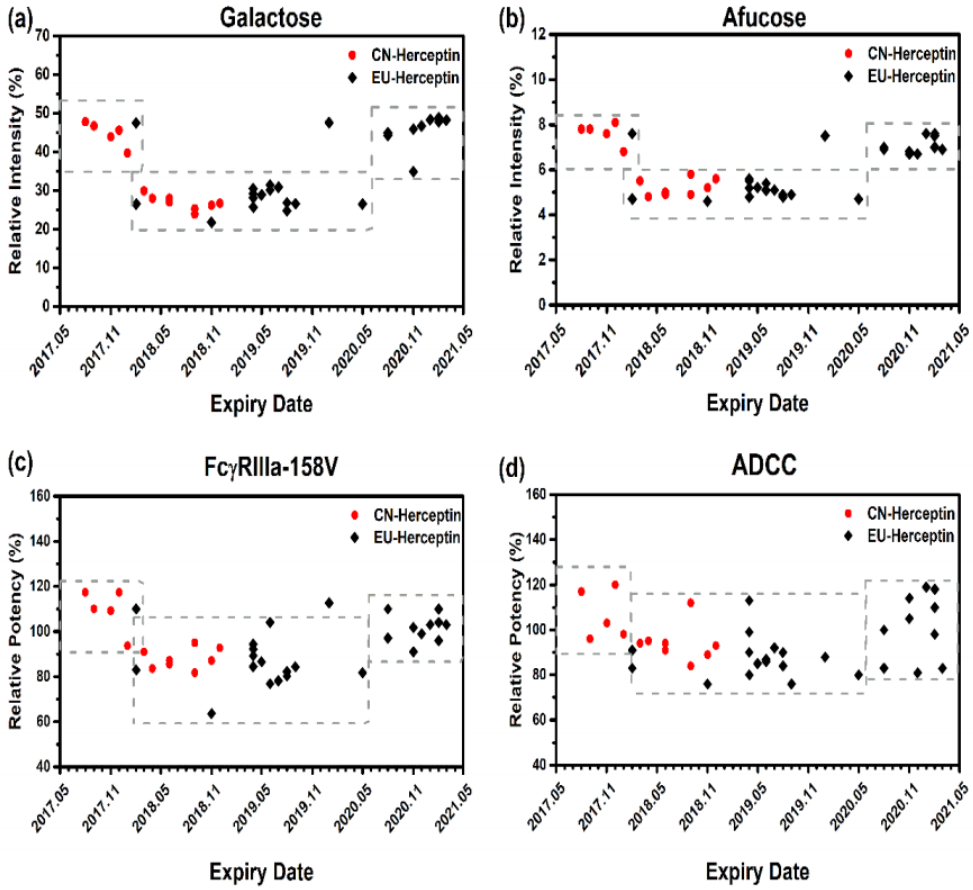


Figure 10: Trends of N-glycan attributes that are related to biologic activities by expiry dates of the examined Herceptin. (a) %Galactose, and (b) %Afucose, (c) FcγRIIIa-158V binding activity by SPR, (d) ADCC (reporter gene) activity

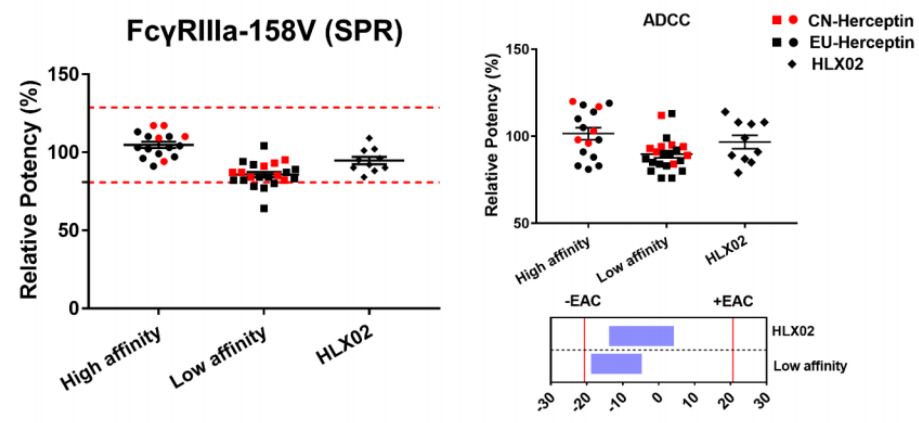


Figure 11: Comparison of FcγRIIIa binding and ADCC (reporter gene) activities for HLX02 and the Herceptin with low affinity and with high affinity, respectively

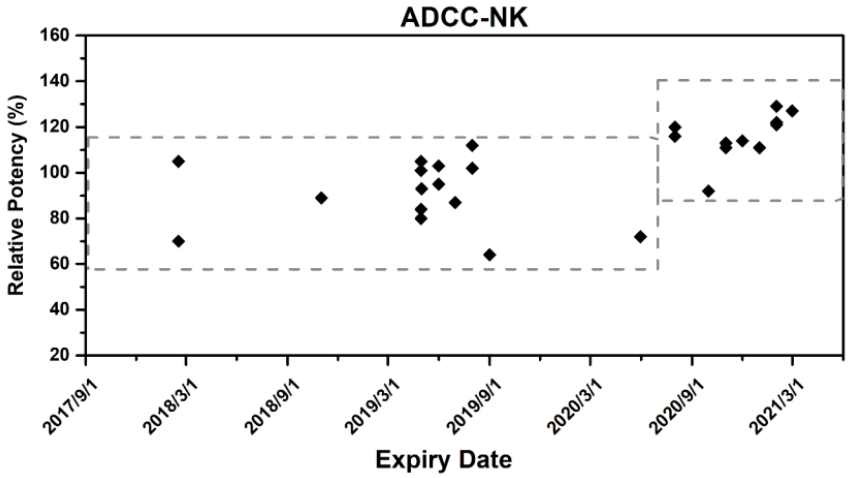


Figure 12: Relevance between ADCC activity and Herceptin-EU expiry dates assessed by NK cells

***In vivo* studies**

Animal studies were undertaken to compare the pharmacodynamic characteristics of HLX02 *versus* China-sourced Herceptin in various cancer types (see discussion on non-clinical aspects). The applicant also performed cynomolgus monkey and human tissue cross-reactivity studies as well as an *in vivo* CNS safety pharmacology in mice. ECGs have been included in the 13-week repeat dose toxicity study performed in monkeys (see discussion safety pharmacology).

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were submitted (see discussion on non-clinical aspects).

Safety pharmacology programme

In vivo behavioural test of ICR mice intravenously injected with HLX02

Fifty ICR mice assigned into 5 groups containing 5 female and 5 male mice were administered a single intravenous injection of HLX02 (process 1.0 batch H20120101) at doses of 8, 16 and 32 mg/kg. Diazepam (2.5 mg/kg) was used as the positive control. Pole climbing and air righting reflex were observed before administration and at 0.5, 1, 3, 6, and 24 h after administration.

There were no effects on mouse behaviour and coordinated movement.

In vivo GLP safety pharmacology study on the effect of intravenous injection of HLX02 in cynomolgus monkeys on cardiovascular system and respiratory rate

Electrocardiogram (ECG) indicators were evaluated as part of the repeat dose toxicity study performed in monkeys at baseline, 2 h and 24 h after the first administration, on Day 29 (2 h after the 5th administration), on Day 42, on Day 57 (2 h after the 9th administration), and on Day 91 and at the end of convalescence period. Blood pressure and respiratory rate were measured before the administration (baseline), 2 h and 24 h after the first administration, on Day 42, on Day 91 and at the end of convalescence period.

Compared with the placebo group, QTcf was significantly shortened in HLX02 groups at 24 and 48 mg/kg as well as 24 mg/kg Herceptin group on Day 29, but compared to the testing results of ECG before administration (baseline), the degree of QTcf change in 24 and 48 mg/kg HLX02 as well as 24 mg/kg Herceptin groups was relatively small, and no significant abnormalities were observed at other testing time points. Intravenous injection of HLX02 with the dosages of 8, 24, 48 mg/kg and Herceptin at 24 mg/kg in cynomolgus monkeys showed no effects on ECG, blood pressure and respiratory rate.

2.3.3. Pharmacokinetics

The applicant provided the results from two studies comparing the exposures of HLX02 and Herceptin sourced from China (see discussion on non-clinical aspects): one study using single IV doses (in comparison with Herceptin) and repeat IV doses of the test product and another study using single IV doses of HLX02 manufactured with different processes.

Table 14: Tabulated overview of HLX02 pharmacokinetic studies

Study number	GLP Compliance	Dose(s) (route of administration) Test product (T) / reference product (R) / control group (C)	Species/Number	Duration	Endpoints
In Vivo Pharmacokinetic Study of HLX02 in Cynomolgus Monkeys	No	T: 1, 4 or 16 mg/kg HLX02 (i.v.; batch H20120101) single dose R: 4 mg/kg Herceptin (i.v.; batch B3458) single dose T: 4 mg/kg HLX02 (i.v. .; batch H20120101) repeat dose (once a week for 4 weeks)	Cynomolgus monkey (4/dose group)	Single dose: HLX02 and Herceptin Repeat dose: HLX02 (168 h)	Serum concentration-time profile over 480 hours for a single dose and after last repeat dose: PK parameters (including $AUC_{0\text{-}480\ h}$, T_{max}, C_{max}, $T_{1/2}$, CL MRT, V_{ss}). For repeat doses: serum concentrations during the 4 weeks.
1662NG1	No	T: 4 mg/kg HLX02 (i.v. .; batch H20150502, Process 2.0) and batch H20160804, Process 4.0)) single dose	Cynomolgus Monkeys (12/group)	Single dose HLX02 (Process 2.0 and HLX02, Process 4.0)	Serum concentration-time profile over 672 hours post dose. PK parameters were C_{max}, AUC_{INF_obs}, AUC_{last}, CL_{obs}, $T_{1/2z}$, V_{z_obs})

Absorption

The first study included 3 single i.v. HLX02 groups at doses of 1 mg/kg, 4 mg/kg and 16 mg/kg, one single i.v. Herceptin group (4 mg/kg, batch B3458) and one repeated i.v. HLX02 group at 4 mg/kg. Four (4) cynomolgus monkeys were used in each dose group. HLX02 batch H20120101 was used in this study. From each animal receiving single administration, 1 mL of blood was collected before administration as well as 5 minutes (min), 15 min, 30 min (test drug needle withdrawal point), 35 min, 45 min, 1 h, 2 h, 3 h, 5 h, 7 h, 9 h, 13 h, 24 h, 48 h, 72 h, 96 h, 120 h, 168 h, 216 h, 264 h, 312 h and 480 h after i.v. infusion (the start of administration was set as point 0). In the repeat dose administration group, the repeat administration was applied at 168 h after the previous administration, and 1 mL of blood was collected before administration and at needle withdrawal point (30 minutes after the start of the infusion) for the second and third administration; the time points for blood collection after the last dose administration were the same as that in single dose administration group.

Table 15: Pharmacokinetic parameters after a SD of HLX02 (administered at 1; 4 or 16 mg/kg) and the reference compound in cynomolgus monkeys

Parameters	Unit	Low Dose (1 mg/kg)	Medium Dose (4 mg/kg)	High Dose (16 mg/kg)	Reference Material (4 mg/kg)	P Values of T-test
$AUC_{(0-480)}$	$\mu g \cdot h \cdot mL^{-1}$	2,059.7±383.9	7,869.1±1,574.2	36,150.5±8,209.4	8,663.0±1,232.5	0.1136
$AUC_{(0-inf)}$	$\mu g \cdot h \cdot mL^{-1}$	2,213.2±425.6	9,422.2±2,513.7	43,552.0±9,973.0	10,817.7±2,135.2	0.0607
$AUC_{(480-inf)}$	$\mu g \cdot h \cdot mL^{-1}$	153.5±48.2	1,553.0±981.8	7,401.6±3,902.9	2,154.8±956.1	0.1536
MRT	h	90.4±18.0	140.5±24.6	135.3±21.3	150.5±11.0	0.3644
CL	$mL \cdot kg^{-1} \cdot h^{-1}$	0.5±0.1	0.5±0.2	0.4±0.1	0.4±0.1	0.1678
Vss	$mL \cdot kg^{-1}$	40.9±3.1	61.5±9.6	50.8±8.5	56.9±8.6	0.0516
$T_{1/2}$	h	119.7±11.8	126.3±28.3	134.9±33.5	140.9±27.7	0.2725
Kel	h^{-1}	0.0058±0.0006	0.0058±0.0016	0.0054±0.0014	0.0051±0.001	0.2554
C_{max}	$\mu g \cdot mL^{-1}$	23.9±3.3	91.4±12.3	404.7±43.9	85.9±11.1	0.5392
T_{max}	h	0.6±0.1	0.8±0.2	0.7±0.1	0.6±0.1	0.5894

A dose proportional increase was observed for HLX02 and the reference product. The study also showed some accumulation of the compound following four weekly administrations.

The second study aimed at comparing the pharmacokinetic profiles of HLX02 produced by 2 different manufacturing processes, namely P2.0 and P4.0. All animals were treated with HLX02 at 4 mg/kg by single intravenous infusion over 30 minutes. Blood samples were collected from each animal at pre-dose, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 96, 168, 240, 336, 504, and 672 hours post-dose. The results showed no difference in pharmacokinetic parameters.

2.3.4. Toxicology

The program contained one single dose assay, one repeat dose (13 weeks treatment with 8 weeks recovery) assay and one *in vitro* haemolysis assay in New Zealand White rabbit erythrocytes. Studies have been conducted with HLX02 DP manufactured with DS P1.0 versus China-sourced Herceptin (see discussion on non-clinical aspects).

Single dose toxicity

In vivo toxicity study of single intravenous injection of HLX02 in cynomolgus monkeys (study 1125AD1)

Table 16: Single-dose toxicity (study 1125AD1)

Study Number	Species/ Strain	Route (Vehicle/ Formulation)	Doses (mg/kg)	Sex and No. /Group	Maximum Nonlethal Dose (mg/kg)	Minimum Lethal Dose (mg/kg)
1125AD1	Cynomolgus Monkeys	Intravenous (vehicle, solvent (0.9% NaCl), HLX02 batch H20120101)	210 mg/kg (HLX02 group) 0 mg/kg (vehicle group) 0 mg/kg (solvent NaCl group)	1 male and 1 female per group Total number of animals=6	210	-

Cynomolgus monkeys about 3-4 years old (n=6 in total; 2 animals/group (1 male and 1 female)) were administered with HLX02 (DS P1.0, batch H20120101) at a single IV dose of 210 mg/kg of body weight. Two control groups were established: solvent group (0 mg/kg, NaCl injection) and vehicle group (0 mg/kg HLX02 placebo solution), mixed with 0.3 ml of NaCl to adjust the osmotic pressure.

The results showed that no animal died during the study. Compared to solvent group, no significant abnormal changes in clinical symptoms, body weight, food intake, body temperature, ECG examination, haematology and blood coagulation indexes, serum biochemical indexes and indexes of immune functions were found in either vehicle group or HLX02 group. At the end of the observation period, no obvious abnormalities were detected in gross necropsy of all test animals, and no evident pathological changes related to toxicity of HLX02 were detected.

According to the results, the NOAEL for single IV administration of HLX02 (Process 1.0) in cynomolgus monkeys was set up at 210 mg/kg.

Repeat dose toxicity

A thirteen-week repeated intravenous injection of HLX02 followed by an eight-week recovery period was also performed in the cynomolgus monkey. The same batch as above was used. The animals were allocated in 5 groups of 6 animals each (3M/3F) and received 0 mg/kg (vehicle control group), 8 mg/kg HLX02 (low-dose group), 24 mg/kg HLX02 (middle-dose group), 48 mg/kg HLX02 (high-dose group) and 24 mg/kg China-sourced Herceptin (referred to as "reference control") once a week.

Table 17: Repeat dose toxicity (study 1125RD1)

Study Number	Species/ Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Sex and No. /Group	NOAEL [a] (mg/kg)
1125RD1	Cynomolgus monkey	Intravenous injection (vehicle, HLX02 batch H20120101, China-sourced Herceptin, batches N3472, N3510, N3503)	Once weekly for 13 weeks, and 8 weeks recovery	HLX02: 8, 24, 48 mg/kg Vehicle: 0 mg/kg Herceptin: 24 mg/kg	3 male and 3 female per group. Total number of animals: 30	-

Histopathological changes that were considered to be test article were noted in thyroid and spleen. At the end of both dosing period and recovery, thyroid of animals from low-, middle-, high-dose groups and comparator group all showed slight to mild colloid goiter. Spleen of animals from low-, middle-, high-dose groups at the end of dosing period and from low- and middle-dose groups and comparator group all showed slight to mild hyperplasia of white pulp in spleen. This was consistent with the enlarged volume of animal thyroid and spleen seen at gross anatomy.

In addition, at the end of administration period and recovery, animals from each group showed slightly mild vacuolar degeneration in myocardial cells.

The toxicokinetic parameters of HLX02 and comparator are presented in Table 18.

No specific antibody against recombinant anti-HER2 antibody was detected in any of the groups.

HLX02 was well tolerated in cynomolgus monkeys following once weekly dosing for 13 weeks at doses up to 48 mg/kg, and the toxicity and TK profile of HLX02 was similar to that of the reference medicinal product China-sourced Herceptin.

Genotoxicity

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

Carcinogenicity

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

Reproduction Toxicity

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

Toxicokinetic data

As part of the repeat dose toxicity study performed in monkeys, serum samples were drawn as follows: Vehicle control group: 2 hours before and after administration; low-, middle- and high-dose group and control group: First and last administration: 2, 24, 48, 72, 120 and 168 hours before and after administration respectively (±2 min for the time point ≤1h, and ±15 min for the rest of time points).

The results are provided in the table below.

Table 18: Toxicokinetic results from repeat dose toxicity study

Numbers of Administration	Parameter	Unit	Low-dose Group	Middle-dose Group	High-dose Group	Control Group
First administation	$AUC_{(0-t)}$	$\mu g.h.mL^{-1}$	11,916.2±1,983.6	37,093.1±6,937.2	55,477.0±10,142.9	42,791.0±4,975.3
	C_{max}	$\mu g.mL^{-1}$	188.2±35.5	508.7±78.4	815.1±121.0	544.2±43.3
	T_{max}	h	0.7±1.0	0.4±0.8	1.0±1.1	1.0±1.1
Last administration	$AUC_{(0-t)}$	$\mu g.h.mL^{-1}$	20,407.4±1,718.8	54,868.8±4,330.0	85,642.2±2,838.9	61,209.9±3,607.5
	C_{max}	$\mu g.mL^{-1}$	240.1±34.6	659.9±39.1	1,062.3±42.0	670.9±53.6
	T_{max}	h	1.3±1.0	0.4±0.8	1.0±1.1	1.2±1.1

Local Tolerance

Local tolerance was assessed as part of the 13-week repeat dose toxicity study performed in monkeys and summarised above. No significant dosing site irritation was observed for any animals during the in-life observation and necropsy examination. Microscopic examination revealed perivascular bleeding (haemorrhage) and vascular wall-thickening, mild proliferation of perivascular fibrous tissue at the injection site in animals of vehicle control group, low-dose group and high-dose group. It was considered that the injection lesions were caused by the mechanical irritation of administration and were not test article related.

2.3.5. Ecotoxicity/environmental risk assessment

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

absence of a formal environmental risk assessment studies is considered justified and HLX02 is not expected to pose a risk to the environment due to its nature.

2.3.6. Discussion on non-clinical aspects

This application is based on the comparison of HLX02 (Zercepac) and the reference product Herceptin. Zercepac is formulated with the same excipients as the reference product.

Successive versions of the HLX02 DS manufacturing process (MP) have been developed and batches from several MPs have been used in studies throughout the development program. HLX02 material from the different manufacturing process are considered analytically comparable (see quality aspects).

The pharmacology program focused on primary pharmacodynamics. The *in vitro* studies were conducted with HLX02 from two different manufacturing processes and comparisons were performed with EU Herceptin batches. The following studies were conducted by the Applicant with the purpose of the assessment of *in vitro* biosimilarity: 1) HER2 binding by ELISA, 2) Binding kinetics to Soluble HER2 by SPR 3) Inhibition of proliferation assay, 4) Antibody-dependent cell-mediated cytotoxicity employing NK92-CD16 effector cells and the reporter cell line NFAT_CD16a_Jurkat, 5) Apoptosis assay, 6) Complement-dependent cytotoxicity, 7) FcγR Receptor-affinity Assay, 8) FcRn Receptor-affinity Assay, 9) C1q binding by ELISA, 10) Antibody-dependent Cellular Phagocytosis.

One of the ADCC assays provided by the Applicant (BAD-TP-051) was conducted using engineered reporter cells, more precisely the reporter cell line NFAT_CD16a_Jurkat with FcγRIIIa 158V genotype. Although in some instances these reporters might be considered more reproducible than the classic assays, current consensus indicates that classic assays are more reliable when a determination on the similarity should be made. For that reason, results from an ADCC assay with NK92-CD16 effector cells, expressing FcγRIIIa V/F (BAD-TP-286) were also provided. Similarity between HLX02 and the reference product Herceptin was concluded in both assays.

ADCP has also been investigated (BAD-TP-252). NFAT_FcγRIIa-H_Jurkat cells were used in the study. For this secondary mechanism of action, similarity between HLX02 and the reference product Herceptin was concluded.

Regarding CDC, HLX02-induced CDC was not observed, similarly to Herceptin, likely due to the presence of membrane-associated complement regulatory proteins such as CD35 (complement receptor 1, CR1), CD55 (decay accelerating factor, DAF), or CD46 (membrane cofactor protein, MCP).

Some differences relative to afucosylation, FCγRIIIa binding and ADCC activity were described in several batches of EU Herceptin that have been employed for the *in vitro* determinations. A total of 39 Herceptin batches were used in the studies, 23 of them (15 EU and 8 CN batches with expiration dates between February 2018 and May 2020) presenting with an atypical profile involving lower percentages of afucosylation and galactosylation, lower FcγRIII binding activity and decreased relative potency of ADCC. The Applicant has compared HLX02 with all those 39 batches, providing a separate analysis of each study for the atypical ones. It was concluded in all the comparisons that HLX02 could be considered similar to Herceptin, but with a profile closer to those batches with high FcγRIIIa-158V affinity.

Overall, the results of the *in vitro* primary pharmacodynamics studies allow concluding on the similarity between Herceptin and HLX02 (Zercepac) from a non-clinical perspective.

In vivo studies investigating primary pharmacodynamics in various mouse models of several cancer types (even those not included in the claimed indications) were provided with a lot of product prepared with an earlier manufacturing process. Comparisons were conducted with China-sourced Herceptin and the relevance of

comparability studies with non-EEA authorised products is limited. Furthermore, in biosimilar applications, *in vitro* pharmacology comparability is considered the paramount of comparability assessment as *in vivo* models are not considered sensitive enough to detect differences and are mostly regarded as supportive.

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

Results from two safety pharmacology studies with HLX02 were provided. Not only those studies are unneeded since the safety of the compound has been characterised following the long-term use in humans but also it is not clarified if the mice and NHP expressed the desired epitope. In addition, the *in vivo* behavioural study in mice did not provide data with the reference product Herceptin, and therefore is not considered relevant for the comparability exercise.

The second study was carried out in monkeys for the assessment of CVS and respiratory effects. It should be noted that stand alone safety pharmacology studies are not required for the evaluation of biotechnology medicinal products as indicated in the ICH guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals and dosing non-human primates for the toxicological assessment of a biosimilar product is not recommended unless justified. The *in vivo* study in monkeys has revealed non relevant effects on the QTcf prolonged QT intervals and increased QTd (QT dispersion). Although long term studies with trastuzumab in breast cancer patients have reported prolonged QT intervals and increased QTd (QT dispersion), the findings seen in cynomolgus monkeys seem unrelated to the clinical findings described in the literature.

Results from two pharmacokinetic studies with the product HLX02 manufactured with DS P1.0 were also provided. In the first study (1125rd1-pk) the test substance (HLX02) was compared with China-sourced Herceptin. As mentioned above, the relevance of comparability studies with non-EEA authorised products is limited, unless a thorough justification and a bridging exercise to the currently EEA authorised reference medicinal product is provided. From the information submitted it is understood that the applicant addressed the pharmacokinetics of HLX02 to fulfil regulatory requirement of other regions. The limited number of animals studied per group does not allow performing statistical analysis on the obtained results and no justification for the selection of cynomolgus monkeys as the selected species was provided by the Applicant. Furthermore, in the context of biosimilarity assessment, animal pharmacokinetic studies are not considered sensitive enough to highlight differences between the biosimilar and the reference product due to a high variability.

In another PK study, HLX02 products manufactured with DS P2.0 and DS P4.0 were compared, as both were used in the Phase 1 and 3 clinical studies. In this case Herceptin was not included in the aforementioned assay, therefore the relevance of the data produced for the determination of biosimilarity is limited.

Considering the type of product, distribution, metabolism, excretion and pharmacokinetic drug interaction studies are not deemed necessary.

Furthermore, toxicity studies are in principle not needed for biosimilarity assessment. The safety profile is already known from the reference product and there is a large clinical experience which is considered as more relevant for safety information. Studies performed in animals are not considered sensitive enough to allow detection of any subtle pharmacological or toxicological differences between the biosimilar candidate product and the reference product. However, it is understood that the applicant evaluated the toxicity of HLX02 in order

to comply with regulatory requirements of other regions. The provided studies were performed with a batch of the biosimilar from an earlier manufacturing process which was compared to China-sourced Herceptin.

The purpose of the single dose toxicity study was to assess the toxicity of HLX02 upon a single administration at a dose of 210 mg/kg in cynomolgus monkeys. The limited number of animals critically limits the conclusions that can be extrapolated from this assay (2 animals per group). In any case, the study showed no significant toxicity in the animals after 14 days. Since no animals were exposed to Herceptin (the reference medicinal product) the data submitted is not considered relevant for the comparability assessment.

The Applicant also provided results from a repeat dose toxicity study using different dosing levels for the test product HLX02. Only the data obtained upon treatment of the animals at 24 mg/kg, either with HLX02 or Herceptin, may be considered supportive for the assessment of biosimilarity. Additional comparative doses would have been desirable should the Applicant aims were to produce relevant safety comparability data between HLX02 and Herceptin. It should be noted that according to the Guideline on similar biological medicinal products containing monoclonal antibodies, non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) the conduct of toxicological studies in non-human primates is usually not recommended. Furthermore, the scarce number of animals in the study does not allow to draw conclusions.

The toxicokinetics determination was not GLP compliant. As in the repeat dose toxicity study, only the comparative data obtained with HLX02 and Herceptin at a dose of 24 mg/kg (middle dose group versus control group) would be considered for the assessment of biosimilarity. Remarkable differences were evident for the determination of T_{max} while the other determinations (AUC and C_{max}) were similar between HLX02 and Herceptin. It is noted that the study is not considered powered enough to conduct a formal toxicokinetic-biosimilarity assessment, as only 6 animals were included in each group.

Considering the type of product and the type of MAA, the lack of genotoxicity, carcinogenicity and reproductive and developmental studies is considered adequate (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, EMEA/CHMP/BMWP/42832/2005 Rev1). Although the same principle is applied for local tolerance studies, observations were conducted as part of the repeat dose toxicity study and did not suggest relevant local tolerance issues.

No ADAs were detected in the repeat dose toxicity study. In any case, the predictive value of the non-clinical data is limited and relevant antigenicity data is obtained in the clinical trials (see section on clinical aspects).

Due to the type of Application and according to the ICH guideline S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (EMA/CHMP/ICH/731268/1998), routine immunotoxicity testing for biotechnology-derived pharmaceuticals is not recommended. Due to the nature of the product no dependence, metabolites and impurities studies are required.

Overall, the provided animal studies are only considered supportive information. In the context of biosimilarity assessment, these studies are not considered necessary if comparability is demonstrated in *in vitro* assays which is the case for HLX02. However, it is acknowledged that, in this case, such studies were conducted for regulatory compliance in other regions.

2.3.7. Conclusion on the non-clinical aspects

The assessment of the non-clinical data indicated similar activity between HLX02 and the reference product Herceptin.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

A routine GCP inspection of trial HLX02-BC01 was performed at two investigator sites (one in the Philippines and one in China) and a CRO in China.

Although there were deficiencies and departures from GCP observed, the trial in general has been conducted according to the ethical principles for clinical trials in humans and the data collected at the investigational sites inspected are considered of acceptable quality and the sites as overall GCP compliant.

In addition, GCP inspections were performed by the US FDA at 1 investigator site in China and the 3 investigator sites in the Ukraine.

Table 19: Tabular overview of clinical studies

Study reference and location of the report	Population	Study design	Dose schedule and duration	Route of administration	N	Objectives	Status
Studies in healthy subjects (single dose)							
HLX02-HV01 Module 5.3.3.1	Healthy Chinese male subjects	Phase 1 Part 1: Open-label, single dose escalation of HLX02 to evaluate safety, tolerability and immunogenicity.	Part 1: Four single-dose of 2, 4, 6 and 8 mg/kg	IV infusion	Part 1: 12 (3 in each group)	Part 1: Primary Objective: To evaluate the safety and tolerability at different doses of HLX02. Secondary Objective: To evaluate the immunogenicity of HLX02 and characterise the PK profile of HLX02 at different doses.	Completed
		Phase 1 Part 2: Double-blind, randomised, parallel study to compare the PK, safety, and immunogenicity among HLX02, CN-sourced Herceptin, and EU-sourced Herceptin.	Part 2: Single dose of 6 mg/kg	IV infusion	Part 2: 111 (37 in each arm)	Part 2: Primary Objective: To compare the PK profile of HLX02, CN- and EU-sourced Herceptin. Secondary Objective: To compare the safety and immuno- genicity among treatment arms.	Completed

Studies in patients (multiple dose)							
HLX02-BC01 Module 5.3.5.1	HER2-Over-expressing recurrent or previously-untreated metastatic breast cancer patients	Phase 3: Double-blind, randomised, parallel-controlled, multicentre, international study to compare the efficacy, safety, and immunogenicity of HLX02 versus EU-sourced Herceptin in combination with docetaxel	HLX02 and EU-sourced Herceptin: Loading dose of 8 mg/kg over 90 minutes on Day 1, Cycle 1; 6 mg/kg every 3 weeks for subsequent cycles. Treatment for a maximum of 12 months Docetaxel: Once every 3 weeks at 75 mg/m² for at least 8 cycles treatment, continuation is at the discretion of the Investigator up to a maximum of 12 months.	IV infusion	~324 in each arm (a total of 649 subjects)	Primary: To compare the efficacy of HLX02 versus EU-sourced Herceptin in combination with docetaxel using ORR_{wk24}, after completion of 8 cycles (each cycle for 3 weeks) of treatment to demonstrate clinical equivalence. Secondary: -To compare the safety, tolerability, and immunogenicity of HLX02 versus EU-sourced Herceptin in combination with docetaxel. -To compare the additional efficacy of HLX02 versus EU-sourced Herceptin in combination with docetaxel in terms of ORR, DoR, CBR, DCR, PFS up to 12 months, and OS at 12, 24, and 36 months. - To evaluate the exposure of trastuzumab following HLX02 or EU-sourced Herceptin Exploratory: Population PK (PopPK) analysis	Ongoing

Abbreviations: IV: intravenous; PK: pharmacokinetics; ORR_{wk24}: overall response rate at week 24 (after 8 -cycle treatment); DoR: duration of response; CBR: clinical benefit rate; DCR: disease control rate; PFS: progression-free survival OS: overall survival

The clinical comparability exercise was performed in a stepwise procedure that begin with a primary pharmacokinetic (PK) comparative study (HLX02-HV01) followed by a comparative clinical efficacy trial versus the chosen reference medicinal product (HLX02-BC01).

2.4.2. Pharmacokinetics

The HLX02 PK programme included a Phase 1 comparative single-dose study conducted in healthy volunteers (HLX02-HV01), and a supportive Phase 3 clinical comparability study in patients with HER2-positive metastatic breast cancer in combination with docetaxel (HLX02-BC01).

Both the EU-Herceptin and the product sourced in China (CN) were used in the PK similarity study (HLX02-HV01) whereas Herceptin used in the clinical comparability Phase 3 Study (HLX02-BC01) was the product sourced in the EU. The EU-Herceptin products were manufactured in Germany while the CN-Herceptin products were manufactured in the United States (US).

Bioanalytical methods

Pre-study validation

In both clinical studies [HLX02-HV01, HLX02-BC01], the bioanalytical method used for measuring serum drug concentrations of HLX02 and Herceptin was a validated ELISA method.

In addition, in clinical study HLX02-BC01, the concentrations of HER2 in human serum were measured by utilising a quantitative sandwich enzyme immunoassay with validated bioanalytical method.

An ELISA analytical method to quantify the concentration of trastuzumab in human plasma and in patients with Her2+ Metastatic Breast Cancer as well as their respective amendments were submitted. The validation of the method included assessment of precision and accuracy of the standard curve, the assay range (defined by the LLOQ and ULOQ), intra-assay and inter-assay accuracy and precision assessment (HLX02 and Herceptin), robustness, selectivity (HLX02), minimum required dilution, dilution linearity and hook effect (HLX02 and Herceptin), Herceptin comparison, short-term stability, freeze-thaw stability and long term stability (HLX02 and Herceptin), target interference and hemolysis and lipemic.

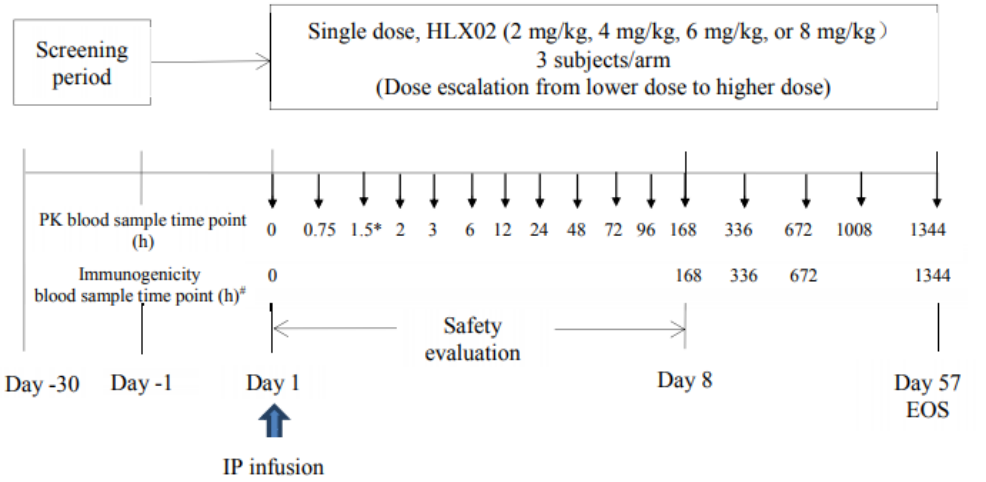
A second ELISA analytical method to quantify the concentration of HER-2 in human serum was also submitted. The validation of the method included assessment of precision and accuracy of the standard curve, the assay range (defined by the LLOQ and ULOQ), intra-assay and inter-assay accuracy and precision assessment, robustness, selectivity, minimum required dilution, dilution linearity and hook effect, target interference, parallelism and the specificity of the method.

Assay for the Determination of anti-drug antibodies and neutralising antibodies to trastuzumab in Human Serum

Please refer to the safety section Clinical Safety; immunological events.

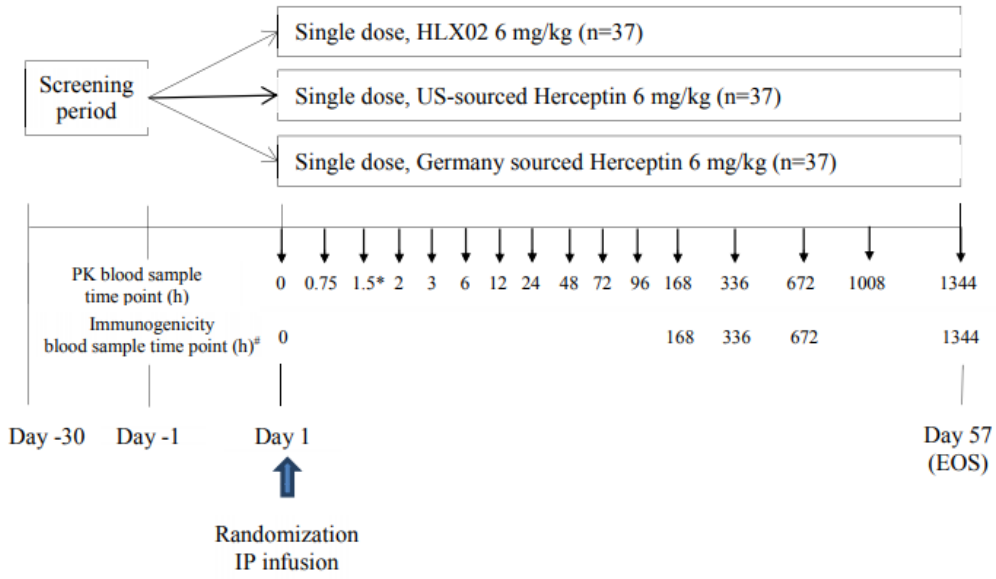
Study HLX02-HV01

There were 2 parts in this study (see the figures below). Part 1 was an open-label study to evaluate the safety and tolerability and assess the pharmacokinetic (PK) profiles of different dosages of HLX02 in healthy Chinese male subjects. Part 2 was a randomized, double-blind, parallel-group study to compare the PK profiles, safety, tolerability, and immunogenicity between HLX02 and US-sourced Herceptin (currently available in the Chinese market), HLX02 and the Germany-sourced Herceptin, and US-sourced and Germany-sourced Herceptin.



*Immediately after the completion of infusion (if the infusion rate is not changed, then it should be 1.5h after the start of infusion)
#ADA test to be conducted in the screening period
Abbreviation: PK = Pharmacokinetics; IP = Investigational Product; EOS = End of Study

Figure 13: Study design of safety evaluation of HLX02 (Study HLX02-HV01, part 1)



*Immediately after the completion of infusion (if the infusion rate is not changed, then it should be 1.5 h after the start of infusion)
#ADA test to be conducted in the screening period
Abbreviation: PK = Pharmacokinetics; IP = Investigational Product; EOS = End of Study

Figure 14: Study design of safety evaluation of HLX02 (Study HLX02-HV01, part 2)

HLX02 and Herceptin were reconstituted with sterile water for injection dependent on the vial size, as follows:

- HLX02: trastuzumab 150 mg vial was reconstituted with 7.2 mL of sterile water for injection without preservative.
- US-sourced Herceptin: trastuzumab 440 mg vial was reconstituted with 20 mL diluent (20 mL sterile water for injection containing 1.1% benzyl alcohol).
- Germany-sourced Herceptin: trastuzumab 150 mg vial was reconstituted with 7.2 mL of sterile water for injection without preservative.

The subjects received a single dose 90-minute IV infusion of HLX02, US-sourced Herceptin, or Germany-sourced Herceptin. The subjects were to be in a supine or semi-recumbent position from the start of the infusion until 2 hours after the completion of infusion.

In Part I of the study, a total of 18 subjects were screened and 12 subjects were assigned in one of the 4 treatment groups (2, 4, 6, and 8 mg/kg groups), according to the study plan; 6 subjects were screening failures due to not meeting the inclusion/exclusion criteria. All of the 12 subjects completed Part 1 as planned. No subjects withdrew or were withdrawn from the study.

The enrolled study population consisted of 12 Chinese males, ranging in age from 19 to 35 years, ranging in weight from 58.0 to 73.5 kg, and ranging in height from 166.0 to 175.0 cm.

In Part 2, a total of 111 subjects were eligible and randomized in one of the 3 treatment groups (HLX02, US-Sourced Herceptin, and Germany-sourced Herceptin groups), according to the study plan. A total 109 subjects completed the study. Two subjects were withdrawn from Part 2 because they were lost to follow-up;

both were from the US-Sourced Herceptin group. These subjects were excluded from the PK-PPS2 because their AUC_{last} could not be reliably calculated.

The enrolled study population consisted of 111 healthy Chinese male subjects, ranging in age from 18 to 45 years, ranging in weight from 51.0 to 80.0 kg, ranging in height from 159.5 to 185.0 cm and ranging in BMI from 19.0 to 27.5 kg/m^2.

Pharmacokinetics Results

Part 1

The individual serum concentrations of HLX02 versus time curves were provided by treatment group in linear scale and in semi-logarithmic scale. Mean serum concentrations on a linear scale (left panel) and semi-logarithmic scale (right panel) over nominal time by treatment group are presented in the Figures below.

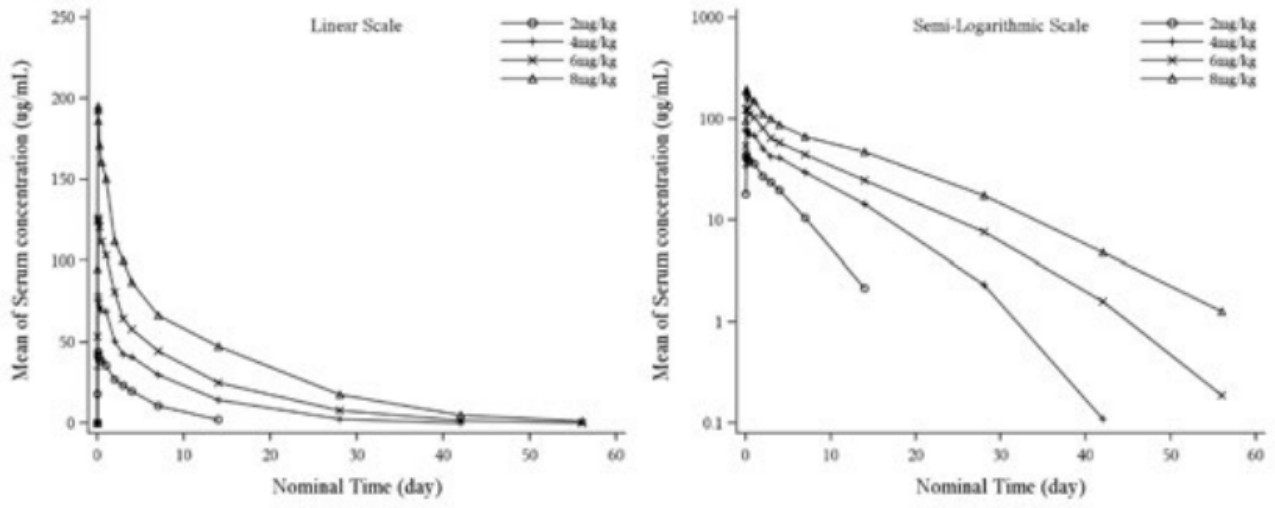


Figure 15: Mean Serum Concentrations on Linear Scale (Left) and Semi-Logarithmic Scale (Right) (PK-PPS 1)

Following single dose IV infusion, HLX02 cleared slowly from serum. At 2 mg/kg, the elimination of HLX02 exhibited single exponential profiles; no serumHLX02 concentrations were detected in all three subjects after 29 days post-dose.

Different PK profiles were observed at doses ≥4 mg/kg, with an initial rapid decline similar to the elimination phase observed at the 2 mg/kg dose followed by a slower decline at higher serum HLX02 concentrations and a gradual increase in elimination rate at lower serum HLX02 concentrations. At doses ≥6 mg/kg, concentrations were still detectible in all subjects after 57 days post-dose.

Table 20: Summary statistics for the PK parameters – Study HLX02-HV01 Part 1

Parameters	Statistics	2mg/kg	4mg/kg	6mg/kg	8mg/kg
AUC_{inf}(μg.h/mL)	n	3	3	3	3
	Mean±SD	4940±819.6	13760±254.4	23760±2834	41070±9494
	Geometric Mean	4896	13760	23650	40400
	Geometric CV%	16.3	1.8	12.4	22.2
AUC_{last}(μg.h/mL)	n	3	3	3	3
	Mean±SD	4683±583.2	13640±414.7	23720±2838	40720±9253
	Geometric Mean	4659	13630	23600	40070
	Geometric CV%	12.2	3.1	12.4	21.8
AUC_{all}(μg.h/mL)	n	3	3	3	3
	Mean±SD	5044±840.1	13750±267.9	23740±2809	40800±9181
	Geometric Mean	4999	13750	23620	40160
	Geometric CV%	16.4	1.9	12.3	21.6
C_{max}(μg/mL)	n	3	3	3	3
	Mean±SD	44.337±5.2288	81.283±6.1988	130.100±5.8026	195.233±31.9852
	Geometric Mean	44.121	81.129	130.012	193.359
	Geometric CV%	12.3	7.5	4.5	17.5
T_{max}(h)	n	3	3	3	3
	Median	2.00	2.00	2.00	3.00
	Minimum	2.00	1.53	1.57	3.00
	Maximum	2.00	24.00	3.00	3.00
V_z(mL)	n	3	3	3	3
	Mean±SD	2760±95.87	2790±311.2	3183±203.3	3217±162.5
	Geometric Mean	2759	2779	3179	3215
	Geometric CV%	3.5	10.9	6.5	5.1
t½(h)	n	3	3	3	3
	Mean±SD	72.72±20.99	112.2±12.69	140.2±14.80	172.9±29.18
	Geometric Mean	70.69	111.7	139.7	171.3
	Geometric CV%	29.9	11.1	10.6	16.3
CL(mL/h)	n	3	3	3	3
	Mean±SD	27.70±7.232	17.24±0.4070	15.93±2.645	13.13±2.135
	Geometric Mean	27.05	17.24	15.78	13.01
	Geometric CV%	27.3	2.4	17.0	17.0
$\%AUC_{extrap}$(%)	n	3	3	3	3
	Mean±SD	4.779±3.796	0.9081±1.364	0.1978±0.1070	0.8178±0.4899
	Geometric Mean	3.663	0.3300	0.1713	0.6834
	Geometric CV%	121.1	450.5	81.9	95.7

Data Source: Table 14.2.1.1

AUC_{inf}=Area under the concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the last quantifiable concentration; AUC_{all}=AUC from the time zero to the time of the last measurement regardless of whether it is quantifiable; C_{max}=Maximum serum concentration; T_{max}=Time to C_{max}; Vz=Volume of distribution during the terminal phase; t½=Terminal half-life; CL=Total body clearance; $\%AUC_{extrap}$= AUC extrapolated from time to infinity as a percentage of total AUC; CV=Coefficient of variation.

Increases in AUC_{0-inf} appeared to be greater than dose proportional. Mean values for the secondary endpoints of AUC_{0-t}, AUC_{all}, C_{max}, and $t_{½}$ all increased with dose, while t_{max} and V_z were similar across the 4 treatment groups. Additionally, the clearance decreased with dose.

Part 2

The mean serum concentration versus nominal time curves on linear and semi-logarithmic scale for the PK population are presented for pairwise comparisons of all study treatments in Figure below (for comparison of HLX02, US-sourced Herceptin, and Germany-sourced Herceptin).

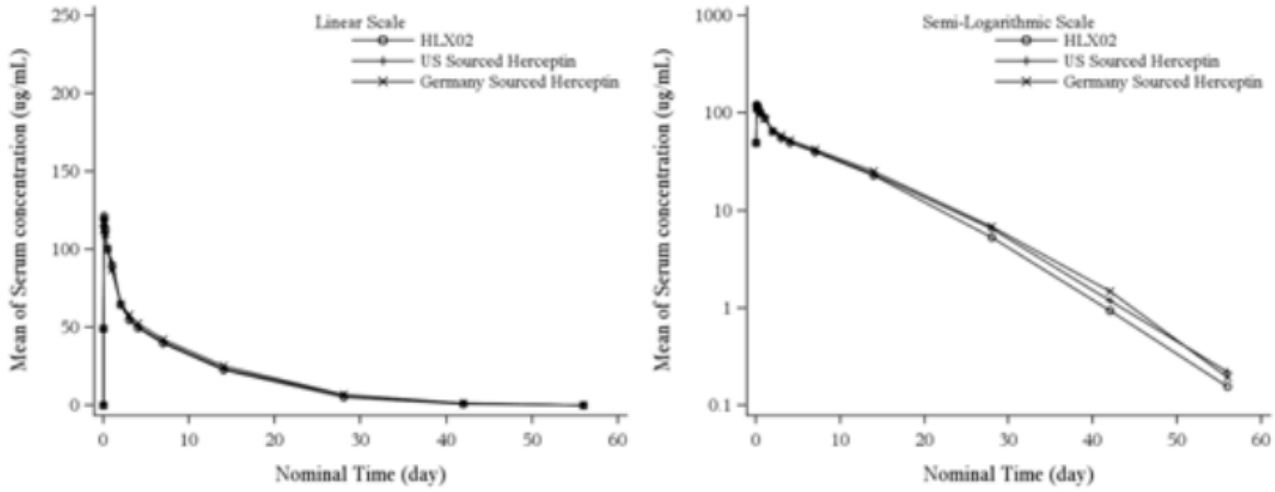


Figure 16: Mean of serum concentrations on linear scale (Left) and semi-logarithmic scale (right) (PK-PPS 2)

Summary statistics of PK parameters based on uncorrected serum concentration data by treatment group in PK-PPS2 population are presented in the table below.

Table 21: Summary of PK parameters based on uncorrected serum concentration data (PK-PPS2) - Study HLX02-HV01 Part 2

Parameters	Statistics	HLX02	US Sourced Herceptin	Germany Sourced Herceptin
		n=37	n=35	n=37
AUC_{inf} (μg·h/mL)	Mean±SD	20719±3789	23425±3661	24111±3547
	Geo Mean	20400	23141	23847
	Geo CV%	17.9	16.1	15.3
	Median	20122	23750	24427
	Minimum	13887	16788	16565
	Maximum	33307	30858	30600
AUC_{last} (μg·h/mL)	Mean±SD	20564±3720	23247±3561	23923±3542
	Geo Mean	20255	22976	23657
	Geo CV%	17.6	15.7	15.4
	Median	20047	23453	24400
	Minimum	13857	16771	16444
	Maximum	33277	30682	30408
AUC_{all} (μg·h/mL)	Mean±SD	20564±3720	23247±3561	23923±3542
	Geo Mean	20255	22976	23657
	Geo CV%	17.6	15.7	15.4
	Median	20047	23453	24400
	Minimum	13857	16771	16444
	Maximum	33277	30682	30408

Parameters	Statistics	HLX02	US Sourced Herceptin	Germany Sourced Herceptin
		n=37	n=35	n=37
C_{max} (μg/mL)	Mean±SD	131.726±20.0445	143.101±24.0634	135.136±24.5651
	Geo Mean	130.160	141.115	133.116
	Geo CV%	16.1	17.2	17.5
	Median	136.200	139.000	128.500
	Minimum	85.54	94.34	94.21
	Maximum	170.10	191.00	198.10
V_z (mL)	Mean±SD	3765±898.5	3613±649.3	3466±650.4
	Geo Mean	3677	3556	3404
	Geo CV%	21.7	18.5	19.9
	Median	3641	3587	3479
	Minimum	2491	2287	2037
	Maximum	7240	5294	4850
λ_z (1/h)	Mean±SD	0.005107± 0.0009508	0.004892± 0.001053	0.004846± 0.0009933
	Geo Mean	0.005021	0.004792	0.004756
	Geo CV%	18.9	20.5	19.4
	Median	0.005019	0.004696	0.004501
	Minimum	0.003124	0.003212	0.003394
	Maximum	0.007465	0.007543	0.008140
$t_{1/2}$ (h)	Mean±SD	140.4±26.78	147.5±28.51	148.3±27.18
	Geo Mean	138.0	144.7	145.7
	Geo CV%	18.9	20.5	19.4
	Median	138.1	147.6	154.0
	Minimum	92.86	91.89	85.16
	Maximum	221.9	215.8	204.2
CL (mL/h)	Mean±SD	18.79±3.705	17.23±2.597	16.46±3.113
	Geo Mean	18.46	17.04	16.19
	Geo CV%	19.1	15.1	18.7
	Median	17.87	17.25	15.90
	Minimum	12.51	11.05	12.04
	Maximum	29.83	24.64	23.85
$\%AUC_{extrap}$ (%)	Mean±SD	0.7047±1.235	0.7061±0.8511	0.7937±0.8122
	Geo Mean	0.3677	0.3978	0.4418
	Geo CV%	136.9	151.6	174.2
	Median	0.3131	0.4441	0.5424
	Minimum	0.07150	0.04940	0.05464
	Maximum	6.988	3.638	3.108

Parameters	Statistics	HLX02	US Sourced Herceptin	Germany Sourced Herceptin
		n=37	n=35	n=37
T_{max} (h)	Median	3.000	2.000	2.000
	Minimum	1.57	1.50	1.50
	Maximum	12.00	12.00	12.00

Data Source: Table 14.2.1.2.2
Geo Mean =Geometric mean; n = number of subjects who contributed to summary statistics. AUC_{inf}=Area under the concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the last quantifiable concentration; AUC_{all}=AUC from the time zero to the time of the last measurement regardless of whether it is quantifiable; C_{max}=Maximum serum concentration; T_{max}=Time to C_{max}; V_z=Volume of distribution during the terminal phase; $t_{½}$=Terminal half-life; CL=Total body clearance; $\%AUC_{extrap}$= AUC extrapolated from time to infinity as a percentage of total AUC; CV=Coefficient of variation.

Summary statistics of PK parameters based on corrected serum concentration data by treatment group in PK-PPS2 population were also submitted. The mean AUC_{inf} values in HLX02, US-sourced Herceptin and Germany-sourced Herceptin were 20115, 21103 and 21919 μg·h/mL, respectively. The mean AUC_{last} values in HLX02, US-sourced Herceptin and Germany-sourced Herceptin were 19965.20943 and 21748 μg h/mL, respectively. AUC_{last} and AUC_{all} values were the same. The mean C_{max} values were also comparable (127.890, 128.920 and 122.851 μg/mL inHLX02, US-sourced Herceptin and Germany-sourced Herceptin, respectively). The median t_{max} values of HLX02, US-sourced Herceptin and Germany-sourced Herceptin were 3.000, 2.000 and

2.000 hours, respectively. The mean $t_{1/2}$ of HLX02 was comparable to that of US-sourced Herceptin and Germany-sourced Herceptin (139.8, 147.5 and 148.3 hours, respectively).

Statistical comparison of PK parameters (based on uncorrected and corrected serum concentration data) between HLX02 and Germany-sourced Herceptin, HLX02 and US-sourced Herceptin, and US-sourced Herceptin and Germany-sourced Herceptin are provided below.

Table 22: Statistical comparison of PK parameters (based on uncorrected serum concentration data) between HLX02 and EU-sourced Herceptin

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio of A/B	90% CI of Ratio
$AUC_{0\text{-}inf}$ (μg·h/mL)	HLX02	37	37	20400.2	0.855	(0.803, 0.911)
	EU-sourced Herceptin	37	37	23846.9		
$AUC_{0\text{-}t}$ (μg·h/mL)	HLX02	37	37	20254.8	0.856	(0.804, 0.911)
	EU-sourced Herceptin	37	37	23656.8		
AUC_{all} (μg·h/mL)	HLX02	37	37	20254.8	0.856	(0.804, 0.911)
	EU-sourced Herceptin	37	37	23656.8		
C_{max} (μg/mL)	HLX02	37	37	130.160	0.978	(0.916, 1.043)
	EU-sourced Herceptin	37	37	133.116		

Table 23: Statistical comparison of PK parameters (based on uncorrected serum concentration data) between HLX02 and CN-sourced Herceptin

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio of A/B	90% CI of Ratio
$AUC_{0\text{-}inf}$ (μg·h/mL)	HLX02	37	37	20400.2	0.882	(0.827, 0.940)
	CN-sourced Herceptin	35	35	23140.6		
$AUC_{0\text{-}t}$ (μg·h/mL)	HLX02	37	37	20254.8	0.882	(0.827, 0.939)
	CN-sourced Herceptin	35	35	22976.3		
AUC_{all} (μg·h/mL)	HLX02	37	37	20254.8	0.882	(0.827, 0.939)
	CN-sourced Herceptin	35	35	22976.3		
C_{max} (μg/mL)	HLX02	37	37	130.160	0.922	(0.864, 0.985)
	CN-sourced Herceptin	35	35	141.115		

Source: Table 11-4 of HLX02-HV01 CSR

Table 24: Statistical comparison of PK parameters (based on uncorrected serum concentration data) between CN-sourced Herceptin and EU-sourced Herceptin

PK Parameter	Treatment	N	n	Geo-LSMean	Ratio of A/B	90% CI of Ratio
$AUC_{0\text{-}inf}$ (μg·h/mL)	CN-sourced Herceptin	35	35	23140.6	0.970	(0.910, 1.035)
	EU-sourced Herceptin	37	37	23846.9		
$AUC_{0\text{-}t}$ (μg·h/mL)	CN-sourced Herceptin	35	35	22976.3	0.971	(0.912, 1.035)
	EU-sourced Herceptin	37	37	23656.8		
AUC_{all} (μg·h/mL)	CN-sourced Herceptin	35	35	22976.3	0.971	(0.912, 1.035)
	EU-sourced Herceptin	37	37	23656.8		
C_{max} (μg/mL)	CN-sourced Herceptin	35	35	141.115	1.060	(0.993, 1.132)
	EU-sourced Herceptin	37	37	133.116		

Source: Table 11-8 of HLX02-HV01 CSR

The 90% CIs for test-to-reference ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were contained within the pre-specified acceptance boundaries of 80% to 125% for all of the pair-wise comparisons among the 3 study drugs, demonstrating pharmacokinetic similarity among HLX02, trastuzumab-EU, and trastuzumab-US.

The median t_{max} for HLX02, EU-sourced Herceptin, CN-sourced Herceptin was 3.000, 2.000 hours and 2.000 hours, respectively, and are not statistically different. These results were obtained in both uncorrected and corrected serum concentrations.

Secondary PK parameters (C_{max} and AUC_{0-t}) support biosimilarity in terms of pharmacokinetics between HLX02, EU-sourced Herceptin and CN-sourced Herceptin.

An additional statistical analysis was requested related to the secondary PK parameters (Vz, CL, and t1/2). These PK parameters were compared between Zercepac and EU Herceptin, presenting the ratios of the geometric means with the 90% confidence. Based on the statistical analysis provided, all the secondary PK parameters (Vz, CL, and t1/2) fell within the predefined bioequivalence margin of 0.8 to 1.25.
No subject did test as ADA positive at any time point, neither in Part 1 nor Part 2.

The use of immunogenicity assays, especially neutralising assay, was based on risk assessment. No neutralising antibody assay for phase 1 study was developed, because there were no positive ADA samples (see also Safety section).

Pharmacokinetics in target population

Study HLX02-BC01 (EUDRACT Number(s): 2016-000206-10)

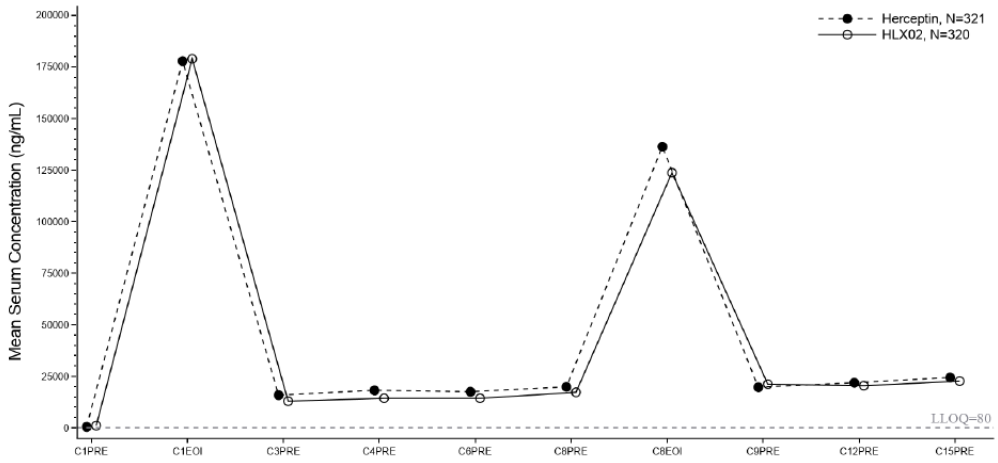
This is a Phase 3, double-blind, randomised, multicentre, international study to compare the efficacy and to evaluate the safety and immunogenicity similarity of HLX02 and EU-sourced Herceptin in patients with HER2-positive, recurrent or previously untreated metastatic breast cancer (see Figure 28).

HLX02 or EU-sourced Herceptin was administered intravenously, initially at a loading dose of 8 mg/kg over 90 minutes on Day 1, Cycle 1 followed by a dose of 6 mg/kg once every 3 weeks in 3-weekly cycles over 30-90 minutes (ie, any duration between 30 and 90 minutes from Cycle 2onwards)for up to a maximum of 12 months. Docetaxel of 75 mg/m^2 was co-administered intravenously (after HLX02 or EU-sourced Herceptin) once every 3 weeks for at least 8 cycles and thereafter at the Investigator's discretion for up to a maximum of 12 months.

On Day 1 of every treatment cycle, body weight was used to calculate the required dose ofHLX02 or Herceptin and docetaxel (study drug). All patients were given prophylactic dexamethasone. The Principal Investigator ensured that any weight change was not due to fluid retention. If it was due to fluid retention, the patient was given oral furosemide (or an equivalent diuretic). The dose was adjusted only if the patient's weight changed by more than±10% from baseline.

PK blood samples were collected from all patients at Cycle 1 within 7 days prior to infusion at the time of blood sampling for assessment of haematology, baseline level of shed antigen, and the test for antibodies against trastuzumab (ADA/NAb). Then, starting at Cycle 3, within 3 days prior to infusion every 3 cycles (approximately every 9 weeks; Cycles 6, 9, 12, and 15), PK samples were collected at the same time as sample collections to assess for the presence of ADA/NAb while on treatment with HLX02 or Herceptin. Extended PK collections were collected from all patients in Cycle 1 on Day 1 at the end of infusion, then at Cycles 4 and 8 prior to infusion (at the same time as blood sampling for assessment of haematology) and Cycle 8 Day 1 at the end of infusion.

Based on PKAS, the mean trastuzumab serum concentration-time curves (in linear scales) for the 2 treatment groups are presented in figure below.



Abbreviations: C = cycle; EOI = end of infusion; PRE = predose; SD = standard deviation.

Source: Figure 14.2.1.1

Due to the limitation of graphic display, standard deviations (SD) were not included in the curve, which was inconsistent with pharmacokinetic statistical analysis plan.

The lines were translated with +/-0.05 unit to make the serum concentration curve clearer.

Figure 17: Mean Trastuzumab Serum Concentration-time Profiles for Both treatments (Linear Scale) - Pharmacokinetic Analysis Set

Trastuzumab serum concentrations by scheduled collections for each treatment are summarized in the following table.

Table 25: Summary Statistics of Trastuzumab Serum Concentrations (ng/mL) by Scheduled Collection for Each Treatment – Pharmacokinetic Analysis Set

Visit	HLX02 (N = 320)			Herceptin® (N = 321)		
	n	n ≥ LLOQ	Arithmetic Mean±SD (CV%)	n	n ≥ LLOQ	Arithmetic Mean±SD (CV%)
C1/PRE	319	27	1081.733 ± 10609.3064 (980.8)	318	22	538.011 ± 8354.1849 (1552.8)
C1/EOI	306	303	178926.141 ± 253784.2849 (141.8)	309	305	177853.188 ± 56666.2342 (31.9)
C3/PRE	281	278	12978.930 ± 8150.6892 (62.8)	290	287	15915.533 ± 8445.8965 (53.1)
C4/PRE	282	282	14386.212 ± 11290.1607 (78.5)	289	287	18211.660 ± 16996.3773 (93.3)
C6/PRE	265	265	14383.648 ± 6706.1732 (46.6)	261	261	17531.318 ± 13119.0457 (74.8)
C8/PRE	222	222	17266.031 ± 14288.0537 (82.8)	211	211	19887.768 ± 15778.7016 (79.3)
C8/EOI	218	218	123713.349 ± 47589.8211 (38.5)	206	206	136344.515 ± 41036.6192 (30.1)
C9/PRE	197	197	21210.782 ± 55731.9850 (262.8)	185	185	19728.886 ± 10730.4197 (54.4)
C12/PRE	134	134	20449.701 ± 14662.5942 (71.7)	130	130	21921.838 ± 16669.4265 (76.0)
C15/PRE	86	86	22707.465 ± 20922.1929 (92.1)	73	73	24478.000 ± 21532.2000 (88.0)

Abbreviations: BLQ = below the limit of quantification; C = cycle; CV = coefficient of variation; EOI =end of infusion; LLOQ = lower limit of quantification; PRE = predose; SD = standard deviation.

Source: Table 14.4.1.1

LLOQ = 80 ng/mL;

N: the number of patients who were included in the PKAS;

n: the number of the available data;

n ≥ LLOQ are the number of patients with concentrations greater or equal to LLOQ;

More than 1/3 samples were below the limit of quantification (BLQ) for the visit, only minimum and maximum were displayed (Except for C1 Predose);

Values of BLQ were replaced by 0 in calculation of arithmetic mean, SD, and CV%.

Tens subjects were found to have quantifiable concentrations of trastuzumab at pre-dose of Cycle 1 for Zercepac (n>=LLOQ: 27) and Herceptin (n>=LLOQ: 22). The majority of these subjects had significant levels of trastuzumab detected in the serum, including one patient with levels over 148 µg/mL.

To investigate the impact of subjects with quantifiable baseline trastuzumab, results from a sensitivity analysis were provided. Of the original pharmacokinetic analysis set, subjects with trastuzumab concentration above LLOQ before first dose were excluded (reduced from 319 to 291 and 322 to 300 subjects in HLX02 and Herceptin group, respectively), and PK comparative analysis was performed in the new PK set.

Table 26: The first sensitivity analysis for bioequivalence results (Pharmacokinetic analysis set)

Parameter (unit)	Treatment Group	N	LSGM	95% CI	CV (%)	Ratio (%)	90% CI	P Value
C1/PRE (ng/mL)	HLX02	291	-	-	-	-	-	-
	Herceptin®	300	-	-	-			
C1/EOI (ng/mL)	HLX02	282	158346	(151757, 165222)	145.3	91.45	(86.98, 96.15)	0.0034
	Herceptin®	291	173157	(166038, 180582)	29.5			
C3/PRE (ng/mL)	HLX02	256	10069	(9188, 11035)	61.4	75.79	(68.09, 84.36)	<.0001
	Herceptin®	272	13286	(12154, 14523)	53.1			
C4/PRE (ng/mL)	HLX02	258	11485	(10433, 12642)	81.2	82.72	(73.87, 92.63)	0.0059
	Herceptin®	268	13884	(12628, 15263)	96.6			
C6/PRE (ng/mL)	HLX02	245	12455	(11616, 13355)	48.6	82.97	(76.36, 90.14)	0.0002
	Herceptin®	243	15013	(13997, 16102)	75.9			
C8/PRE (ng/mL)	HLX02	225	13684	(12668, 14782)	78.8	85.15	(77.60, 93.43)	0.0045
	Herceptin®	213	16071	(14846, 17398)	50.0			
C8/EOI (ng/mL)	HLX02	222	116534	(111000, 122343)	39.4	90.20	(85.08, 95.64)	0.0039
	Herceptin®	210	129191	(122888, 135817)	30.1			
C9/PRE (ng/mL)	HLX02	207	15032	(13937, 16212)	266.9	89.02	(81.34, 97.43)	0.0342
	Herceptin®	202	16886	(15642, 18228)	53.1			
C12/PRE (ng/mL)	HLX02	179	16752	(15470, 18141)	43.0	92.56	(84.09, 101.89)	0.1851
	Herceptin®	168	18099	(16670, 19650)	72.6			
C15/PRE (ng/mL)	HLX02	155	18720	(17232, 20337)	98.0	98.43	(88.87, 109.02)	0.7987
	Herceptin®	133	19019	(17391, 20798)	76.5			

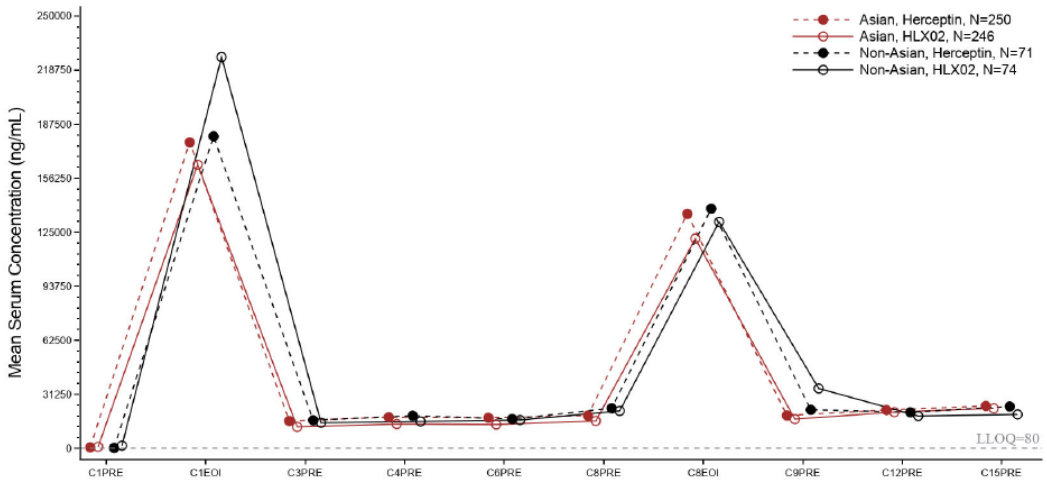
Abbreviations: C = cycle; EOI = end of infusion; PRE = predose.
Notes: The subjects with above LLOQ value at C1/PRE was not be included in this sensitivity analysis.
Source: Adapted from Table 14.6.1 in CSR.

The trastuzumab serum concentrations of the patients in both the HLX02 and Herceptin groups reached the peak values at the EOI of Cycle 1, of which the mean concentrations (± SD) were 178926.141 ± 253784.2849 ng/mL and 177853.188 ± 56666.2342 ng/mL, respectively. At the EOI of HLX02 or Herceptin at Cycle 8, the concentrations also reached the highest values of the current cycle with the mean concentrations (± SD) were 123713.349 ± 47589.8211 ng/mL and 136344.52 ± 41036.6192 ng/mL, respectively, which were a little lower than those values obtained at the EOI of Cycle 1.

Before infusion at Cycle 3, the mean concentrations (± SD) for HLX02 and Herceptin treatment groups were 12978.930 ± 8150.6892 ng/mL and 15915.533 ± 8445.8965 ng/mL, respectively. For both treatment groups, the mean trough concentrations obtained at the subsequent cycles increased slightly as time went by.

Stratified by Asian and non-Asian Patients

Based on PKAS, the mean trastuzumab serum concentration-time curves (in linear scales) stratified by Asian and non-Asian patients are presented in the following figure. In Asian patients, the mean trastuzumab serum concentrations for both HLX02 and Herceptin treatments were comparable at each time point from Cycle 1 to Cycle 15. In non-Asian patients, the two curves were also very similar except for the EOI of Cycle 1 and pre-infusion at Cycle 9.



Abbreviations: C = cycle; EOI =end of infusion; PRE = predose; SD = standard deviation.
Source: Figure 14.2.1.3
Due to the limitation of graphic display, standard deviations (SD) were not included in the curve, which was inconsistent with pharmacokinetic statistical analysis plan.
The lines were translated with +/-0.05 unit to make the serum concentration curve clearer.

Figure 18: Mean Trastuzumab Serum Concentration-time Profiles for Both Treatments (Stratified by Asian and non-Asian patients, Linear Scale) -Pharmacokinetic Analysis Set

Trastuzumab serum concentrations by scheduled collections stratified by Asian and non-Asian patients are summarized in the following tables.

Table 27: Summary Statistics of Trastuzumab Serum Concentrations (ng/mL) by Scheduled Collection for Each Treatment in Asian Patients –Pharmacokinetic Analysis Set

Visit	HLX02-Asian Patients (N = 246)			Herceptin®-Asian Patients (N = 250)		
	n	n ≥ LLOQ	Arithmetic Mean±SD (CV%)	n	n ≥ LLOQ	Arithmetic Mean±SD (CV%)
C1/PRE	245	6	923.883 ± 10053.6643 (1088.2)	248	2	615.250 ± 9450.8889 (1536.1)
C1/EOI	233	231	164072.485 ± 91638.0924 (55.9)	239	236	177072.971 ± 53444.1080 (30.2)
C3/PRE	212	212	12408.988 ± 7671.3268 (61.8)	225	223	15823.787 ± 8294.7269 (52.4)
C4/PRE	214	214	14021.643 ± 12169.3687 (86.8)	224	223	18011.300 ± 17085.3137 (94.9)
C6/PRE	202	202	13765.271 ± 6773.1896 (49.2)	205	205	17695.971 ± 14007.1742 (79.2)
C8/PRE	167	167	15831.035 ± 7983.5049 (50.4)	165	165	18966.558 ± 12752.4830 (67.2)
C8/EOI	164	164	121303.476 ± 40383.6148 (33.3)	161	161	135683.354 ± 39138.6712 (28.8)
C9/PRE	149	149	16882.020 ± 8936.9677 (52.9)	144	144	18997.188 ± 8741.6775 (46.0)
C12/PRE	105	105	20932.486 ± 16117.2565 (77.0)	106	106	22165.425 ± 17820.4334 (80.4)
C15/PRE	76	76	23118.895 ± 22019.8101 (95.2)	64	64	24512.953 ± 22413.0950 (91.4)

Abbreviations: BLQ = below the limit of quantification; C = cycle; CV = coefficient of variation; EOI =end of infusion; LLOQ = lower limit of quantification; PRE = predose; SD = standard deviation.

Source: Table 14.4.1.3

LLOQ = 80 ng/mL;

N: the number of patients who were included in the PKAS;

n: the number of the available data;

n ⩾ LLOQ are the number of patients with concentrations greater or equal to LLOQ;

More than 1/3 samples were below the limit of quantification (BLQ) for the visit, only minimum and maximum were displayed (Except for C1 Predose);

Values of BLQ were replaced by 0 in calculation of arithmetic mean, SD, and CV%.

Table 28: Summary Statistics of Trastuzumab Serum Concentrations (ng/mL) by Scheduled Collection for Each Treatment in non-Asian Patients –Pharmacokinetic Analysis Set

Visit	HLX02-non Asian Patients (N = 74)			Herceptin®-non Asian Patients (N = 71)		
	n	n ≥ LLOQ	Arithmetic Mean±SD (CV%)	n	n ≥ LLOQ	Arithmetic Mean±SD (CV%)
C1/PRE	74	21	1604.345 ± 12333.4645 (768.8)	70	20	264.364 ± 897.6923 (339.6)
C1/EOI	73	72	226335.753 ± 492728.4435 (217.7)	70	69	180517.071 ± 66873.4477 (37.0)
C3/PRE	69	66	14730.058 ± 9317.7589 (63.3)	65	64	16233.117 ± 9009.6105 (55.5)
C4/PRE	68	68	15533.531 ± 7876.4288 (50.7)	65	64	18902.129 ± 16798.9386 (88.9)
C6/PRE	63	63	16366.381 ± 6126.0978 (37.4)	56	56	16928.571 ± 9241.7450 (54.6)
C8/PRE	55	55	21623.200 ± 24776.2282 (114.6)	46	46	23192.109 ± 23556.1937 (101.6)
C8/EOI	54	54	131032.222 ± 64689.1482 (49.4)	45	45	138710.000 ± 47626.6191 (34.3)
C9/PRE	48	48	34647.979 ± 111613.6153 (322.1)	41	41	22298.756 ± 15740.5700 (70.6)
C12/PRE	29	29	18701.690 ± 7233.7207 (38.7)	24	24	20846.000 ± 10355.6534 (49.7)
C15/PRE	10	10	19580.600 ± 9016.6695 (46.0)	9	9	24229.444 ± 14719.3810 (60.7)

Abbreviations: BLQ = below the limit of quantification; C = cycle; CV = coefficient of variation; EOI =end of infusion; LLOQ = lower limit of quantification; PRE = predose; SD = standard deviation.

Source: Table 14.4.1.3

LLOQ = 80 ng/mL;

N: the number of patients who were included in the PKAS;

n: the number of the available data;

n ⩾ LLOQ are the number of patients with concentrations greater or equal to LLOQ;

More than 1/3 samples were below the limit of quantification (BLQ) for the visit, only minimum and maximum were displayed (Except for C1 Predose);

Values of BLQ were replaced by 0 in calculation of arithmetic mean, SD, and CV%.

As shown in Figure 11-5, in Asian patients, the mean trastuzumab serum concentrations for both HLX02 and Herceptin treatments were comparable at each time point from Cycle 1 to Cycle 15. In non-Asian patients, the two curves were also very similar except for the EOI of Cycle 1 and pre-infusion at Cycle 9.

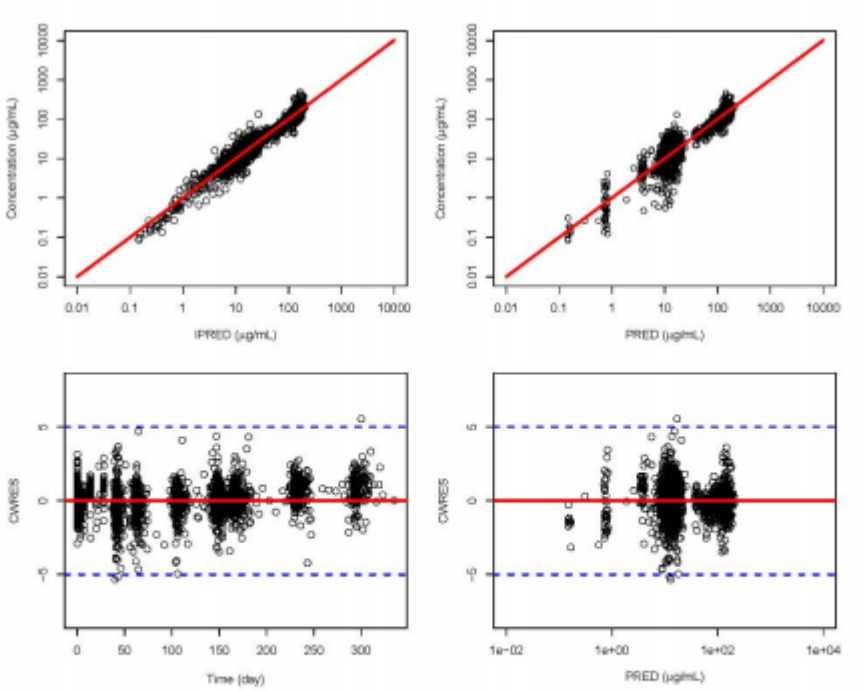
Population PK analysis

Per request, a population PK analysis combining data from Study HLX02-BC01 and HLX02-HV01 was provided to identify factors that have impact on HLX02 and EU-sourced Herceptin PK profiles, and to compare PK profiles under different circumstances.

The popPK (population PK) analysis was based on the HLX02-HV01 and HLX02-BC01 studies, containing 754 subjects with 5,882 samples. Suitable covariates of popPK model were selected based on statistical evaluation, clinical judgment, mechanistic plausibility and prior knowledge. The following covariates were tested: age, body weight, race (Asian vs Non-Asian), baseline albumin, baseline alanine aminotransferase, baseline aspartate aminotransferase, baseline bilirubin, baseline creatinine clearance, formulation (EU-sourced herceptin vs. US-sourced herceptin), health status (healthy volunteer vs. MBC patients) and shed antigen. The identified parameter-covariates relationships were incorporated, generating a final popPK model of two-compartment with first order elimination from the central compartment and redistribution into the peripheral compartments.

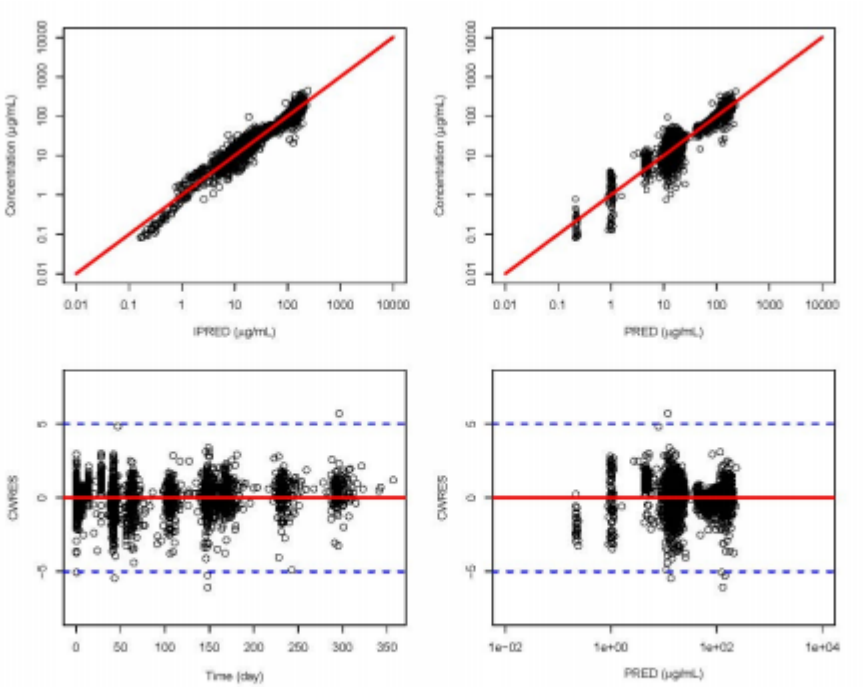
Table 29: Summary of final population PK parameters

Parameter	Parameter Description	Population Estimate (RSE%)	Inter-Individual Variability (RSE%)
$exp(\theta_1)$	Clearance of HLX02, CL_{HLX} (L/hr)	0.0172 (1.88%)	19.5 (4.17%)
$exp(\theta_2)$	Clearance of Herceptin, CL_{HER} (L/hr)	0.0155 (1.44%)	
θ_9	Influence of WT on clearance	0.427 (12.0%)	—
θ_{11}	Influence of PAT on clearance	0.113 (14.1%)	—
θ_{12}	Influence of SHED on clearance	0.0300 (18%)	—
$exp(\theta_3)$	Central volume of HLX02, $V_{c,HLX}$ (L)	3.23 (1.29%)	9.44 (18.2%)
$exp(\theta_4)$	Central volume of Herceptin, $V_{c,HER}$ (L)	2.94 (1.19%)	
θ_{10}	Influence of WT on central volume	0.486 (11.0%)	—
$exp(\theta_7)$	Peripheral volume of HLX02, $V_{p,HLX}$ (L)	0.759 (14.2%)	—
$exp(\theta_8)$	Peripheral volume of Herceptin, $V_{p,HER}$ (L)	0.839 (7.39%)	—
$exp(\theta_5)$	Inter-compartmental clearance of HLX02, Q_{HLX} (L/hr)	0.0442 (16.3%)	—
$exp(\theta_6)$	Inter-compartmental clearance of Herceptin, Q_{HER} (L/hr)	0.0480 (10.1%)	—
$\omega^2_{Cl,Vc}$	Covariance (CL, V_c)	0.00612 (38.7%)	—
σ	Residual error (%)	30.5 (1.93%)	—



Observed versus individual predicted concentrations (upper left) and observed versus population predicted concentrations (upper right) for the final PopPK model. Points are individual data and red lines represent the unit diagonal. Conditional weighted residuals (CWRES) versus time (lower left) and PRED (lower right). Points are individual data. Red solid lines represent the unit line at zero. Blue dashed lines represent |CWRES| of 5.

Figure 19: Predicted versus observed HLX02 concentration diagnostic plots for the final PopPK model

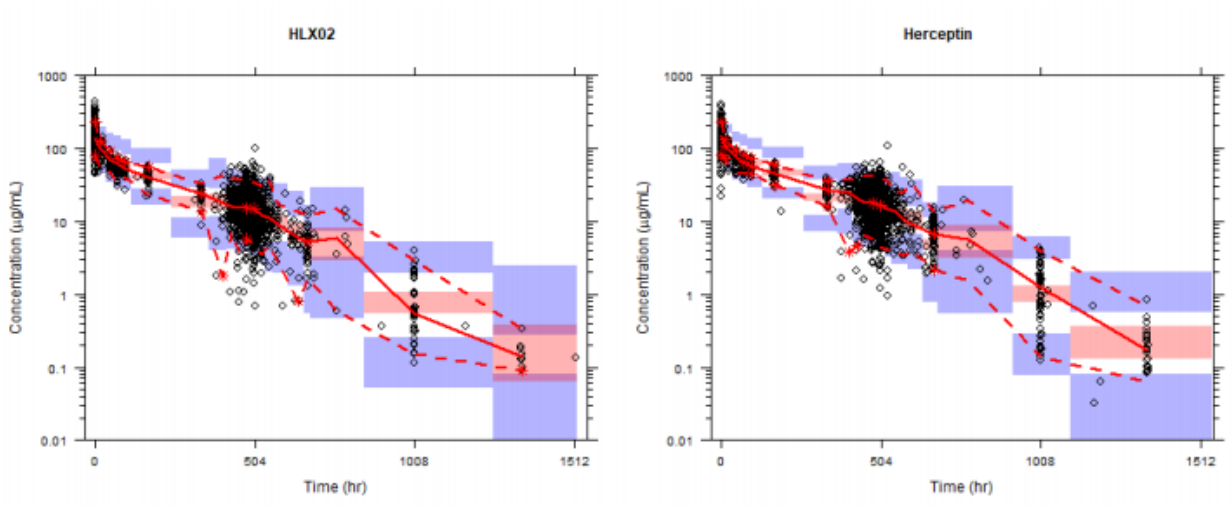


Observed versus individual predicted concentrations (upper left) and observed versus population predicted concentrations (upper right) for the final PopPK model. Points are individual data and red lines represent the unit diagonal. Conditional weighted residuals (CWRES) versus time (lower left) and PRED (lower right). Points are individual data. Red solid lines represent the unit line at zero. Blue dashed lines represent |CWRES| of 5.

Figure 20: Predicted versus observed herceptin concentration and residual diagnostic plots for the final PopPK model

A total of 1000 replicates of the trials were simulated using the observed covariates for each subject, the final PopPK model parameter estimates, the estimated subject specific random effects, and the residual error.

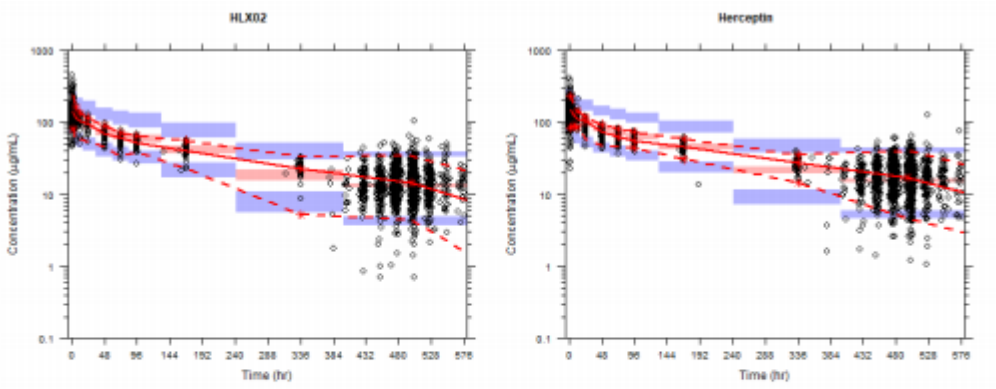
The Prediction-Corrected Visual Predictive Check (pcVPC) of HLX02 and Herceptin serum concentration time profiles are shown in Figure 21.



Points are observed concentrations, solid red line represents the median observed value, and dashed red lines represent 2.5%ile and 97.5%iles of the observed values. Pink shaded area represents the spread of the median predicted values (2.5th to 97.5th %ile), and purple shaded areas represent the spread (2.5%ile and 97.5%ile) of the 2.5th and 97.5th predicted percentile concentrations.

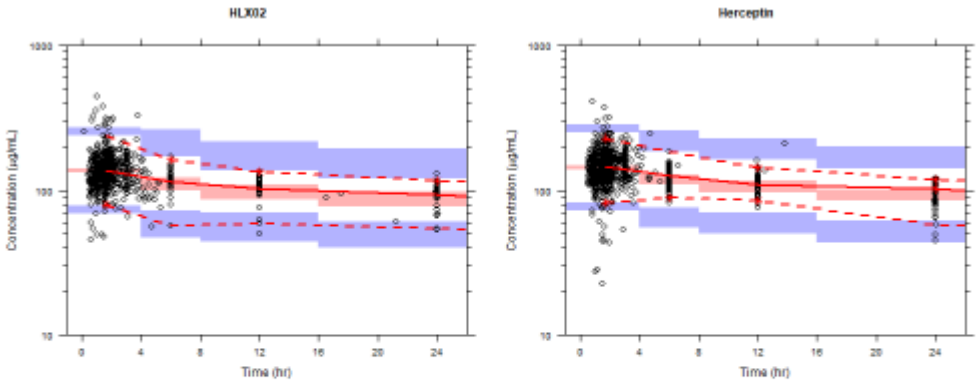
Figure 21: pcVPC of HLX02 and herceptin serum concentration-time profiles across all studies

The pcVPC of 576-hour (Figure 22), and a 24-hour (Figure 23) plots gradually zoom in deviation between observations and predictions for review. The pcVPC also present by HLX02-HV01 Phase I study and HLX02-BC01 Phase III study separately for HLX02 (Figure 24) and Herceptin (Figure 25).



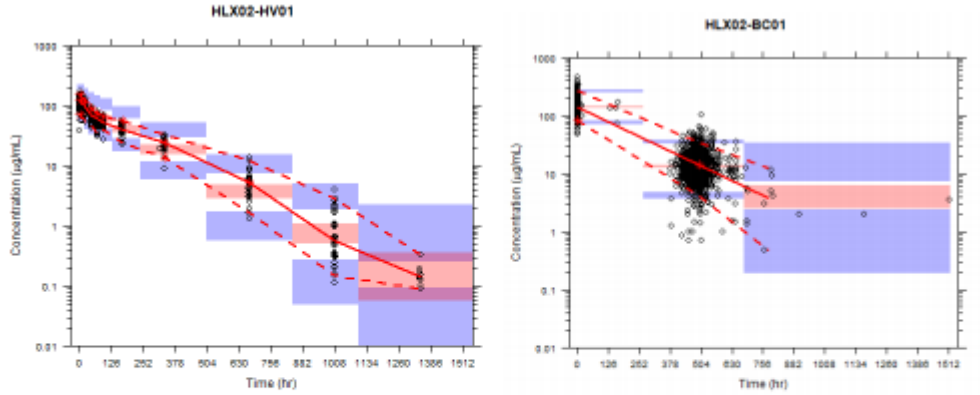
Points are observed concentrations, solid red line represents the median observed value, and dashed red lines represent 2.5%ile and 97.5%ile of the observed values. Pink shaded area represents the spread of the median predicted values (2.5th to 97.5th %ile), and purple shaded areas represent the spread (2.5%ile and 97.5%ile) of the 2.5th and 97.5th predicted percentile concentrations. Time in these plots is the time after previous dose. In study HLX02-HV01, the scheduled PK sampling time was pre-infusion, 0.75 h, Immediately after the completion of infusion, 2 h, 3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h, 168 h, 336 h, 672 h, 1008 h and 1344 h from the start of infusion.In study HLX02-BC01, the scheduled PK sampling time was pre-infusion in Cycle 1, end of infusion in Cycle 1 Day1, pre-infusion in Cycles 3, 4, 6, 8, 9, 12, and 15 and end of infusion in Cycle 8 day 1.

Figure 22: pcVPC of HLX02 and Herceptin serum concentration-time Profiles across all studies(Time frame: 0~576 hr, TFDS)



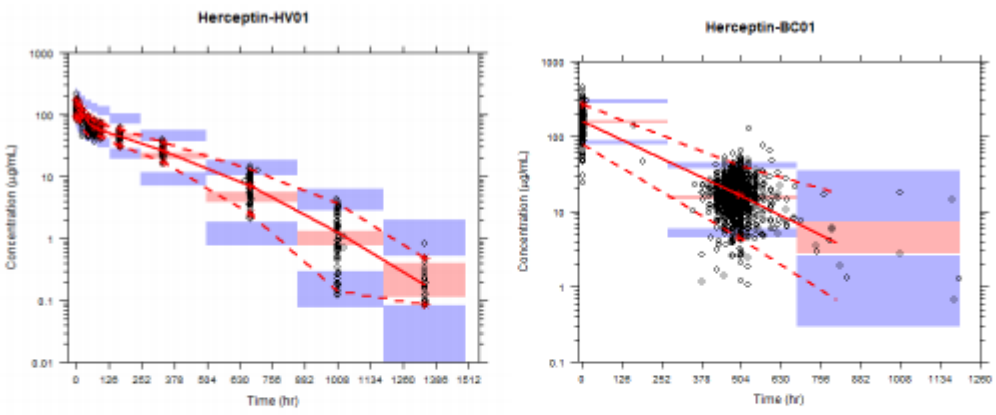
Points are observed concentrations, solid red line represents the median observed value, and dashed red lines represent 2.5%ile and 97.5%ile of the observed values. Pink shaded area represents the spread of the median predicted values (2.5th to 97.5th % percentile), and purple shaded areas represent the spread (2.5%ile and 97.5%ile) of the 2.5th and 97.5th predicted percentile concentrations. Time in these plots is the time after previous dose. In study HLX02-HV01, the scheduled PK sampling time was pre-infusion, 0.75 h, Immediately after the completion of infusion, 2 h, 3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h, 168 h, 336 h, 672 h, 1008 h and 1344 h after infusion.In study HLX02-BC01, the scheduled PK sampling time was pre-infusion (-7 days) in Cycle 1, end of infusion in Cycle 1 Day1, pre-infusion (-3 days) in Cycles 3, 4, 6, 8, 9, 12, and 15 and end of infusion in Cycle 8 day 1.

Figure 23: pcVPC of HLX02 and Herceptin serum concentration-time Profiles across all studies (Time frame: 0~24 hr, TFDS)



Points are observed concentrations, solid red line represents the median observed value, and dashed red lines represent 2.5%ile and 97.5%ile of the observed values. Pink shaded area represents the spread of the median predicted values (2.5th to 97.5th % percentile), and purple shaded areas represent the spread (2.5%ile and 97.5%ile) of the 2.5th and 97.5th predicted percentile concentrations. Time in these plots is the time after previous dose. In study HLX02-HV01, the scheduled PK sampling time was pre-infusion, 0.75 h, Immediately after the completion of infusion, 2 h, 3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h, 168 h, 336 h, 672 h, 1008 h and 1344 h after infusion.In study HLX02-BC01, the scheduled PK sampling time was pre-infusion (-7 days) in Cycle 1, end of infusion in Cycle 1 Day1, pre-infusion (-3 days) in Cycles 3, 4, 6, 8, 9, 12, and 15 and end of infusion in Cycle 8 day 1.

Figure 24: pcVPC of HLX02 Serum Concentration-Time Profiles Stratified by Study



Points are observed concentrations, solid red line represents the median observed value, and dashed red lines represent 2.5%ile and 97.5%ile of the observed values. Pink shaded area represents the spread of the median predicted values (2.5th to 97.5th % percentile), and purple shaded areas represent the spread (2.5%ile and 97.5%ile) of the 2.5th and 97.5th predicted percentile concentrations. Time in these plots is the time after previous dose. In study HLX02-HV01, the scheduled PK sampling time was pre-infusion, 0.75 h, Immediately after the completion of infusion, 2 h, 3 h, 6 h, 12 h, 24 h, 48 h, 72 h, 96 h, 168 h, 336 h, 672 h, 1008 h and 1344 h after infusion.In study HLX02-BC01, the scheduled PK sampling time was pre-infusion (-7 days) in Cycle 1, end of infusion in Cycle 1 Day1, pre-infusion (-3 days) in Cycles 3, 4, 6, 8, 9, 12, and 15 and end of infusion in Cycle 8 day 1.

Figure 25: pcVPC of Herceptin serum concentration-time profiles stratified by study

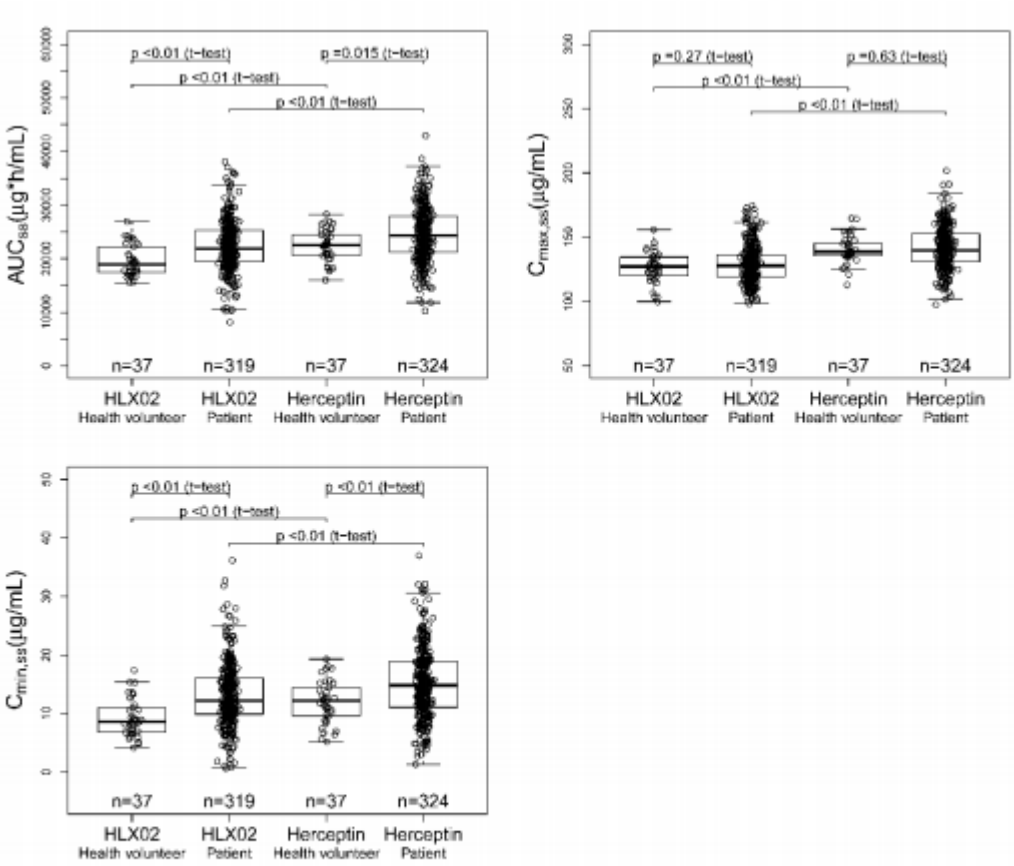
The final popPK model was used to compare PK profiles of HLX02 and Herceptin-EU in subjects of specific health status (healthy volunteer vs. HER2-positive MBC patient) and ethnicity (Asian vs. non-Asian). The impact of other factors such as formulation, HER-2 Shed Antigen, body weight, ADA and NAb were also assessed.

Assessment of steady-state exposure of HLX02 and Herceptin in patients with HER2-positive MBC and healthy volunteers

Post-hoc estimated exposures (AUCss, Cmax,ss and Cmin,ss) in patients with HER2-positive MBC and healthy volunteers are provided in Table 30 and Figure 26.

Table 30: Geometric mean (%CV) steady state exposure of HLX02 and Herceptin in patients with MBC and healthy volunteers

Characteristics	HLX02		EU-Sourced Herceptin®	
	Healthy Volunteer	Patient	Healthy Volunteer	Patient
No. of subjects (%)	37 (5.16)	319 (44.5)	37 (5.16)	324 (45.2)
AUC_{ss} (µg·h/mL)	19380.2 (15.0)	21839.8 (21.5)	22263.4 (13.3)	24019.7 (20.9)
$C_{max,ss}$ (µg/mL)	125.7 (9.54)	128.2 (11.4)	139.9 (7.75)	140.7 (11.4)
$C_{min,ss}$ (µg/mL)	8.70 (34.7)	11.7 (41.6)	11.4 (30.8)	13.9 (40.1)
Body Weight (kg) [min, median, max]	[52.0; 63.4; 77.4]	[41.5; 62.0; 118]	[52.0; 62.6; 80]	[37.2; 62.0; 120]



The median is represented by the horizontal line in the middle of each box. The top and bottom ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extending from the ends of the box to the outermost data represent 1.5 × (the upper or lower interquartile range).

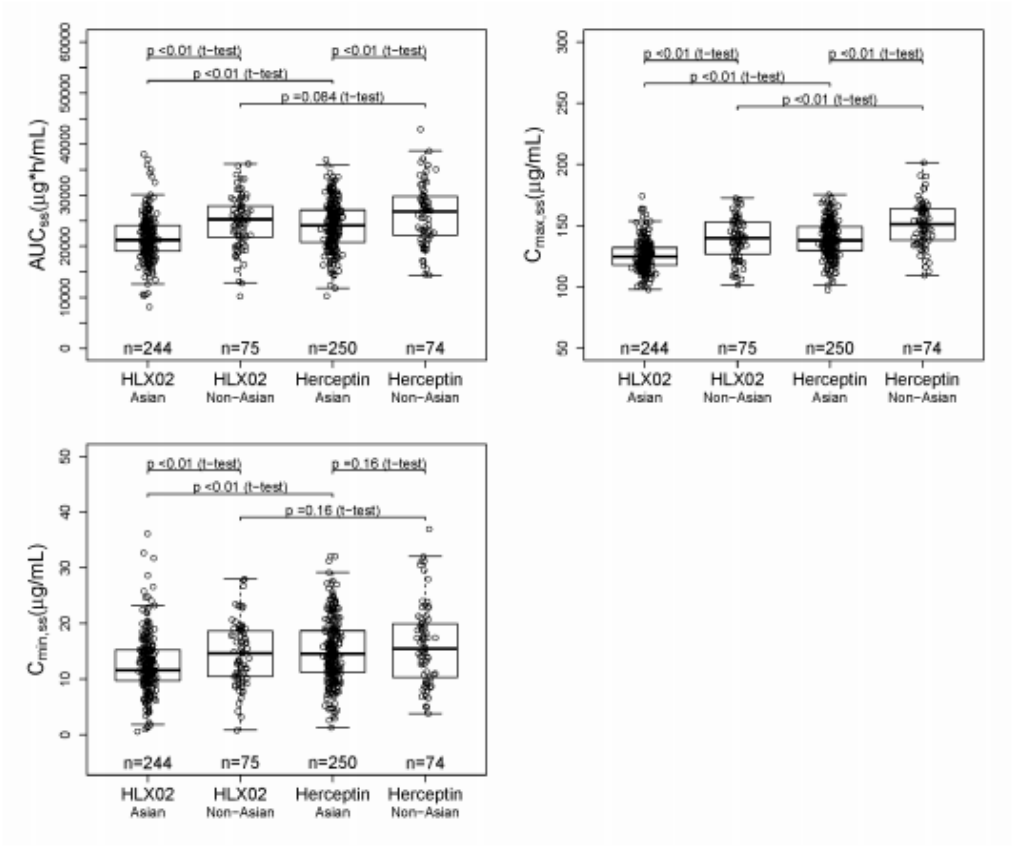
Figure 26: Simulated steady state exposures of HLX02 and EU-Sourced Herceptin stratified by health status

Examination of steady-state exposure of HLX02 and Herceptin in different ethnicities (Asian vs. non-Asian)

Post-hoc estimated exposures in different ethnic groups in patients treated with HLX02 or Herceptin are shown in Table 31 and Figure 27.

Table 31: Simulated PK parameters of HLX02 and Herceptin in Asian and non-Asian

Characteristics	HLX02		Herceptin®	
	Asian	Non-Asian	Asian	Non-Asian
No. of subjects (%)	244 (37.9)	75 (11.7)	250 (38.9)	74 (11.5)
AUC_{ss} (µg·h/mL)	21182.2 (20.5)	24123.8 (21.2)	23558.4 (19.7)	25645.7 (22.8)
$C_{max,ss}$ (µg/mL)	125.2 (9.67)	138.6 (12.4)	138.1 (10.2)	150.1 (12.3)
$C_{min,ss}$ (µg/mL)	11.3 (42)	13.2 (38.6)	13.8 (38.3)	14.5 (44.6)
Body Weight (kg) [min, median, max]	[41.5; 60.0; 97.0]	[46.5; 75.0; 118]	[37.2; 60.0; 99.0]	[48.5; 72.0; 120]
SHED (ng/mL) [min, median, max]	[0.7832; 11.54; 2478]	[0.7832; 14.01; 1404]	[0.7832; 9.396; 1762]	[0.7832; 11.83; 783.5]



The median is represented by the horizontal line in the middle of each box. The top and bottom ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extending from the ends of the box to the outermost data represent 1.5 × (the upper or lower interquartile range).

Figure 27: Simulated steady state exposures of HLX02 and Herceptin stratified by ethnicity

To investigate the differences in drug exposures, the Applicant provided actual figures of the 90% CI of the two one side test (as per bioequivalence guideline) on the model predicted relevant PK parameters/metrics in Asian and non-Asian populations. Simulations were based on the individual parameters estimated by final popPK model.

Table 32: Comparison of simulated PK parameters between Asian and Non-Asian of HLX02 and Herceptin

PK parameters	HLX02					Herceptin				
	geometric mean and ratio		90%CI (%)	GCV# (%)	Power (%)	geometric mean and ratio		90%CI (%)	GCV# (%)	Power (%)
	Asian/ Non-Asian*	Ratio (%)				Asian/ Non-Asian*	Ratio (%)			
AUC_{ss} (μg·h/mL)	21182.2/ 24123.8*	87.81	83.52 - 92.31	22.66	92.25	23558.4/ 25645.7*	91.86	87.34 - 96.62	22.06	99.79
$C_{max,ss}$ (μg/mL)	125.2/ 138.6*	90.33	87.98 - 92.75	11.20	>99.99	138.1/ 150.1*	92.00	89.62 - 94.45	11.44	>99.99
$C_{min,ss}$ (μg/mL)	11.3/ 13.2*	85.74	76.49 - 96.12	55.99	25.92	13.8/ 14.5*	94.90	85.45 - 105.39	48.46	84.74

Sample size of HLX02: Asian 244; Non-Asian 75; Sample size of Herceptin: Asian 250; Non-Asian 74;
*PK parameters of Non-Asian
GCV is geometric coefficient of variation. Power is calculated based on two one-sided t-test.

Table 33: Comparison of body weight adjusted PK parameters between Asian and Non-Asian of HLX02 and Herceptin

PK parameters	HLX02					Herceptin				
	geometric mean and ratio		90%CI (%)	GCV# (%)	Power (%)	geometric mean and ratio		90%CI (%)	GCV# (%)	Power (%)
	Asian/ Non-Asian*	Ratio (%)				Asian/ Non-Asian*	Ratio (%)			
AUC_{ss} (μg·h/mL)	21460.0/ 21804.6*	98.42	94.37 - 102.65	19.49	>99.99	23998.2/ 23500.6*	102.12	97.86 - 106.56	18.91	>99.99
$C_{max,ss}$ (μg/mL)	126.7/ 126.5*	100.17	98.83 - 101.52	5.70	>99.99	140.4/ 138.7*	101.23	99.85 - 102.63	6.09	>99.99
$C_{min,ss}$ (μg/mL)	11.5/ 12.0*	95.30	85.35 - 106.40	54.38	82.62	14.0/ 13.4*	104.25	94.29 - 115.26	47.02	90.58

Sample size of HLX02: Asian 244; Non-Asian 75; Sample size of Herceptin: Asian 250; Non-Asian 74;
*PK parameters of Non-Asian
GCV is geometric coefficient of variation. Power is calculated based on two one-sided t-test.

Impact of Formulation on HLX02 and Herceptin Steady-State Exposure

There was no significant difference in steady state exposures between EU-source Herceptin and US-sourced Herceptin. The AUCss, Cmax,ss and Cmin,ss of HLX02 were 13.0%, 10.2%, and 23.1%, respectively, lower than that of EU-sourced Herceptin. Similarly, the AUCss, Cmax,ss and Cmin,ss of HLX02 were 12.2%, 10.9%, and 19.7%, respectively, lower than that of US-sourced Herceptin.

Impact of HER-2 Shed Antigen on HLX02 and Herceptin Steady-State Exposure

Subjects with higher shed antigen demonstrated lower AUCss, Cmax,ss and Cmin,ss in both HLX02 (13.4% for AUCss, 4.54% for Cmax,ss, and 33.1% for Cmin,ss) and Herceptin (7.55% for AUCss, 2.12% for Cmax,ss, and 18.3% for Cmin,ss). The shed antigen difference in exposures between HLX02 and Herceptin was less than 15% (7.55~13.4% for AUCss, 2.12~4.54% for Cmax,ss, and 18.3~33.1% for Cmin,ss).

Impact of Body Weight on HLX02 and Herceptin Steady-State Exposure

Body weight was tested as a significant covariate in the population PK analysis. To assess the impact of weight, the final population PK model predicted steady-state exposures were compared in body weight stratified by median. Subjects with higher body weight demonstrated higher AUCss, Cmax,ss and Cmin,ss values. The HLX02 exposures (AUCss, Cmax,ss, and Cmin,ss) observed in subjects in the equal and below median of body weight were 15.8%, 13.9%, and 15.5% higher, respectively than that in subjects in the body weight above median. The Herceptin exposures (AUCss, Cmax,ss, and Cmin,ss) observed in subjects in the equal and below median of

body weight were 16.7%, 14.4%, and 17.0% lower, respectively than that in subjects in the body weight above median.

Impact of ADA on HLX02 and Herceptin Steady-State Exposure

The HLX02 exposures in ADA negative subjects were higher than that in ADA positive subjects (73.4%, 9.92%, and 419% for AUCss, Cmax,ss and Cmin,ss, respectively), as well as the Herceptin exposures in ADA negative subjects were higher than that in ADA positive subjects (6.95%, 0.988%, and 18.5% for AUCss, Cmax,ss and Cmin,ss, respectively). This was partially attributed to the higher Shed in ADA positive group (121.2 vs 11.67 ng/mL for HLX02, 249.9 vs 10.18 ng/mL for Herceptin). It is noted that the numbers of ADA -positive patients was low (less than 1% ADA positive patients).

Impact of NAb on HLX02 and Herceptin Steady-State Exposure

The HLX02 exposures in NAb negative subjects were higher than that in NAb positive subjects (73.4%, 9.92%, and 419% for AUCss, Cmax,ss and Cmin,ss, respectively), as well as the Herceptin exposures in NAb negative subjects were higher than that in NAb positive subjects (6.95%, 0.988%, and 18.5% for AUCss, Cmax,ss and Cmin,ss, respectively). This was partially attributed to the higher Shed in NAb positive group (121.2 vs 11.67 ng/mL for HLX02, 249.9 vs 10.18ng/mL for Herceptin). It is noted that the numbers of NAb-positive patients was low (less than 1% NAb positive patients).

2.4.3. Pharmacodynamics

See discussion on clinical pharmacology.

2.4.4. Discussion on clinical pharmacology

The HLX02 clinical development plan consisted of two clinical studies, including a clinical pharmacokinetic (PK) similarity study (HLX02-HV01), and a Phase 3 clinical efficacy and safety comparability study (HLX02-BC01). PK data were provided from the PK study in healthy volunteers and from PK sampling in all patients enrolled in the comparative efficacy and safety study. A pivotal PK study in patients was not conducted. The PK profile of HLX02 and of Herceptin was determined through a Population PK analysis.

In general, the development program to demonstrate the similarity between HLX02 and Herceptin-EU with respect to the pharmacokinetic (PK) is considered adequate and was generally performed according to the guidance on biosimilars and the recommendations given in the Scientific Advice procedures. The design and the proposed endpoints of the PK study are deemed sufficient and sensitive to fulfil the trastuzumab PK similarity requirement for the proposed trastuzumab formulation intended for intravenous administration only.

The applicant did not claim subcutaneous use. As only PK data on IV administration were submitted under this application, only the IV route of administration can be authorised under this MA procedure (see SmPC section 4.2.).

The test and reference products and the mode of administration are considered suitable for a bioequivalence study. However, as outlined in the guideline for biosimilars (EMA/CHMP/BWP/247713/2012) it is strongly recommended to generate the required quality, safety and efficacy data for the demonstration of biosimilarity against the reference medicinal product using product manufactured with the commercial manufacturing process and therefore representing the quality profile of the batches to be commercialised. This recommendation has not been followed during the development of HLX02; the material used in the bioequivalence study in healthy Chinese volunteers was produced using a prior manufacturing process. To

address this issue, a comprehensive analytical comparability study according to ICH Q5E guideline was subsequently performed to compare the different DS manufacturing process. Overall, HLX02 material from the different manufacturing process are considered analytically comparable. Accordingly, non-clinical material and batches used in the clinical trials are considered comparable to and thus representative for the PV and commercial batches (see also quality and non-clinical aspects).

The comparability between US licensed Herceptin formulations were used as supportive data.

Two ELISA analytical methods to quantify the concentration of trastuzumab in human plasma and to quantify the concentration of HER-2 in human serum were submitted. Based on the evaluated parameters, both ELISA methods are considered suitable for the quantification the concentration of trastuzumab and the quantification of HER-2 in human plasma.

With regards to the method to quantify the concentration of HER-2 in human serum, additional stability tests are being carrying out and the applicant is recommended to submit this report.

A safety evaluation with the escalation of four doses of HLX02 (2, 4, 6, and 8 mg/kg) was performed in Part 1 of study HLX02-HV01 as HLX02 was to be administered to humans for the first time in China. As the four doses represent the current clinical dose range for the reference drug Herceptin, the safety evaluation provides human safety data for HLX02.

The proposed study design of study HLX02-HV01 Part 2 (parallel design instead of a cross-over design) is acceptable due to the long half-life of monoclonal antibodies in general (approx. 22 days for trastuzumab) and is in line with the requirements as outlined in the Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004).

According to the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1, for drugs with non-linear pharmacokinetics, the bioequivalence study should in general be conducted at the highest strength, i.e. 8 mg/kg for Herceptin. However, the proposed dose of 6 mg/kg is considered adequate based on the posology of the reference product. This is also in line with the Scientific Advice (EMA/CHMP/SAWP/476339/2016) in which it was considered that a lower dose could also have been appropriate to establish biosimilarity with less risk for toxicity.

According to the above Scientific Advice, the proposed 57 days of blood sampling may not be sufficient to adequately characterize $AUC_{0\text{-}inf}$ given the uncertainty around the half-life in healthy volunteers. However, the choice of an interval of 57 days allows covering at least 80% of the AUC since the extrapolated AUC was less than 20% in all of the pharmacokinetic evaluable subjects (%Mean AUC_{extrap} ±SD 0.7047±1.235, 0.7061±0.8511 and 0.7937±0.8122 for HLX02, for the US-sourced Herceptin and the EU-sourced Herceptin respectively).

The results obtained from the PK comparability study (HLX02-HV01) concluded that HLX02 is bioequivalent with both EU-sourced and CN-sourced Herceptin since the 90% CIs for the primary PK parameter $AUC_{0\text{-}inf}$ and secondary PK parameters (i.e., C_{max} and $AUC_{0\text{-}t}$) fall within the pre-defined bioequivalence limits of 0.8 to 1.25. The t_{max} for the HLX02 and two reference products were not statistically significantly different. In addition, bioequivalence was also confirmed between the EU-sourced Herceptin and US-sourced Herceptin.

An additional statistical analysis was performed for the secondary PK parameters (Vz, CL, and t1/2). PK parameters were calculated based on uncorrected and corrected serum concentration data, respectively. Geometric means ratio and 90% CI were calculated between HLX02 vs. CN-sourced Herceptin, HLX02 vs. EU-sourced Herceptin, and CN-sourced vs. EU-sourced Herceptin. All measured PK parameters (Vz, CL, and t1/2) fell within the predefined bioequivalence margin of 0.8 to 1.25.

It was noted that the measured protein concentrations of EU Herceptin and CN Herceptin differed from the concentration of HLX02 by more than 5%. However, this difference is not expected to impact the conclusions of bioequivalence since the PK analysis has been carried both on corrected and uncorrected serum concentration data and in both cases, the 90% confidence intervals around the point estimates of the "test/reference" least squares mean ratios of the primary PK parameter AUCinf and secondary PK parameters AUClast and Cmax were within the acceptance range of 80-125%.

A PK analysis with data collected in study HLX02-BC01 was also submitted. In the overall population, from Cycle 1 to Cycle 15 both treatments, HLX02 and Herceptin showed similar mean serum concentration-time profiles. Slight differences have been observed between Asian and non-Asian population for the pre-infusion at Cycle 1 and Cycle 9 regardless of treatment arm. At these time points there were also slight differences between treatments in non-Asian population. This could be explained by limited number of non-Asian patients.

Ten subjects were found to have quantifiable concentrations of trastuzumab at pre-dose of Cycle 1 for Zercepac (n>=LLOQ: 27) and Herceptin (n>=LLOQ: 22). The applicant explained that repeated tests were performed by the laboratory and it was confirmed there was no sample mix-up error during the sample analysis. Hence, it is highly likely that the samples were mis-labelled during sample collection. The rationale given by the applicant to explain the quantifiable concentrations of trastuzumab observed at pre-dose of Cycle 1 for Zercepac and Herceptin in study HLX02-BC01 is deemed plausible. In addition, the applicant has conducted a sensitivity analysis excluding the subjects with trastuzumab concentration above LLOQ before first dose. In this analysis, all geometric mean ratios of HLX02 and Herceptin concentration, as well as their 90% CI fell within 80%-125% with the exception of Cycle 3. The geometric mean ratio of cycle 3 concentration (75.788%) fell below the lower boundary of 80%-125%, but within the widened range 70%-143%, with 90% CI of 68.09%-84.36%. Comparing to the other 8 sampling points that fulfil the bioequivalent criteria, a single data exceeding bioequivalent limit might be considered minor and acceptable.

Given the high variability linked to disease and to therapy, no reasonable bioequivalence approach can be proposed for a parallel group design in phase III trials in patients with metastatic breast cancer. Therefore, the PK results presented from the phase III are overall judged acceptable. Bioequivalence has been adequately demonstrated in study HLX02-HV01 which is the pivotal study in PK.

In the population PK model report model parameters were predicted with acceptable precision. GOF plots of the final PopPK model seem to show a good agreement between the predicted concentrations and the observed concentrations. No bias was apparent in the residual plots over time and across predicted concentrations. Prediction corrected visual predictive check (PcVPC) suggested that the final PopPK model adequately predicts the central tendency and variability of the plasma HLX02 and Herceptin concentrations in subjects across all studies even if a slightly over-prediction on 97.5%ile of the observed values can be confirmed for HLX02 and Herceptin during the first 240 hours.

According to the final population PK model, health status, race, shed antigen and body weight were found to significantly influence drug CL whereas volume of distribution was influenced by body weight. ADA and NAb were not tested during the modelling exercise due to the limited number of individuals tested positive. While graphical comparisons displayed differences between HLX02 and Herceptin patients, it is agreed that the limited number of positive patients precludes any robust conclusion.

Subjects with higher shed antigen demonstrated lower AUCss, Cmax,ss and Cmin,ss in both arms, however, the impact of shed antigen on exposure was less than 15%. Additionally, although several statistically significant differences ($p<0.01$) were stated, box plots were overall overlapped (data not shown). Therefore, differences observed between patients with shed ≤ median and shed > median are not considered clinically relevant.

Regarding the comparison of model predicted parameters for HLX02 and Herceptin in healthy vs patients and in Asians vs non-Asians, the geometric means for all the relevant PK parameters were lower for HLX02 as compared to Herceptin.

At the request of the CHMP and to investigate the differences in drug exposures, the Applicant provided the figures of the 90% CI of the two one side test (as per bioequivalence guideline) on the model predicted (or simulated) relevant PK parameters/metrics in Asian and non-Asian patients. The applicant has shown the robustness of popPK model at two orthogonal levels: 1. pcVPC diagnosis based on phase I and III studies as a whole and pcVPC diagnosis by phase I or phase III study separately 2. EBEs based diagnostics. Taken together, the final popPK model was adequately evaluated and diagnosed using graphical pcVPC and EBE based diagnostics. Exposure ratios of Asian and non-Asian patients, as well as AUCss and Cmax,ss were still within 80-125% range for both HLX02 and Herceptin, even with no body weight adjustments.

The mechanism of action of trastuzumab is well established. 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 consequence, proliferation of human tumour cells that overexpress HER2 is inhibited (see SmPC section 5.1). Studies on the mechanism of action were not provided, which is acceptable for a biosimilar product application.

No pharmacodynamics comparison between treatments (i.e. percent decrease from baseline of serum HER2 concentration) have been conducted. However, as no validated pharmacodynamics biomarker has been established for Herceptin so far, this approach is considered acceptable.

Immunogenicity data are discussed under section 2.6.1.

2.4.5. Conclusions on clinical pharmacology

In conclusion, PK results support demonstration of biosimilarity between HLX02 and Herceptin.

2.5. Clinical efficacy

2.5.1. Dose response study

No dose response study was provided (see discussion on clinical efficacy).

2.5.2. Main study

Study HLX02-BC01

This is a Phase 3, double-blind, randomised, multicentre, international, parallel-group, active-controlled study to compare the efficacy and to evaluate the safety and immunogenicity similarity of HLX02 and EU-sourced Herceptin in patients with HER2-positive, recurrent or previously untreated metastatic breast cancer.

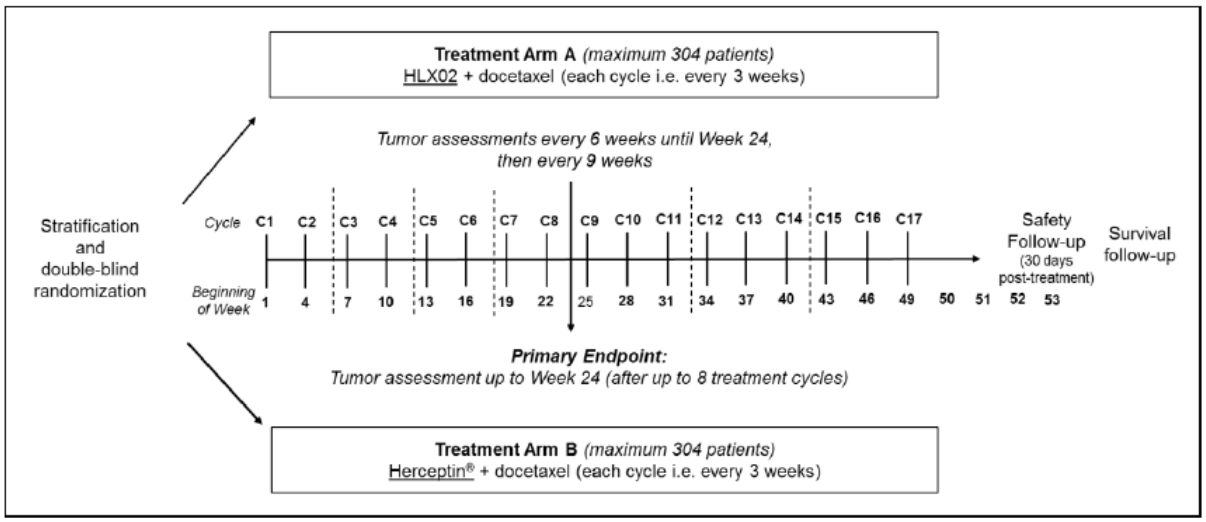


Figure 28: Schematic of Study Design for Protocol HLX02-BC01

Methods

Study Participants

Diagnosis

Patients with HER2 positive, recurrent or metastatic breast cancer as centrally assessed by fluorescence in-situ hybridization (FISH) or immunohistochemistry (IHC) who had not received prior systemic chemotherapy, biological or targeted agents for their recurrent or metastatic disease.

Key inclusion criteria:

- Male or female ≥18 years of age on day of signing the ICF.
- Histologically or cytologically confirmed adenocarcinoma of the breast.
- Recurrent disease not amenable to curative surgery or radiation therapy, or metastatic disease with an indication for a taxane-containing therapy.

- Availability of formalin-fixed paraffin-embedded (FFPE) tissue block from the primary tumor, or a metastatic lesion, to confirm HER2-positivity by the central laboratory, based on fluorescence in-situ hybridization (FISH) amplification ratio ≥2.0 or immunohistochemistry (IHC) score 3+, and for hormone status (ER/PgR) determination (local or central laboratory). If not possible, a fresh biopsy was required.
- No prior systemic anticancer agent such as chemotherapy, biological or targeted agent for metastatic disease with the exception of hormonal therapy, which had been stopped at least 2 weeks before randomization.
- For patients with recurrent disease, prior neo-/adjuvant therapy containing trastuzumab and/or lapatinib had been stopped at least 12 months before the diagnosis of recurrent (local or metastatic) disease (i.e., a disease-free interval of ≥12 months). If trastuzumab/lapatinib was not used, prior neo-/adjuvant therapy with a taxane had been stopped at least 6 months before the diagnosis of recurrent (local or metastatic) disease (i.e., a disease-free interval of ≥6 months). If only other cytotoxics were given, they had been stopped at least 4 weeks before randomization. Any hormonal therapy had been stopped at the time of the ICF signature (at least 2 weeks before randomization).
- Measurable disease (at least 1 measurable target lesion assessed by central imaging review (CIR); bone-only or central nervous system [CNS]-only metastases were not allowed).
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1.
- Left ventricular ejection fraction (LVEF) within institutional range of normal at baseline (within 42 days before randomization) as determined by either electrocardiogram (ECHO) or multigated acquisition (MUGA) scan.

Key exclusion criteria:

- Previously- or on-treated (systemic chemotherapy, biological, or targeted agent, or any other anticancer agent) metastatic breast cancer with the exception of hormonal therapy.
- Known brain metastasis or other CNS metastasis that was either symptomatic or untreated. Central nervous system metastases that had been treated by complete resection and/or radiotherapy demonstrating stability or improvement were not an exclusion criterion provided they were stable as shown by computed tomography (CT) scan for at least 4 weeks before Screening without evidence of cerebral oedema and no requirements for corticosteroids or anticonvulsants.
- Participation in another clinical study within 4 weeks before enrolment (3 months for studies involving monoclonal therapy) or the intention of participating in another clinical study during any part of the study period.
- History of other malignancy within the last 5 years, except for carcinoma in-situ of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin that had been previously treated with curative intent.
- Current uncontrolled hypertension (systolic >150 mmHg and/or diastolic >100 mmHg) or unstable angina.
- History of chronic heart failure based on any New York Heart Association (NYHA) criteria or left ventricular hypertrophy. Current serious cardiac arrhythmia requiring treatment (except atrial fibrillation, paroxysmal supraventricular tachycardia) or clinically significant conduction defects as seen on ECG. History of myocardial infarction within 6 months of randomization. History of LVEF declined to below 50% during or after previous trastuzumab neo-adjuvant or adjuvant therapy. Significant cardiac

murmurs either on examination or ECHO.

- Use of oral, injected or implanted hormonal methods of contraception.
- Chronic daily use of corticoids (equivalent to >10 mg/day methylprednisolone) by oral intake (inhalation is permitted).
- Known hypersensitivity to any of the study drugs.
- Residual non-hematologic toxicity ≥Grade 2 from prior therapy.

Treatments

Patients were randomized to 1 of 2 treatment groups:

Arm A, HLX02 (IV) + docetaxel (IV), or **Arm B, EU-sourced Herceptin** (IV) + docetaxel (IV)

- **HLX02 or Herceptin**: a loading dose of **8 mg/kg** over 90 minutes, then **6 mg/kg every 3 weeks** over 30-90 minutes (i.e. any duration between 30 and 90 minutes from Cycle 2 onwards) if the previous dose was well tolerated, on Day 1 of each cycle.
- **Docetaxel**: dose of **75 mg/m²** administered on Day 2, Cycle 1 over 60 minutes, then **every 3 weeks** on Day 1 of each subsequent cycle after HLX02 or Herceptin. Dose increase to **100 mg/m²** for patients who tolerated at least 1 administration at 75 mg/m². Dexamethasone was given as premedication at oral dose of 7.5-8 mg or IV dose of 20 mg dexamethasone until Herceptin/HLX02 have been stopped and if they have been previously tolerated. Granulocyte colony stimulating factor may be used according to the prescribing information for docetaxel but not as prophylaxis before the first cycle.

Duration of treatment with **HLX02 or Herceptin**: a maximum of **12 months (17 cycles)**, or until Investigator-assessed disease progression, excessive toxicity, Investigator's judgment, withdrawal of consent, lost to follow-up, death, start of a new anticancer therapy, or study termination by the Sponsor, whichever occurs first.

Duration of treatment with **docetaxel 75 mg/m²**: at least **8 cycles** (24 weeks) unless there is disease progression or excessive toxicity. Then continuation is at the discretion of the Investigator.

Objectives

Primary Objective

To compare the efficacy of HLX02 versus EU-sourced Herceptin in combination with docetaxel using overall response rate (ORR) up to Week 24 (ORR24) after up to 8 cycles of treatment.

Secondary Objectives

- To evaluate the safety, tolerability, and immunogenicity of HLX02 and EU-sourced Herceptin given in combination with docetaxel.
- To compare the efficacy of HLX02 versus EU-sourced Herceptin in combination with docetaxel, in terms of ORR until end of treatment or up to a maximum of 12 months, clinical benefit rate (CBR), disease control rate (DCR), and progression-free survival (PFS) and OS rates up to 1 year.
- To measure the exposure to trastuzumab following HLX02 or EU-sourced Herceptin given in combination with docetaxel.

Exploratory Objective

- To explore population pharmacokinetic (PopPK) analysis (not included in the interim analysis)

Outcomes/endpoints

Primary Efficacy Endpoint:

- ORR24 (overall response rate at Week 24), calculated as the proportion of patients with a best response of complete response (CR) or partial response (PR) from first assessment up to Week 24 according to RECIST 1.1. Overall tumour response was assessed by blinded, independent CIR according to RECIST 1.1, without confirmation.

Secondary Efficacy Endpoints:

• ORR (overall response rate) at Weeks 6, 12, 18, and 24.

• DoR (duration of response), defined as the time from first documentation of CR or PR to the first documentation of progression. After Week 24, assessments were made by the Investigator.

• DCR (disease control rate), defined as the proportion of patients who achieved CR, PR, or stable disease (SD) of at least 12 weeks.

• CBR (clinical benefit rate), defined as the proportion of patients who achieved CR, PR, or durable SD (SD ≥24 weeks).

• PFS (progression-free survival) up to 12 months, defined as the probability of being alive without documented progression up to 12 months after randomization, calculated using the Kaplan-Meier method.

• OS (Overall survival) at 12, 24, and 36 months, defined as the probability of being alive 12, 24, and 36 months after randomization, calculated using the Kaplan-Meier method.

Randomisation

Patients were randomized (1:1) to receive HLX02 plus docetaxel or EU Herceptin plus docetaxel. A complete block randomization scheme was applied.

Randomization was stratified by:

• Prior neo-/adjuvant therapy with trastuzumab (Yes/No)

• ER/PgR status (ER/PgR positive versus ER/PgR negative)

• Ethnicity/Race (Asian versus non-Asian)

Blinding (masking)

This study was double-blinded.

Statistical methods

- **Sample size**

The primary efficacy endpoint was ORR up to week 24 derived from the CIR (central imaging review). To yield a 84% power to demonstrate equivalence between HLX02 and EU-Herceptin on the primary ORR analysis (difference in rate of ORR, Herceptin - control) with the pre-defined equivalence limits of [-0.1350, 0.1350], a sample size of 578 patients (289 per arm) was required. Assuming a 5% dropout rate, the sample size was increased to 608 patients (304 per arm). This sample size calculation assumed a conservative ORR rate of 60 %. This rate was based on ORRs from 3 studies: Marty et al, 2005 (61%), CLEOPATRA (Baselga et al, 2012) (69%), and HERITAGE (Rugo et al, 2017) (69.6%).

The ORR difference was to be analysed with a two-sided 95%CI (alpha controlled ≤0.05). If the 95% CI completely falls in an equivalence region defined as -13.5% - 13.5%, then the equivalence can be declared.

- **Equivalence margin**

The applicant identified 2 published randomised studies comparing ORR following treatment with Herceptin + 'paclitaxel or equivalent', versus 'paclitaxel or equivalent alone' (Herceptin US labelling text, Table 9; Marty M, et al, Table 2). The results of the subgroup of patients with HER2-positive tumours defined as FISH positive or IHC 2+ and 3+ have been pooled.

The equivalence margin was derived using a random-effect meta-analysis of these two historical trastuzumab trials to estimate the treatment effect of trastuzumab with 'paclitaxel or equivalent alone' versus 'paclitaxel or equivalent alone'. The Der Simonian-Laird (Der Simonian R, et al) estimate random effect model approach was used for the meta-analysis. Using this approach, the difference in ORR and its 95% CI was estimated to be 0.2493 [0.1579; 0.3407]. The metabin function of the meta library of the R language was used to implement this estimate.

An equivalence limit tighter than the lower bound of this confidence interval is used as the criterion of equivalence: [-0.1350, 0.1350].

- **Analysis Sets/Populations**

• Enrolled set (ENR) contained all patients who provided informed consent for this study.

• Intent-to-treat set (ITT) contained all patients who were randomized. The intention-to-treat principle was preserved.

• Safety analysis set (SAS) comprised all patients who received study drug (HLX02 or EU-sourced Herceptin) once. The SAS set were used for analysis of safety endpoints.

• Per-protocol (PP) analysis set comprised all patients who had at least 8 cycles of treatment and had at least 1 tumor measurement after treatment, or discontinued treatment early due to Investigator-assessed disease progression or excessive toxicity and did not have major protocol deviations/violations (such as not receiving Docetaxel). The ITT and PP sets were used for analyses of ORR, PFS, OS, DoR, CBR, and DCR.

• PK analysis set (PKAS) comprised all patients who received study drug and who had at least 1 measured concentration at a scheduled PK time point after the start of study drug without any protocol deviations or events which might affect the PK results.

- **General Approaches**

Continuous variables were summarized using descriptive statistics, i.e., number of patients (n), mean, median, standard deviation, 25th and 75th percentiles (Q1, Q3), minimum and maximum. Qualitative variables were

summarized by counts and percentages. For statistical tests, the default significance level was 2-sided 5%; 2-sided 95% confidence intervals (CIs) were presented and all tests were 2-sided unless otherwise specified. All analyses, summaries, and listings were performed using SAS software (Version 9.4 or higher).

1- Primary efficacy analysis: Primary efficacy analysis was based on the ITT population. The Per-Protocol population was used as a supportive analysis population for efficacy. The primary endpoint was ORRwk24, the risk difference in ORR (HLX02/EU-sourced Herceptin) between the 2 treatment groups was calculated using a Chi-squared test and 95% Wald Cis were presented. Equivalence would be declared if the two-sided 95% CI for the difference of ORR is completely within the equivalence range of (-13.5%; 13.5%)

2- Secondary efficacy analyses: Time-to-event secondary efficacy variables of DoR, PFS up to 12 months and at 12 months, OS at 12, 24, and 36 months and OS up to the cut off date are to be estimated using the Kaplan-Meier method. Curves together with a summary of associated statistics (ie, the probability of being event-free) and corresponding 2-sided 95% Cis were presented. The CIs for the survival function estimated at the time points defined above were derived using the log-log transformation according to Kalbfleisch and Prentice. The estimate of the standard error was computed using Greenwood's formula. A Cox model was used to compare the hazard ratio (HR). The point estimates and 95% CIs of the HR were reported.

The ITT and PP will be used for analyses of ORR, PFS, OS, DoR, CBR, and DCR.

- **Sensitivity analyses**

Sensitivity analyses were performed on the primary endpoint of ORR in the PP population. The treatment difference was characterized by the "HLX02/Herceptin" HR estimated using a stratified Cox proportional hazards model. HR with its p-value and corresponding 95% CI were presented.

Sensitivity analysis to assess the robustness of conclusions to missing data was planned to be carried out if there are more than 5% of patients missing evaluations in either treatment arm.

- **Interim analysis**

Interim analysis was planned after the primary efficacy data at Week 24 are available for all patients. There was a first database lock and the designated unblinded study team conducted analyses on the primary efficacy data, as well as PK, safety/immunogenicity and survival data, up to Week 24.

All Investigators, site teams, and patients remain blinded for the rest of the Treatment Period (up to 12 months after the last patient randomized), which is when the second database lock will occur.

A blinded sample size re-estimation procedure was planned after the primary efficacy data at Week 24 become available in the first 300 patients. A Data Monitoring Committee oversees the re-estimation procedure as well as review safety data and monitors the overall conduct of the study.

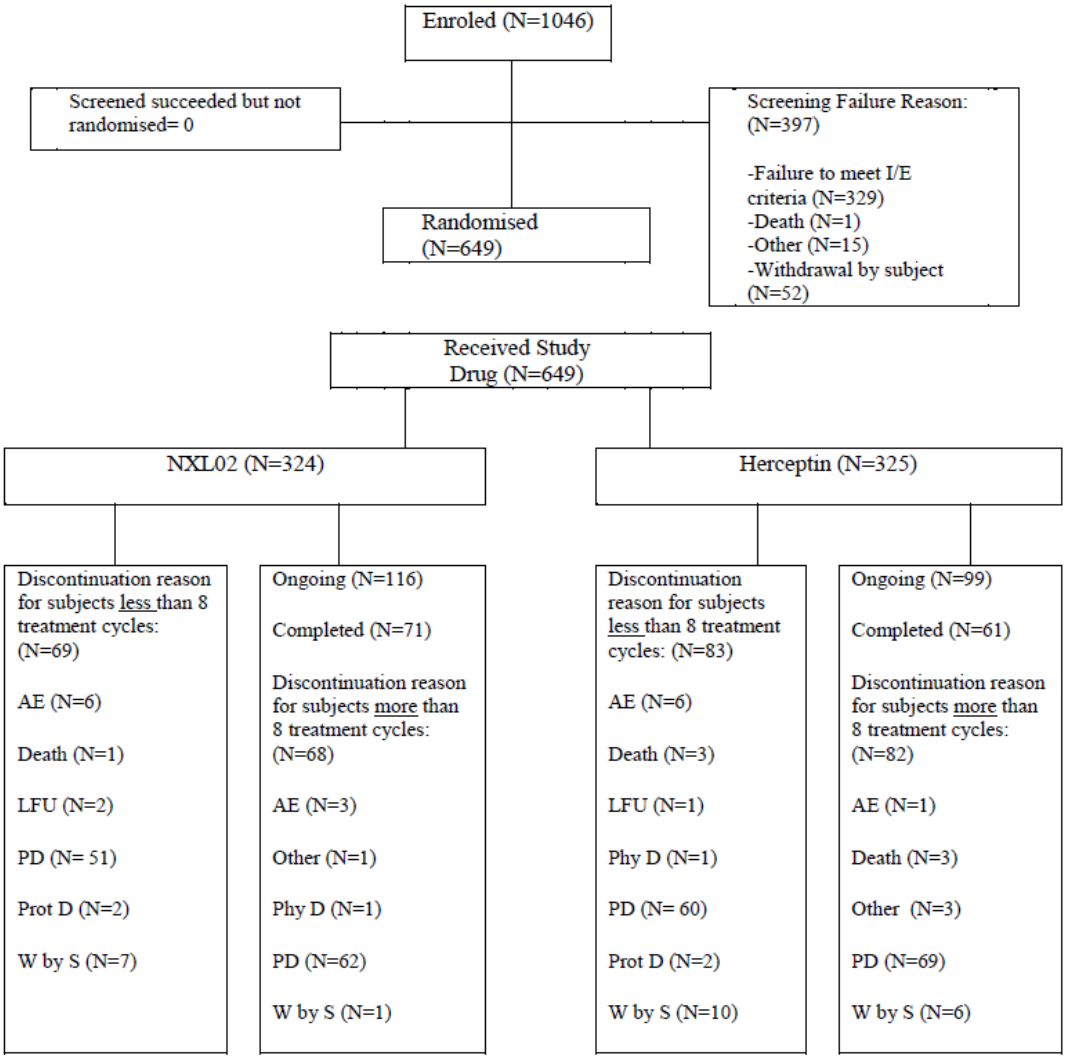
The final version 5 of the SAP is dated 25 December 2018.

Results

Participant flow

By the cut-off date 23 November 2018, a total of 1046 patients were enrolled into the study, and 397 of them were screening failures. A total of 649 patients were randomized at a 1:1 ratio to the 2 study treatment groups

(324 [100%] patients in the HLX02 treatment group and 325 [100%] patients in the Herceptin treatment group).



AE=Adverse event, LFU: Lost to follow-up, PD=Progressive disease, Prot D=Protocol deviation, Phy D= Physician's Decision, W by S= Withdrawal by subject

Figure 29: Participant flow (data cut-off 23 November 2018)

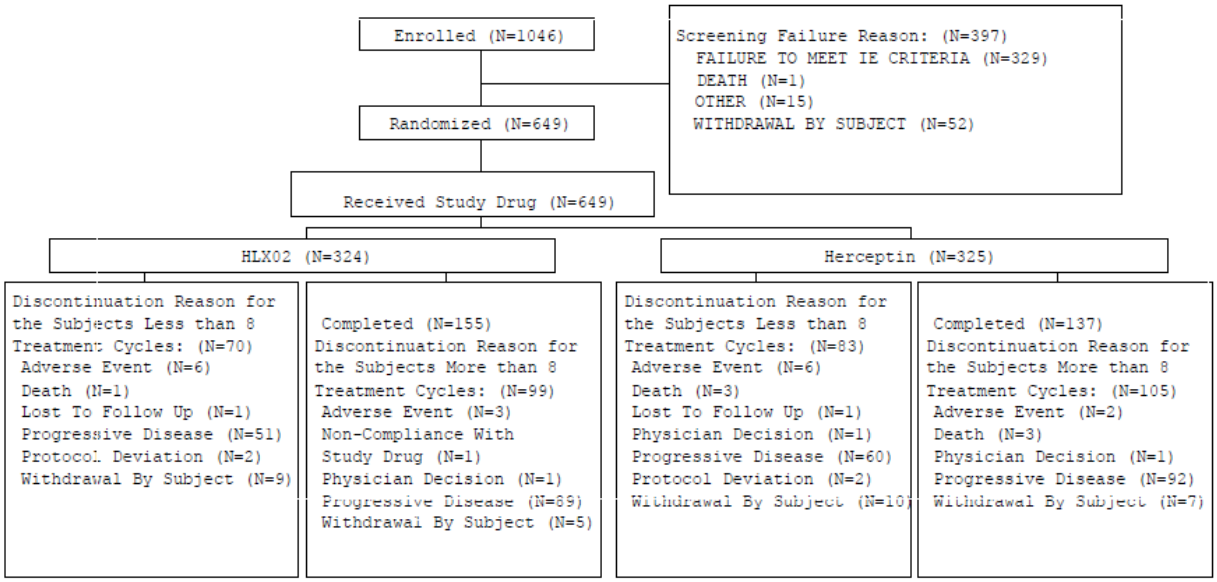
A higher proportion of Asian patients (14.3%) than non-Asian patients (6.5%) have withdrawn the informed consent at screening.

The most common reasons for discontinuation from study treatments were: progressive disease (total 242 [37.3%] patients: 113 [34.9%] in the HLX02 treatment group and 129 [39.7%] in the Herceptin treatment group); withdrawal by patient (total 24 [3.7%] patients: 8 [2.5%] in the HLX02 treatment group and 16 [4.9%]

in the Herceptin treatment group); and AEs (total 16 [2.5%] patients: 9 [2.8%] in the HLX02 treatment group and 7 [2.2%] in the Herceptin treatment group).

At the 23 November 2018 cut off date, a total of 215 (33.1%) patients were ongoing under the study treatment with 116 (35.8%) patients in the HLX02 treatment group and 99 (30.5%) patients in the Herceptin treatment group.

In the second interim analysis, a total of 292 (45.0%) patients had completed the 12-month study treatment (47.8% in the HLX02 treatment group and 42.2% in the Herceptin treatment group).



Source: Figure 14.1.1.1.1
Abbreviations: N= patient numbers.

Figure 30*:* Participant flow (data cut-off *10 Jul 2019*)

Table 34*:* Screen Failure Reasons in Two Interim Analyses (Enrolled Set)

	First Interim Analysis			Second Interim Analysis		
The reason for screen failure	**All N=397**	**Asian N=335**	**Non-Asian N=62**	**All N=397**	**Asian N=335**	**Non-Asian N=62**
Death	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0
Failure to meet the criteria	329 (82.9%)	272 (81.2%)	57 (91.9%)	329 (82.9%)	272 (81.2%)	57 (91.9%)
Withdrawal by patient	52 (13.1%)	48 (14.3%)	4 (6.5%)	52 (13.1%)	48 (14.3%)	4 (6.5%)
Other	15 (3.8%)	14 (4.2%)	1 (1.6%)	15 (3.8%)	14 (4.2%)	1 (1.6%)

Source: Table 14.97.1.AD4

Table 35*:* Number of Patients Randomized Under Each Protocol Amendment for Second Interim Analysis (Intention-to-treat Set)

		All			HLX02			Herceptin		
Protocol Number	Version date	Total N=649	Asian N=499	Non-Asian N=150	Total N=324	Asian N=248	Non-Asian N=76	Total N=325	Asian N=251	Non-Asian N=74
2.0	2016.5.23	28 (4.3%)	28 (5.6%)	0	15 (4.6%)	15 (6.0%)	0	13 (4.0%)	13 (5.2%)	0
3.0	2016.10.14	238 (36.7%)	215 (43.1%)	23 (15.3%)	125 (38.6%)	113 (45.6%)	12 (15.8%)	113 (34.8%)	102 (40.6%)	11 (14.9%)
4.0	2017.5.17	29 (4.5%)	29 (5.8%)	0	13 (4.0%)	13 (5.2%)	0	16 (4.9%)	16 (6.4%)	0
5.0	2017.7.17	353 (54.4%)	227 (45.5%)	126 (84.0%)	171 (52.8%)	107 (43.1%)	64 (84.2%)	182 (56.0%)	120 (47.8%)	62 (83.8%)
Missing	1	1 (0.2%)	0	1 (0.7%)	0	0	0	1 (0.3%)	0	1 (1.4%)

Source: Table 14.97.4.2.AD4

- Patient 319-005 is missing version number and date due to data issue, version number should be "5.0".

Recruitment

The study was initiated (first patient enrolled) on 11 November 2016.

A total of 89 study centres in 4 countries (China, Poland, Ukraine and Philippines) participated in the study. Among these, a total of 81 study centres in 3 countries (China, Ukraine and Philippines) consented at least 1 patient by the data cut-off date.

- Screening period: days -28 to -1.
- Treatment Period: up to 12 months (52 weeks; each cycle is 3 weeks).
- Safety follow-up 30 days post-treatment.
- Survival follow-up: 24 months.

End of study will occur 36 months after the last patient is randomized.

Conduct of the study

Protocol amendments

The version of study protocol that was originally submitted to and instituted in EC was Version 2.0. Version 2.0 was instituted before the first patient was enrolled. As of cut-off date, the protocol had been amended 3 times. Brief summaries of the non-administrative changes are outlined below.

Protocol Version 3.0 dated 14 October 2016 implemented the following changes:

- Tumor assessments changed from every 9 weeks (3 cycles) to every 6 weeks (2 cycles) to ensure tumour assessments were at regular intervals up to the new primary endpoint of Week 24.

- The removal of Extension Study.

- Duration of follow-up period revised to 36 months after randomization.

- In accordance with EMA Scientific Advice, the primary endpoint has been changed: the primary endpoint changed from Week 18 to Week 24 to improve the sensitivity of the primary efficacy analysis in accordance with EMA Scientific Advice.

- Stratification factors changed.

- Increase in sample size to ensure power in the study and to reflect the change of the primary efficacy analysis to the ITT population; the interim blinded evaluation deleted because the sample size was considered sufficient to achieve the desired power.

- Deleting the inclusion of patients who had received prior first line anti-hormonal treatment for metastatic disease, in accordance with the EMA Scientific Advice;

- The statistical methods section (PK) updated to include shed antigen (in accordance with EMA Scientific Advice).

- A fasting glucose test at baseline has added to discover any patients with undiagnosed diabetes.

- Confirmation of HER2-overexpression based on FISH further clarified to add gene copies.

Protocol Version 4.0 dated 17 May 2017 implemented the following changes:

- Primary objective updated to "ORR up to Week 24" from "ORR at Week 24" to be consistent with the ORR evaluation as reported in the reference trials; primary endpoint updated accordingly

The endpoint of ORR up to 12 months removed

- Clarification added that a CIR was not necessary after Week 24 because efficacy endpoints after this time were secondary.

- To demonstrate the pattern of response was equivalent in both arms, ORR added at 6-week intervals up to Week 24.

- The endpoint of ORR at end of treatment removed; DoR added.

- Changes to the in/exclusion criteria including:

    - Change to the inclusion criterion regarding the various disease-free intervals after different prior therapy
    - In/Exclusion criteria changed to allow men with breast cancer into the study and, as a result, a criterion added on contraception for male patients and their partners
    - The criterion of gene copies >4 removed
    - Requirement on the stop details of prior hormone therapy removed
    - A requirement added on the disease-free interval with regard to prior therapy

- A blinded sample size re-estimation procedure was added to increase the chance of meeting the required power to show equivalence

- The frequency of ECG measurements changed from 3 cycles to every cycle

Protocol Version 5.0 dated 17 July 2017 implemented the following changes:

- The details and frequency of pregnancy testing updated in accordance with the European Clinical Trial Facilitation Group recommendation on contraception and pregnancy testing

- Inclusion Criterion 11 updated to be consistent with docetaxel label restrictions and to allow patients with liver metastases to be enrolled and have access to effective therapy

- It was clarified that if either trastuzumab or docetaxel was delayed due to toxicity, the other agent was also to be delayed

No changes were made to the planned analyses after the finalization of the statistical analysis plan.

Protocol deviations

Summary of Major Protocol Deviations by Treatment Group – Overall (ITT Set)

Number of Patients	HLX02 (N = 324) n (%)	Herceptin (N = 325) n (%)	Total (N = 649) n (%)
With at least one major protocol deviation	2 (0.6)	6 (1.8)	8 (1.2)
Eligibility and Entry Criteria	1 (0.3)	5 (1.5)	6 (0.9)
IP Compliance	1 (0.3)	1 (0.3)	2 (0.3)

Abbreviations: IP Investigational product.
Source: Table 14.1.1.4
Percentages were based on the number of patients in ITT set; subgroup percentages were based on the number of patients in the subgroup ITT set.
Patients may have more than one major protocol deviation

Baseline data

Table 36: Demographics and Baseline Characteristics by Treatment Group -Overall (ITT Set)

Characteristics	HLX02 N=324	Herceptin N=325	Total N=649
Age (years)			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	53.6 (9.73)	52.8 (10.08)	53.2 (9.90)
Median	54.0	53.0	54.0
Q1, Q3	47.0, 60.0	45.0, 60.0	46.0, 60.0
Min, Max	30, 80	26, 76	26, 80
Sex, n (%)			
Female	324 (100.0)	325 (100.0)	649 (100.0)
Male	0	0	0
Race, n (%)			
Asian excluding Chinese	11 (3.4)	15 (4.6)	26 (4.0)
American Indian or Alaska Native	0	0	0
Chinese	237 (73.1)	236 (72.6)	473 (72.9)
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islanders	0	0	0
White	76 (23.5)	74 (22.8)	150 (23.1)
Other	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	2 (0.6)	1 (0.3)	3 (0.5)
Not Hispanic or Latino	316 (97.5)	319 (98.2)	635 (97.8)
Not Reported	5 (1.5)	4 (1.2)	9 (1.4)
Unknown	1 (0.3)	1 (0.3)	2 (0.3)
Childbearing potential (a), n (%)			
Yes	105 (32.4)	111 (34.2)	216 (33.3)

Characteristics	HLX02 N=324	Herceptin N=325	Total N=649
No	219 (67.6)	214 (65.8)	433 (66.7)
Last Menstrual Period (a), n (%)			
More than 12 Months	217 (67.0)	210 (64.6)	427 (65.8)
Equal or less than 12 Months	107 (33.0)	114 (35.1)	221 (34.1)
Missing	0	1 (0.3)	1 (0.2)
ECOG performance status, n (%)			
0	138 (42.6)	139 (42.8)	277 (42.7)
1	186 (57.4)	186 (57.2)	372 (57.3)
Left Ventricular Ejection Fraction			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	64.7 (5.06)	64.0 (4.94)	64.4 (5.01)
Median	65.0	64.0	64.0
Q1, Q3	61.0, 68.0	60.0, 67.0	60.0, 67.0
Min, Max	52, 82	50, 80	50, 82
ECG result, n (%)			
Normal	200 (61.7)	203 (62.5)	403 (62.1)
Abnormal Finding	123 (38.0)	122 (37.5)	245 (37.8)
Missing	1 (0.3)	0	1 (0.2)
Height (cm)			
n (missing)	322 (2)	325 (0)	647 (2)
Mean (SD)	159.4 (6.12)	158.9 (5.99)	159.1 (6.05)
Median	159.5	158.0	159.0
Q1, Q3	155.0, 163.0	155.0, 163.0	155.0, 163.0
Min, Max	145, 181	143, 175	143, 181
Weight (kg)			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	64.60 (12.628)	63.69 (12.458)	64.14 (12.542)
Median	62.00	62.00	62.00
Q1, Q3	55.25, 70.00	55.50, 70.00	55.50, 70.00
Min, Max	41.5, 118.0	37.2, 120.0	37.2, 120.0
BMI (kg/m^2)			
n (missing)	322 (2)	325 (0)	647 (2)
Mean (SD)	25.36 (4.275)	25.21 (4.556)	25.28 (4.416)
Median	24.65	24.52	24.54
Q1, Q3	22.46, 27.53	22.27, 27.43	22.35, 27.53

Characteristics	HLX02 N=324	Herceptin N=325	Total N=649
Min, Max	17.3, 42.1	16.2, 44.6	16.2, 44.6
Body Surface Area (m^2)			
n (missing)	322 (2)	325 (0)	647 (2)
Mean (SD)	1.69 (0.179)	1.67 (0.173)	1.68 (0.176)
Median	1.66	1.65	1.65
Q1, Q3	1.56, 1.78	1.56, 1.77	1.56, 1.77
Min, Max	1.3, 2.4	1.2, 2.3	1.2, 2.4
Country, n (%)			
China	241 (74.4)	247 (76.0)	488 (75.2)
Philippines	7 (2.2)	4 (1.2)	11 (1.7)
Ukraine	76 (23.5)	74 (22.8)	150 (23.1)

Source: Table 14.1.3.1

- Percentages were based on the number of patients in intention-to-treat set.
- Age was derived as the difference in years between the date of birth and the date of informed consent.
- ECOG: Eastern Cooperative Oncology Group; ECG: Electrocardiogram.
- Body Mass Index (BMI) (kg/m^2) = weight (kg) / (height/100 [cm])^2.
- (a) Denominator of 'Childbearing potential' and 'Last Menstrual Period' only based on female patients.

Overall, 66 (10.2%) patients presented with primary diagnosis at screening with local disease and 581 (89.5%) patients presented with metastatic disease, the majority of patients had stage IV disease (91.2%). Of total of 144 (22.2%) patients slightly patients had more than 1 visceral metastasis at screening in HLX02 treatment group, with 67 (20.7%) patients, while there were 77 (23.7%) patients in Herceptin treatment group. One visceral metastasis at screening was detected in about half of patients, 175 (54.9 %) patients in HLX02 treatment group and 157 (48.3%) patients in Herceptin treatment group. A total of 304 (46.8%) patients showed positive ER/PgR status in the study with corresponding proportion in HLX02 treatment group as 149 (46.0%), in Herceptin treatment group as 155 (47.7%), with similar proportions by ER and PgR status. Other baseline disease characteristics (clinical and pathological TNM stage, staging of primary tumour nodal involvement and presence of metastases at screening) appear balanced between the groups.

Table 37: Summary of Most Relevant Baseline Characteristics – Overall (ITT Set)

Characteristics	HLX02 N=324	Herceptin N=325	Total N=649
Primary Tumor Status at Screening, n (%)			
TX	81 (25.0)	86 (26.5)	167 (25.7)
T0, Tis, T1	78 (24.1)	87 (26.8)	165 (25.4)
T2	76 (23.5)	70 (21.5)	146 (22.5)
T3, T4	68 (21.0)	63 (19.4)	131 (20.2)
Missing	21 (6.5)	19 (5.8)	40 (6.2)
ER/PgR, n (%)			
Positive	149 (46.0)	156 (48.0)	305 (47.0)
Negative/Unknown	175 (54.0)	169 (52.0)	344 (53.0)
Previous Trastuzumab and/or Lapatinib Adjuvant Therapy, n (%)			
Yes	13 (4.0)	21 (6.5)	34 (5.2)
No	308 (95.1)	299 (92.0)	607 (93.5)
Age, n (%)			
< 50	98 (30.2)	120 (36.9)	218 (33.6)
>= 50	226 (69.8)	205 (63.1)	431 (66.4)
Previous Neo-/Adjuvant Therapy with Herceptin, n (%)			
Yes	16 (4.9)	20 (6.2)	36 (5.5)
No	308 (95.1)	305 (93.8)	613 (94.5)
Ethnicity Status, n (%)			
Asian	248 (76.5)	251 (77.2)	499 (76.9)
Non-Asian	76 (23.5)	74 (22.8)	150 (23.1)
ECOG, n (%)			

Characteristics	HLX02 N=324	Herceptin N=325	Total N=649
0	138 (42.6)	139 (42.8)	277 (42.7)
1	186 (57.4)	186 (57.2)	372 (57.3)
Metastatic site number (CIR), n (%)			
> 2	123 (38.0)	104 (32.0)	227 (35.0)
<= 2	190 (58.6)	207 (63.7)	397 (61.2)
Metastatic site number (INV), n (%)			
> 2	124 (38.3)	130 (40.0)	254 (39.1)
<= 2	199 (61.4)	191 (58.8)	390 (60.1)
Metastatic Site Status (CIR), n (%)			
Liver Metastasis: Yes	157 (48.5)	164 (50.5)	321 (49.5)
Liver Metastasis: No	167 (51.5)	161 (49.5)	328 (50.5)
Bone Metastasis: Yes	94 (29.0)	102 (31.4)	196 (30.2)
Bone Metastasis: No	230 (71.0)	223 (68.6)	453 (69.8)
Brain Metastasis: Yes	2 (0.6)	0	2 (0.3)
Brain Metastasis: No	322 (99.4)	325 (100.0)	647 (99.7)
Metastatic Site Status (INV), n (%)			
Liver Metastasis: Yes	146 (45.1)	141 (43.4)	287 (44.2)
Liver Metastasis: No	178 (54.9)	184 (56.6)	362 (55.8)
Bone Metastasis: Yes	115 (35.5)	132 (40.6)	247 (38.1)
Bone Metastasis: No	209 (64.5)	193 (59.4)	402 (61.9)
Brain Metastasis: Yes	0	0	0
Brain Metastasis: No	324 (100.0)	325 (100.0)	649 (100.0)

Source: Table 14.1.3.1.2.AD3, Listing 16.2.4.1.1, Listing 16.2.9.1.1, Listing 16.2.9.1.3, Listing 16.2.9.1.5, and Listing 16.2.9.1.6

- Percentages were based on the number of patients in intention-to-treat set. Subgroup percentages were based on the number of patients in the subgroup intention-to-treat set.
- Age was derived as the difference in years between the date of birth and the date of informed consent.
- ECOG: Eastern Cooperative Oncology Group; ECG: Electrocardiogram.

There was a median of 2 target lesions at baseline in both arms.

Table 38: Target Lesions at Baseline (ITT set)

Characteristics	HLX02 N=324	Herceptin N=325	Total N=649
Number of Target Lesions			
n (missing)	324(0)	325(0)	649(0)
Mean (SD)	2.1(1.16)	2.1(1.11)	2.1(1.14)
Median	2.0	2.0	2.0
Q1, Q3	1.0, 3.0	1.0, 3.0	1.0, 3.0
Min, Max	1, 5	1, 5	1, 5
Number of Target Lesions, n(%)			
0	0	0	0
1	114 (35.2)	108 (33.2)	222 (34.2)
2	113 (34.9)	128 (39.4)	241 (37.1)
3	53 (16.4)	44 (13.5)	97 (14.9)
4	24 (7.4)	30 (9.2)	54 (8.3)
>=5	20 (6.2)	15 (4.6)	35 (5.4)

Overall, 36 (5.5%) patients (16 [4.9%] in HLX02 treatment group and 20 [6.2%] patients in Herceptin treatment group) had received prior neo-/adjuvant therapy with Herceptin.

Previous and concomitant systemic therapy for breast cancer included trastuzumab (36 [11.1%] in HLX02 arm and 32 [9.8%] in EU Herceptin arm, lapatinib (6 [3.1%] in HLX02 arm and [1.8%] in EU Herceptin arm.

Table 39: Prior and concomitant medication – overall (ITT)

Preferred Term	HLX02 N=324 n (%)	Herceptin N=325 n (%)	Total N=649 n (%)
ENDOCRINE THERAPY	11 (3.4)	19 (5.8)	30 (4.6)
LETROZOLE	4 (1.2)	7 (2.2)	11 (1.7)
EXEMESTANE	3 (0.9)	5 (1.5)	8 (1.2)
ANASTROZOLE	2 (0.6)	3 (0.9)	5 (0.8)
TAMOXIFEN	2 (0.6)	3 (0.9)	5 (0.8)
LEUPRORELIN	1 (0.3)	2 (0.6)	3 (0.5)
GOSERELIN	1 (0.3)	1 (0.3)	2 (0.3)
FULVESTRANT	0 (0.0)	1 (0.3)	1 (0.2)
Preferred Term	**HLX02 N=324 n (%)**	**Herceptin N=325 n (%)**	**Total N=649 n (%)**
ANTINEOPLASTIC AGENTS	87 (26.9)	78 (24.0)	165 (25.4)
TRASTUZUMAB	36 (11.1)	32 (9.8)	68 (10.5)
CAPECITABINE	20 (6.2)	19 (5.8)	39 (6.0)
VINORELBINE	13 (4.0)	17 (5.2)	30 (4.6)
GEMCITABINE	13 (4.0)	11 (3.4)	24 (3.7)
LEUCOGEN	11 (3.4)	12 (3.7)	23 (3.5)
CISPLATIN	9 (2.8)	8 (2.5)	17 (2.6)
LAPATINIB	10 (3.1)	6 (1.8)	16 (2.5)
COIX LACRYMA-JOBI SUBSP. MA-YUEN	5 (1.5)	6 (1.8)	11 (1.7)
DOCETAXEL	6 (1.9)	3 (0.9)	9 (1.4)
CARBOPLATIN	5 (1.5)	2 (0.6)	7 (1.1)
POLYPEPTIDE	4 (1.2)	2 (0.6)	6 (0.9)
BRUCEA JAVANICA	1 (0.3)	3 (0.9)	4 (0.6)
CYCLOPHOSPHAMIDE	2 (0.6)	2 (0.6)	4 (0.6)
PACLITAXEL	3 (0.9)	1 (0.3)	4 (0.6)
ASPARAGINASE	2 (0.6)	1 (0.3)	3 (0.5)
BETA ELEMENE;DELTA ELEMENE;GAMMA ELEMENE	2 (0.6)	0 (0.0)	2 (0.3)
CELECOXIB	2 (0.6)	0 (0.0)	2 (0.3)
DOXORUBICIN	1 (0.3)	1 (0.3)	2 (0.3)
MARSDENIA TENACISSIMA	1 (0.3)	1 (0.3)	2 (0.3)
PYROTINIB	1 (0.3)	1 (0.3)	2 (0.3)
VINCRISTINE	1 (0.3)	1 (0.3)	2 (0.3)
ASTRAGALUS PROPINQUUS ROOT;ATRACTYLODES MACRO	0 (0.0)	1 (0.3)	1 (0.2)
BEVACIZUMAB	1 (0.3)	0 (0.0)	1 (0.2)
DISODIUM CANTHARIDINATE	1 (0.3)	0 (0.0)	1 (0.2)
DISODIUM CANTHARIDINATE W/PYRIDOXINE HYDROCHL	0 (0.0)	1 (0.3)	1 (0.2)
DISODIUM CANTHARIDINATE;PYRIDOXINE	0 (0.0)	1 (0.3)	1 (0.2)
FLUOROURACIL	0 (0.0)	1 (0.3)	1 (0.2)
MITOXANTRONE	1 (0.3)	0 (0.0)	1 (0.2)
MONOCLONAL ANTIBODIES	1 (0.3)	0 (0.0)	1 (0.2)
PIRARUBICIN	1 (0.3)	0 (0.0)	1 (0.2)
RITUXIMAB	1 (0.3)	0 (0.0)	1 (0.2)
SODIUM GLYCIDIDAZOLE	1 (0.3)	0 (0.0)	1 (0.2)
THALIDOMIDE	0 (0.0)	1 (0.3)	1 (0.2)

Table 40: Disposition of Patients with Different Prior Oncologic Therapy by Treatment Group (Intention-to-treat Set)

Prior oncologic treatment history	All N=649	HLX02 All N=324	Herceptin All N=325	Asian All N=499	HLX02 Asian N=248	Herceptin Asian N=251	Non-Asian All N=150	HLX02 Non-Asian N=76	Herceptin Non-Asian N=74
Trastuzumab	37 (5.7%)	17 (5.2%)	20 (6.2%)	30 (6.0%)	15 (6.0%)	15 (6.0%)	7 (4.7%)	2 (2.6%)	5 (6.8%)
Lapatinib	0	0	0	0	0	0	0	0	0
Taxane	339 (52.2%)	171 (52.8%)	168 (51.7%)	315 (63.1%)	160 (64.5%)	155 (61.8%)	24 (16.0%)	11 (14.5%)	13 (17.6%)
Other cytotoxics	430 (66.3%)	212 (65.4%)	218 (67.1%)	360 (72.1%)	175 (70.6%)	185 (73.7%)	70 (46.7%)	37 (48.7%)	33 (44.6%)
Hormonal therapy	151 (23.3%)	70 (21.6%)	81 (24.9%)	137 (27.5%)	62 (25.0%)	75 (29.9%)	14 (9.3%)	8 (10.5%)	6 (8.1%)

Source: Table 14.97.6.2.AD4

The most common medical history by SOCs were hepatobiliary disorders (34.5%) in HLX02 treatment group and 34.8% in Herceptin treatment group), neoplasms benign, malignant and unspecified (33.3%%in HLX02 treatment group and 34.8% in Herceptin treatment group), vascular disorders (28.7%] in HLX02 treatment group and 32.6% in Herceptin group). Other medical history of interest by SOC is presented below, in the overall population in and subgroups Asian/non-Asian.

Table 41: Table Medical History by Treatment Group (ITT)

System Organ Class Preferred Term	HLX02 N=324	Herceptin N=325	Total N=649
Respiratory, thoracic and mediastinal disorders	34(10.5)	43(13.2)	77(11.9)
Cardiac disorders	25(7.7)	43(13.2)	68(10.5)
Blood and lymphatic system disorders	16(4.9)	15(4.6)	31(4.8)
Immune system disorders	12(3.7)	8(2.5)	20(3.1)
Vascular disorders	46(18.5)	46(18.3)	92(18.4)

Asian

System Organ Class Preferred Term	HLX02 N=248	Herceptin N=251	Total N=499
Respiratory, thoracic and mediastinal disorders	25(10.1)	33(13.1)	58(11.6)
Cardiac disorders	13(5.2)	26(10.4)	39(7.8)
Blood and lymphatic system disorders	12(4.8)	14(5.6)	26(5.2)
Immune system disorders	9(3.6)	5(2.0)	14(2.8)
Vascular disorders	46(18.5)	46(18.3)	92(18.4)

Non-Asian

System Organ Class Preferred Term	HLX02 N=76	Herceptin N=74	Total N=150
Respiratory, thoracic and mediastinal disorders	9(11.8)	10(13.5)	19(12.7)
Vascular disorders	22(28.9)	26(35.1)	48(32.0)
Blood and lymphatic system disorders	4(5.3)	1(1.4)	5(3.3)
Cardiac disorders	12(15.8)	17(23.0)	29(19.3)
Immune system disorders	3(3.9)	3(4.1)	6(4.0)

Numbers analysed

Table 42: Analysis sets by treatment group (data cut-off: 23 Nov 2018)

Number of patients	HLX02 N=324	Herceptin N=325	Total N=649
Enrolled set			1046
Intention-to-treat set	324 (100.0)	325 (100.0)	649 (100.0)
Safety analysis set	324 (100.0)	325 (100.0)	649 (100.0)
Per-protocol set	311 (96.0)	306 (94.2)	617 (95.1)
Reason for exclusion from PPS			
Cycles	13 (4.0)	15 (4.6)	28 (4.3)
Measurement	7 (2.2)	3 (0.9)	10 (1.5)
Major PD	2 (0.6)	6 (1.8)	8 (1.2)
Pharmacokinetic population	320 (98.8)	321 (98.8)	641 (98.8)

Source: Table 14.1.2.1 and Listing 16.2.3.1.1

The ITT population (649 [100%] patients) was used for the efficacy analysis and the safety population was used for the analyses of AEs and laboratory data. The PP population was used for sensitivity analyses of the primary and secondary efficacy analyses.

By the cut-off date of 23 November 2018:

- 132 (20.3%) patients had completed the study treatment (71 [21.9%] in the HLX02 treatment group and 61 [18.8%] in the Herceptin treatment group).

- 302 (46.5%) patients had discontinued the study treatment (137 [42.3%] in the HLX02 treatment group and 165 [50.8%] in the Herceptin treatment group) and 79 patients withdrew from the study prematurely of which 58 discontinued due to death.

- 215 (33.1%) patients were ongoing under the study treatment with 116 (35.8%) patients in the HLX02 treatment group and 99 (30.5%) patients in the Herceptin treatment group.

Table 43: Analysis sets by treatment group (data cut-off: 10 Jul 2019)

Number of Patients	HLX02 (N = 324) n (%)	Herceptin (N = 325) n (%)	Total (N = 649) n (%)
Enrolled			1046
Screen failed			397
ITT set	324 (100.0)	325 (100.0)	649 (100.0)
PP set	310 (95.7)	306 (94.2)	616 (94.9)
Treatment status			
Discontinued	169 (52.2)	188 (57.8)	357 (55.0)
Completed	155 (47.8)	137 (42.2)	292 (45.0)
Ongoing[a]	0	0	0
Reason for Treatment Discontinued Status	169 (52.2)	188 (57.8)	357 (55.0)
Adverse event	9 (2.8)	8 (2.5)	17 (2.6)
Death	1 (0.3)	6 (1.8)	7 (1.1)
Lost to follow-up	1 (0.3)	1 (0.3)	2 (0.3)
Non-compliance with study drug	1 (0.3)	0	1 (0.2)
Physician decision	1 (0.3)	2 (0.6)	3 (0.5)
Progressive disease	140 (43.2)	152 (46.8)	292 (45.0)
Protocol deviation	2 (0.6)	2 (0.6)	4 (0.6)
Withdrawal by patient	14 (4.3)	17 (5.2)	31 (4.8)
Study Status			
Screen failed	0	2 (0.6)	2 (0.3)
Discontinued	75 (23.1)	77 (23.7)	152 (23.4)
Ongoing[a]	249 (76.9)	246 (75.7)	495 (76.3)
Reason for Study Discontinued Status	75 (23.1)	77 (23.7)	152 (23.4)
Death	58 (17.9)	70 (21.5)	128 (19.7)
Lost to follow-up	6 (1.9)	1 (0.3)	7 (1.1)
Progressive disease	2 (0.6)	0	2 (0.3)
Withdrawal by patient	8 (2.5)	6 (1.8)	14 (2.2)
Other	1 (0.3)	0	1 (0.2)

Abbreviations: ITT = intention-to-treat; PP = per-protocol; I/E = inclusion/exclusion.

Source: Table 14.1.1.1

Percentages were based on the number of patients in ITT set; subgroup percentages were based on the number of patients in the subgroup ITT set.

[a] "Ongoing" removed for final analysis.

Each re-screening patient had a unique patient identification.

Patients 110-017 and 109-040 were assigned to 'Herceptin' but discontinued, while the end of study reason for them were screen failed. However, they should not be excluded from ITT set as they were randomized.

Outcomes and estimation

The data provided in Marketing Authorization Application (MAA) were based on the cut-off date 23 November 2018 when the primary efficacy data at Week 24 were available for all patients. Data from the second interim analysis (DCO 10 July 2019) were also provided.

The date for the database lock for first interim analysis was 29 Dec 2018 (cut-off date 27 Nov 2018).

The date for the database lock for second interim analysis is 16 Aug 2019 (cut-off date 10 July 2019).

Primary efficacy endpoint: ORR24

Similarity between HLX02 and EU Herceptin was statistically demonstrated for the primary efficacy endpoint, ORR24 (as the proportion of patients with a best response of complete response (CR) or partial response (PR) from first assessment up to Week 24 according to RECIST 1.1) assessed by central imaging review (CIR) in ITT set. Overall, the efficacy of primary endpoint, ORR24, assessed by CIR was similar between the 2 treatment groups after completion of up to 8 cycles of treatment.

Table 44: Analysis Overall Response Rate (ORR) up to Week 24 by central imaging review (CIR) in ITT set (First interim analysis- data cut-off: 23 Nov 2018)

Characteristics	HLX02 N=324	Herceptin N=325
Objective Response Rate (ORR)		
n(%)	230 (71.0)	232 (71.4)
Asymptotic 95% CI of the Rate	66.0, 75.9	66.5, 76.3
Difference and 95% CI	-0.4 (-7.4, 6.6)	

ORR24 was 71% in HLX02 treatment group and 71.4% in Herceptin treatment group. The proportion of patients with complete response (CR) were 17 (5.2%) in HLX02 treatment group versus 12 (3.7%) in Herceptin treatment group. Similar proportion of patients in both treatment groups had partial response (PR): 213 (65.7%) patients in HLX02 treatment group and 220 (67.7%) patients in Herceptin treatment group.

The analysis of ORR derived from central radiology assessments showed a risk difference of the ORR between the 2 treatment groups was -0.4% (95% CI: -7.4%, 6.6%) (HLX02 minus EU Herceptin). The 95% CI was within the pre-specified equivalence margin of -13.5% to 13.5%.

Table 45: Analysis Overall Response Rate (ORR) up to Week 24 by central imaging review in ITT set (Second interim analysis – data cut-off: 10 Jul 2019)

Characteristics	HLX02 N=324	Herceptin N=325
Best Overall Response		
Complete Response (CR), n (%)	17 (5.2)	12 (3.7)
Partial Response (PR), n (%)	214 (66.0)	220 (67.7)
non-Complete Response/non-Progressive Disease (non CR/non PD), n (%)	5 (1.5)	3 (0.9)
Stable Disease (SD), n (%)	48 (14.8)	65 (20.0)
Progressive Disease (PD), n (%)	24 (7.4)	16 (4.9)
Inevaluable (NE)	16 (4.9)	9 (2.8)
Objective Response Rate (ORR)		
n (%)	231 (71.3)	232 (71.4)
Risk Ratio and 90% CI	0.999 (0.920, 1.084)	
Asymptotic 95% CI of the Rate	66.4, 76.2	66.5, 76.3
Difference and 95% CI	-0.1 (-7.0, 6.9)	
Stratified difference and 95% CI	0.1 (-6.9, 7.0)	
CMH Test P-value	0.983	

Abbreviations: CI = confidential interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; ITT = intention-to-treat; NE = Inevaluable; non CR/non PD = non-complete response/non-progressive disease; ORR= objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.
Source: Table 14.2.2.2.1

Sensitivity analyses

The following sensitivity analyses were performed to explore the robustness of the primary efficacy analysis result at first interim analysis (data cut-off: 23 Nov 2018):

1) The adjusted risk difference in ORR (HLX02/Herceptin) between the 2 treatment groups was -0.2 as calculated using a stratified Cochran-Mantel-Haenszel (CMH) test and 95% Wald CIs were -7.2% and 6.8% (p-value of 0.952), within the equivalence margin.

2) The ORR derived from CIR – Per Protocol Population. The risk difference of the ORR between the two treatments groups was 0.8, with 95%CI being -6.2% and 7.7%. The 95% CI is within the recommended equivalence margin of -13.5% to 13.5%.

Table 46: Analysis of Best Overall Response (BOR) up to Week 24 by CIR (PP) (data cut-off: 23 Nov 2018)

Characteristics	HLX02 N=311	Herceptin N=306
Best Overall Response		
Complete Response (CR), n(%)	17 (5.5)	12 (3.9)
Partial Response (PR), n(%)	213 (68.5)	212 (69.3)
Non-Complete Response/Non-Progressive Disease (Non CR/Non PD), n(%)	5 (1.6)	3 (1.0)
Stable Disease (SD), n(%)	46 (14.8)	58 (19.0)
Progressive Disease (PD), n(%)	22 (7.1)	16 (5.2)
Inevaluable (NE)	8 (2.6)	5 (1.6)
Objective Response Rate (ORR)		
n(%)	230 (74.0)	224 (73.2)
Asymptotic 95% CI of the Rate	69.1, 78.8	68.2, 78.2
Difference and 95% CI	0.8 (-6.2, 7.7)	
Stratified difference and 95% CI	1.0 (-5.9, 8.0)	
CMH Test P-value	0.778	

3) The ORR derived from Investigator Assessments- ITT Population. The risk difference of the ORR between the two treatments groups was 2.7, with 95%CI being -4.4% and 9.8%. The 95% CI is within the recommended equivalence margin of -13.5% to 13.5%.

Table 47: Analysis Objective Response Rate (ORR) up to Week 24 by investigator (ITT) (data cut-off: 23 Nov 2018)

Characteristics	HLX02 N=324	Herceptin N=325
Best Overall Response		
Complete Response (CR), n(%)	9 (2.8)	12 (3.7)
Partial Response (PR), n(%)	220 (67.9)	209 (64.3)
Non-Complete Response/Non-Progressive Disease (Non CR/Non PD), n(%)	0	0
Stable Disease (SD), n(%)	57 (17.6)	72 (22.2)
Progressive Disease (PD), n(%)	26 (8.0)	24 (7.4)
Inevaluable (NE)	12 (3.7)	8 (2.5)
Objective Response Rate (ORR)		
n(%)	229 (70.7)	221 (68.0)
Asymptotic 95% CI of the Rate	65.7, 75.6	62.9, 73.1
Difference and 95% CI	2.7 (-4.4, 9.8)	
Stratified difference and 95% CI	2.7 (-4.3, 9.8)	
CMH Test P-value	0.450	

4) ORR analysis in the ITT set where patients with missing ORR assessment were regarded as non-responders.

Patients with missing ORR assessment were regarded as non-responders. As the result of the second interim analysis, ORRwk24 was 71.3% in HLX02 treatment group and 71.4% in Herceptin treatment group. No statistical difference was found between 2 treatment groups (p=0.983). Equivalence was concluded as the 2-sided 95% CI of the risk difference in the 2 proportions (-0.1% [-7.0%, 6.9%]) was completely contained within predefined equivalence boundaries [-0.1350; 0.1350].

Subgroup analysis

In order to assess the homogeneity of treatment effects across the relevant subgroups, subgroup analysis was conducted by stratification and other factors. Forest plot is provided below.

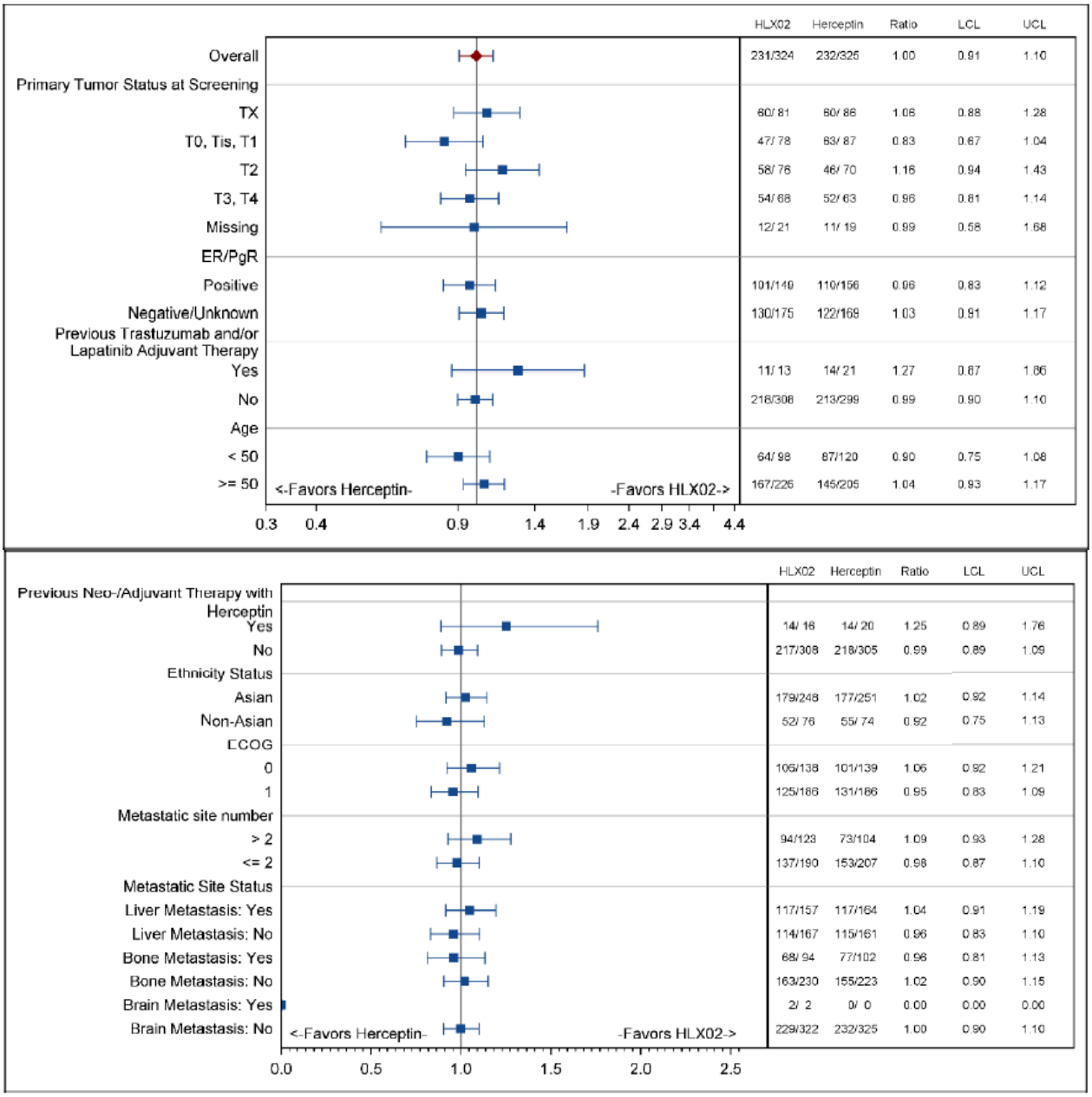


Figure 31: Forest plot of ORR risk differences subgroup analysis by CIR – Overall (ITT set), first interim analysis

Table 48: Analysis of ORR up to Week 24 by CIR for patients with (A) or without (B) Prior neo-/adjuvant therapy with Herceptin – ITT

A

Characteristics	HLX02 N=16	Herceptin N=20
Objective Response Rate (ORR)		
n(%)	14 (87.5)	14 (70.0)
Asymptotic 95% CI of the Rate	71.3, 100.0	49.9, 90.1
Difference and 95% CI	17.5 (-8.3, 43.3)	

B

Characteristics	HLX02 N=308	Herceptin N=305
Objective Response Rate (ORR)		
n(%)	216 (70.1)	218 (71.5)
Asymptotic 95% CI of the Rate	65.0, 75.2	66.4, 76.5
Difference and 95% CI	-1.3 (-8.5, 5.9)	

Table 49: Analysis of ORR up to Week 24 by CIR for ER/PgR Positive (A) and ER/PgR Negative (B) - ITT

A

Characteristics	HLX02 N=149	Herceptin N=155
Objective Response Rate (ORR)		
n(%)	101 (67.8)	109 (70.3)
Asymptotic 95% CI of the Rate	60.3, 75.3	63.1, 77.5
Difference and 95% CI	-2.5 (-12.9, 7.9)	

B

Characteristics	HLX02 N=149	Herceptin N=155
Objective Response Rate (ORR)		
n(%)	127 (73.4)	123 (72.4)
Asymptotic 95% CI of the Rate	66.8, 80.0	65.6, 79.1
Difference and 95% CI	1.1 (-8.4, 10.5)	

Table 50: Analysis of ORR up to Week 24 by CIR - Asian and Non-Asian (ITT)

Asian

Characteristics	HLX02 N=248	Herceptin N=251
Objective Response Rate (ORR)		
n(%)	179 (72.2)	177 (70.5)
Asymptotic 95% CI of the Rate	66.6, 77.8	64.9, 76.2
Difference and 95% CI	1.7 (-6.3, 9.6)	

Non-Asian

Characteristics	HLX02 N=76	Herceptin N=74
Objective Response Rate (ORR)		
n(%)	51 (67.1)	55 (74.3)
Asymptotic 95% CI of the Rate	56.5, 77.7	64.4, 84.3
Difference and 95% CI	-7.2 (-21.7, 7.3)	

Secondary efficacy endpoints

Analysis of Overall Response by Week by CIR - ORR at 6, 12, 28 and 24 weeks

Table 51: Analysis of ORR by week by CIR (ITT set) (First interim analysis- data cut-off: 23 Nov 2018)

Characteristic	HLX02 N=324	Herceptin N=325
Week 6		
Objective Response Rate (ORR)		
n(%)	146 (45.1)	138 (42.5)
Asymptotic 95% CI of the Rate	39.6, 50.5	37.1, 47.8
Difference and 95% CI	2.6 (-5.0, 10.2)	
CMH Test P-value	0.493	
Week 12		
Objective Response Rate (ORR)		
n(%)	190 (58.6)	187 (57.5)
Asymptotic 95% CI of the Rate	53.3, 64.0	52.2, 62.9
Difference and 95% CI	1.1 (-6.5, 8.7)	
CMH Test P-value	0.822	
Week 18		
Objective Response Rate (ORR)		
n(%)	197 (60.8)	192 (59.1)
Asymptotic 95% CI of the Rate	55.5, 66.1	53.7, 64.4
Difference and 95% CI	1.7 (-5.8, 9.3)	
CMH Test P-value	0.612	
Week 24		
Objective Response Rate (ORR)		
n(%)	193 (59.6)	175 (53.8)
Asymptotic 95% CI of the Rate	54.2, 64.9	48.4, 59.3
Difference and 95% CI	5.7 (-1.9, 13.3)	
CMH Test P-value	0.135	

Of note, the secondary endpoint ORR at Week 24 was calculated as the proportion of patients with an overall response of CR or PR at the Week 24 visit, whereas the primary endpoint ORRwk24, was calculated as the proportion of patients with a best response of complete response (CR) or partial response (PR) from the first assessment up to Week 24 (after up to 8 cycles of treatment) according to RECIST 1.1.

Ancillary analyses by subgroups Asian/non-Asian are presented in the relevant section below.

Table 52: Analysis of Best Overall Response (BOR) by Week (by CIR and Investigator) – Overall (ITT Set) (Second interim analysis – data cut-off: 10 Jul 2019)

Characteristic	CIR		Investigator	
	HLX02 N=423	Herceptin N=325	HLX02 N=423	Herceptin N=325
Week 6				
Objective Response Rate (ORR)	146 (45.1)	139 (42.8)	136 (42.0)	130 (40.0)
CMH Test P-value	0.548		0.588	
Week 12				
Objective Response Rate (ORR)	190 (58.6)	187 (57.5)	183 (56.5)	177 (54.5)
CMH Test P-value	0.825		0.667	
Week 18				
Objective Response Rate (ORR)	199 (61.4)	189 (58.2)	202 (62.3)	180 (55.4)
CMH Test P-value	0.368		0.077	
Week 24				
Objective Response Rate (ORR)	192 (59.3)	175 (53.8)	194 (59.9)	171 (52.6)
CMH Test P-value	0.154		0.055	
Week 33				
Objective Response Rate (ORR)			162 (50.0)	134 (41.2)
CMH Test P-value			0.022	
Week 42				
Objective Response Rate (ORR)			139 (42.9)	116 (35.7)
CMH Test P-value			0.055	
Week 51				
Objective Response Rate (ORR)			90 (27.8)	86 (26.5)
CMH Test P-value			0.675	

Abbreviations: CMH = Cochran-Mantel-Haenszel;; ITT = intention-to-treat; ORR= objective response rate;
Source: Table 14.2.2.3.1 and Table 14.2.4.5.1.2.AD3

Time-to-event secondary efficacy variables

Time-to-event secondary efficacy variables of CBR, DCR, DoR, PFS up to 12 months and OS at 12, 24, and 36 months are planned to be analysed at the time of final analysis.

The analyses of these variables at the time of interim analysis have been provided, with the exception of the OS event-free rate 24 and 36 months, not available at the cut-off date of 23 November 2018.

Table 53: Analysis of Clinical Benefit Rate (CBR) and Disease Control Rate (DCR) by Investigator – Overall Intention-to-treat Set (Source - Table 14.2.3.1.1 of the CSR) -(First interim analysis- data cut-off: 23 Nov 2018)

Characteristics	HLX02 N=324	Herceptin N=325
Clinical Benefit Rate (CBR)		
n(%)	260 (80.2)	260 (80.0)
Asymptotic 95% CI of the Rate	75.9, 84.6	75.7, 84.3
Difference and 95% CI	0.2 (-5.9, 6.4)	
Disease Control Rate (DCR)		
n(%)	273 (84.3)	285 (87.7)
Asymptotic 95% CI of the Rate	80.3, 88.2	84.1, 91.3
Difference and 95% CI	-3.4 (-8.8, 1.9)	

Table 54: Analysis of CBR and DCR by Investigator – Overall (ITT Set) (Second interim analysis – data cut-off: 10 Jul 2019)

Characteristics	HLX02 N=324	Herceptin N=325
CBR		
Best Overall Response		
Complete Response (CR), n (%)	12 (3.7)	16 (4.9)
Partial Response (PR), n (%)	228 (70.4)	209 (64.3)
non-Complete Response/non-Progressive Disease (non CR/non PD), n (%)	0	0
Stable Disease (SD), n (%)	23 (7.1)	38 (11.7)
Progressive Disease (PD), n (%)	44 (13.6)	47 (14.5)
Inevaluable (NE)	17 (5.2)	15 (4.6)
Clinical Benefit Rate (CBR)		
n (%)	263 (81.2)	263 (80.9)
Asymptotic 95% CI of the Rate	76.9, 85.4	76.7, 85.2
Difference and 95% CI	0.2 (-5.8, 6.3)	
Stratified difference and 95% CI	0.3 (-5.8, 6.3)	
CMH Test P-value	0.933	
DCR		
Best Overall Response		
Complete Response (CR), n (%)	12 (3.7)	16 (4.9)
Partial Response (PR), n (%)	228 (70.4)	209 (64.3)
non-Complete Response/non-Progressive Disease (non CR/non PD), n (%)	0	0
Stable Disease (SD), n (%)	34 (10.5)	60 (18.5)
Progressive Disease (PD), n (%)	35 (10.8)	31 (9.5)
Inevaluable (NE)	15 (4.6)	9 (2.8)
Disease Control Rate (DCR)		
n (%)	274 (84.6)	285 (87.7)

Characteristics	HLX02 N=324	Herceptin N=325
Asymptotic 95% CI of the Rate	80.6, 88.5	84.1, 91.3
Difference and 95% CI	-3.1 (-8.4, 2.2)	
Stratified difference and 95% CI	-3.3 (-8.6, 2.1)	
CMH Test P-value	0.233	

Abbreviations: CBR = clinical benefit rate; CI = confidential interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; ITT = intention-to-treat; NE = Inevaluable; non CR/non PD = non-complete response/non-progressive disease; ORR= objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

Source: Table 14.2.3.1.1, Listing 16.2.6.1.6

- %: Percentage of patients in each category relative to the total number of patients in the relevant analysis set for each treatment group.
- CBR is defined as the proportion of patients who achieve CR, PR, or SD of at least 24 weeks.
- DCR is defined as the proportion of patients who achieve CR, PR, or SD of at least 12 weeks.
- Stratified difference, its 95% CI and P-value are calculated from a stratified CMH with hormone receptor status, prior neo-/adjuvant therapy with Herceptin, and ethnicity (Asian and non-Asian) as stratification factors.

Duration of response

Table 55: Analysis of duration of response (DOR) by Investigator (ITT Set)) - (First interim analysis- data cut-off: 23 Nov 2018)

Characteristics	HLX02 N=324	Herceptin N=325
Number of subjects with event, n(%)	70 (21.6)	79 (24.3)
Progressive Disease (PD), n(%)	68 (21.0)	77 (23.7)
Death, n(%)	2 (0.6)	2 (0.6)
Number of subjects censored, n(%)	169 (52.2)	145 (44.6)
Reason for censoring:		
No PD or death at the time of cut-off, n(%)	167 (51.5)	145 (44.6)
Non-study anti-tumor treatment initiated before PD, n(%)	2 (0.6)	0
Death or PD after two consecutive missed adequate / inadequate tumor assessment, n(%)	0	0
DoR (months)		
n	239	224
Median (95% CI)	10.41 (9.49, 11.47)	9.92 (8.31, 11.27)
HR (HLX02/Herceptin)(95% CI)	0.75 (0.55, 1.04)	
Stratified HR (HLX02/Herceptin)(95% CI)	0.75 (0.54, 1.04)	
p-value	0.089	
Event-free rate at 12 months, (%)	-	-

Source: Listing 16.2.6.1.4

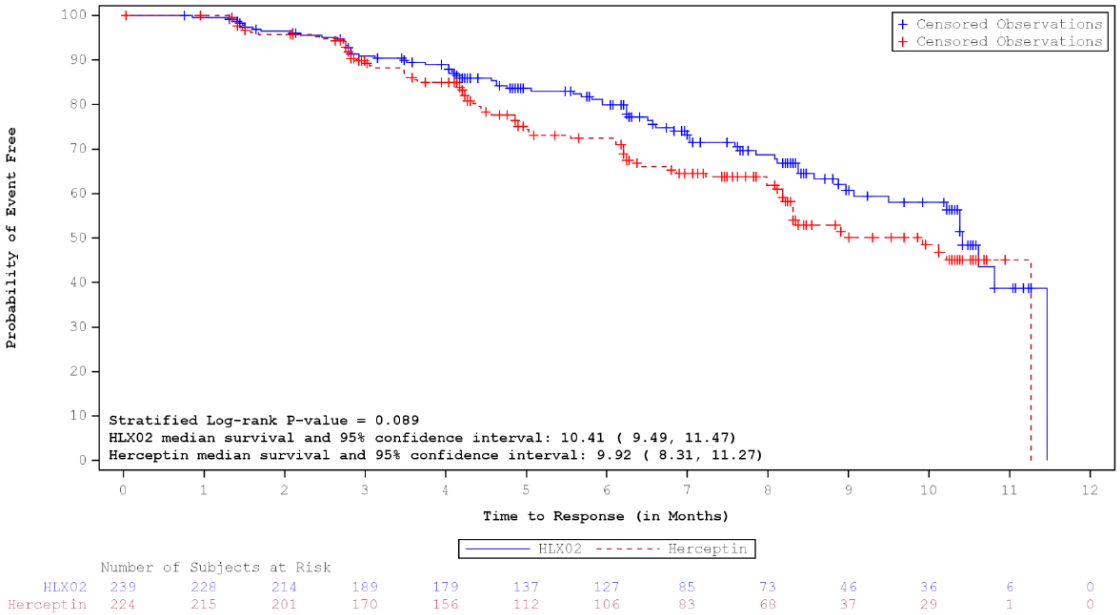


Figure 32: Kaplan-Meier Curve for Duration of Response (DoR) by Investigator-ITT - (First interim analysis- data cut-off: 23 Nov 2018)

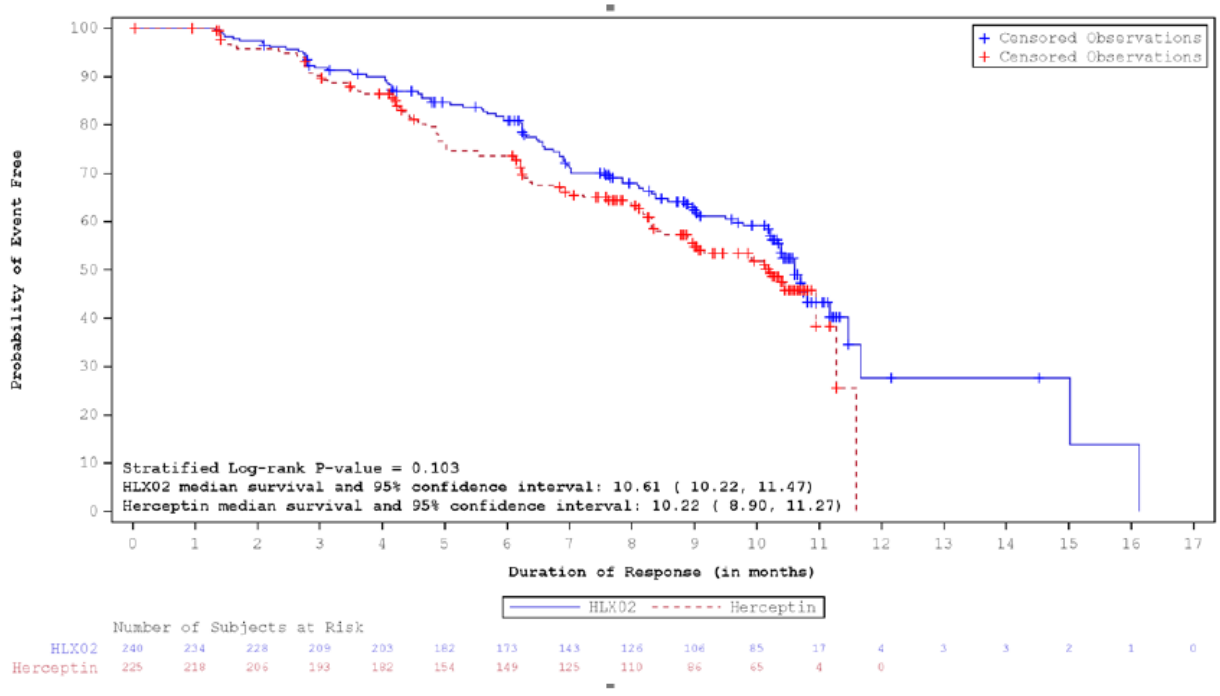
Table 56: Analysis of DoR by Investigator – Overall (ITT Set) (Second interim analysis – data cut-off: 10 Jul 2019)

Characteristics	HLX02 N=324	Herceptin N=325
Number of patients with event, n (%)	102 (31.5)	102 (31.4)
Progressive Disease (PD), n (%)	95 (29.3)	96 (29.5)
Death, n (%)	7 (2.2)	6 (1.8)
Number of patients censored, n (%)	138 (42.6)	123 (37.8)
Reason for censoring:		
No PD or death at the time of cut-off, n (%)	131 (40.4)	119 (36.6)
Non-study anti-tumor treatment initiated before PD, n (%)	7 (2.2)	4 (1.2)
Death or PD after 2 consecutive missed adequate / inadequate tumor assessment, n (%)	0	0
DoR (months)		
N	240	225
Median (95% CI)	10.61 (10.22, 11.47)	10.22 (8.90, 11.27)
HR (HLX02/Herceptin) (95% CI)	0.80 (0.61, 1.06)	
Stratified HR (HLX02/Herceptin) (95% CI)	0.79 (0.60, 1.05)	
P-value	0.103	
Event free rate at 12 months, (%)	27.6	-

Abbreviations: CI = confidential interval; DoR = duration of response; HR = Hazard Ratio; ITT = intention-to-treat; PD = progressive disease.

Source: Table 14.2.4.1.1. and Listing 16.2.6.1.4

- %: Percentage of patients in each category relative to the total number of patients in the relevant analysis set.
- Stratified HR, its 95% CI is calculated from a stratified Cox proportional hazard model with hormone receptor status, prior neo-/adjuvant therapy with Herceptin, and ethnicity (Asian and non-Asian) as stratification factors. P-value (stratified) is calculated from log-rank test.
- DoR is defined as the time from first documentation of CR or PR to the first documentation of progression.
- Point estimator of Median and Event free rate has generated by Kaplan-Meier estimates.



Source: Figure 14.2.1.1.1.

Figure 33: Analysis of DoR by Investigator – Overall (ITT Set) - (Second interim analysis – data cut-off: 10 Jul 2019)

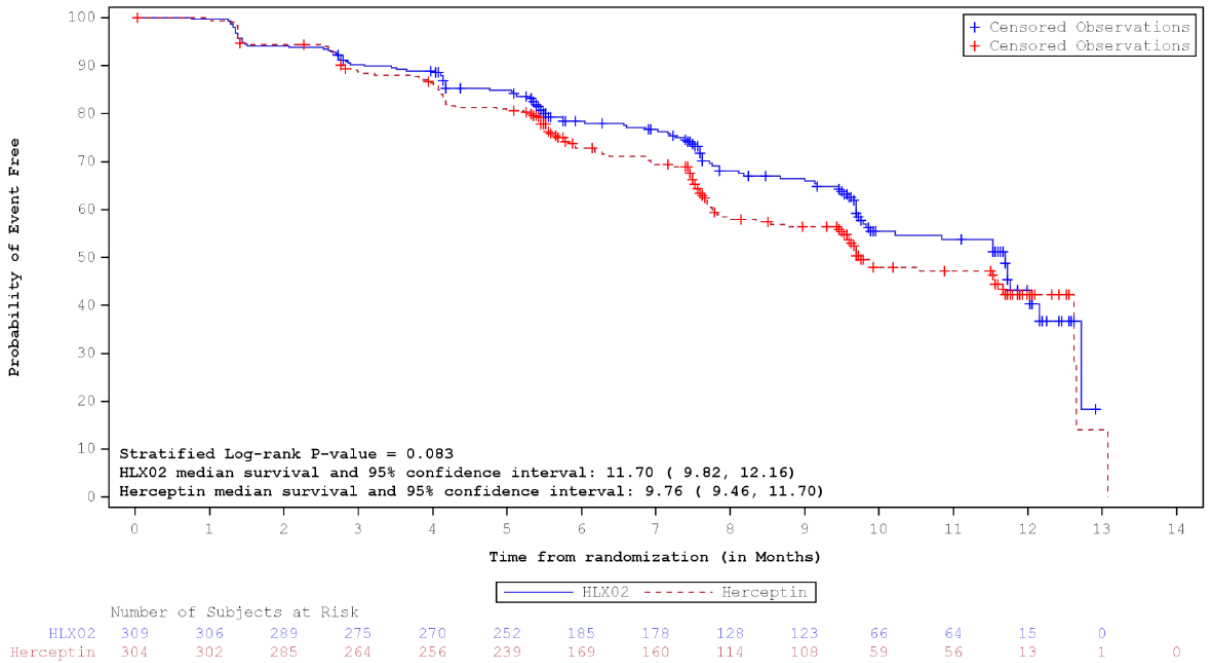
PFS

Table 57: Analysis of PFS by investigator (ITT set) - (First interim analysis- data cut-off: 23 Nov 2018)

Characteristics	HLX02 N=324	Herceptin N=325
Number of subjects with event, n(%)	123 (38.0)	143 (44.0)
Progressive Disease (PD), n(%)	119 (36.7)	133 (40.9)
Death, n(%)	4 (1.2)	10 (3.1)
Number of subjects censored, n(%)	201 (62.0)	182 (56.0)
Reason for censoring:		
PD /Death after two consecutive missed adequate tumor assessment, n(%)	0	0
No PD or death at the time of cut-off, n(%)	196 (60.5)	181 (55.7)
No baseline tumor assessment and without death occurred within two consecutive tumor assessment visit, n(%)	0	0
No post-baseline (with baseline) tumor assessment and without death occurred within two consecutive tumor assessment visit, n(%)	0	0
Initiation of non-study anti-cancer therapy before PD/death (without two consecutive missed adequate tumor assessment), n(%)	5 (1.5)	1 (0.3)
PFS (months)		
Median (95% CI)	11.70 (9.79, 12.16)	9.69 (8.34, 11.66)
HR (HLX02/Herceptin) (95% CI)	0.83 (0.65, 1.06)	
Stratified HR (HLX02/Herceptin) (95% CI)	0.80 (0.63, 1.03)	
p-value	0.079	
Event-free rate at 12 months, (%)	43.0	41.5

Source: Listing 16.2.6.1.4
- HR: Hazard Ratio. CI: Confidence Interval. %: Percentage of subjects in each category relative to the total number of subjects in the relevant analysis set.
- Stratity HR, its 95% CI is calculated from a stratified Cox proportional hazard model with hormone receptor status, prior neo-/adjuvant therapy with Herceptin, and ethnicity (Asian and non-Asian) as stratification factors. P-value (stratified) is calculated from logrank test.
- PFS up to 12 months is defined as the probability of being alive without documented progression up to 12 months after randomization.
- Point estimator of Median and Event-free rate has generated by Kaplan-Meier estimates.

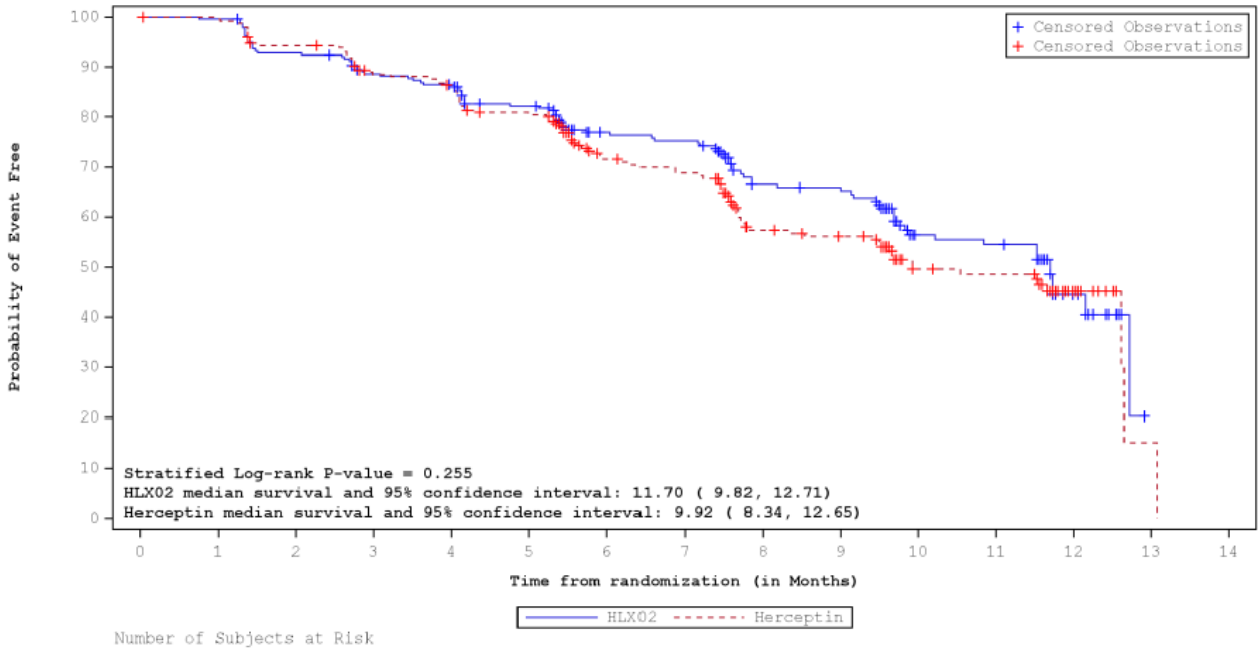
ITT



Number of Subjects at Risk

HLX02	309	306	289	275	270	252	185	178	128	123	66	64	15	0
Herceptin	304	302	285	264	256	239	169	160	114	108	59	56	13	1	0

Asian



Number of Subjects at Risk

HLX02	247	238	221	208	202	186	139	136	97	95	58	56	12	0
Herceptin	251	247	229	210	202	187	130	124	90	85	51	49	14	1	0

Non-Asian

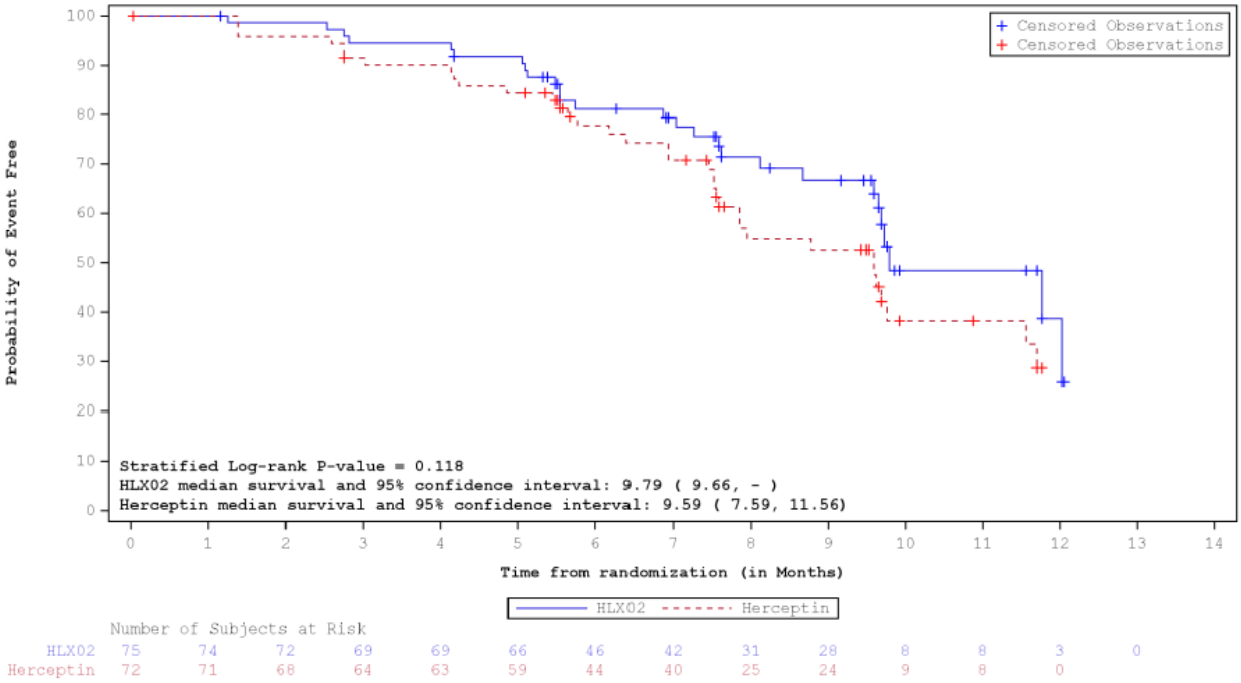


Figure 34: Kaplan-Meier Curves of PFS by Investigator – ITT, Asian and non-Asian - (First interim analysis- data cut-off: 23 Nov 2018)

Table 58: Analysis of PFS by Investigator – Overall (ITT Set) - (Second interim analysis – data cut-off: 10 Jul 2019)

Characteristics	HLX02 N=324	Herceptin N=325
Number of patients with event, n (%)	159 (49.1)	174 (53.5)
Progressive Disease (PD), n (%)	146 (45.1)	159 (48.9)
Death, n (%)	13 (4.0)	15 (4.6)
Number of patients censored, n (%)	165 (50.9)	151 (46.5)
Reason for censoring:		
PD/Death after 2 consecutive missed adequate tumor assessment, n (%)	0	0
No PD or death at the time of cut-off, n (%)	155 (47.8)	146 (44.9)
No baseline tumor assessment and without death occurred within 2 consecutive tumor assessment visits, n (%)	0	0
No post-baseline (with baseline) tumor assessment and without death occurred within 2 consecutive tumor assessment visits, n (%)	0	0
Initiation of non-study anticancer therapy before PD/death (without 2 consecutive missed adequate tumor assessment), n (%)	10 (3.1)	5 (1.5)
PFS (months)		
Median (95% CI)	11.73 (11.10, 12.02)	10.55 (9.49, 11.73)
HR (HLX02/Herceptin)) (95% CI)	0.84 (0.68, 1.04)	
Stratified HR (HLX02/Herceptin) (95% CI)	0.83 (0.67, 1.03)	
P-value	0.086	
Event free rate at 12 months, (%)	45.8	42.4

Abbreviations: CI = confidential interval; HR = Hazard Ratio; ITT = intention-to-treat; PD = progressive disease; PFS = progression-free survival.

Source: Table 14.2.5.1.1 and Listing 16.2.6.1.4

- %: Percentage of patients in each category relative to the total number of patients in the relevant analysis set.
- Stratified HR, its 95% CI is calculated from a stratified Cox proportional hazard model with hormone receptor status, prior neo-/adjuvant therapy with Herceptin, and ethnicity (Asian and non-Asian) as stratification factors. P-value (stratified) is calculated from log-rank test.
- PFS up to 12 months is defined as the probability of being alive without documented progression up to 12 months after randomization.
- Point estimator of Median and Event free rate has generated by Kaplan-Meier estimates.

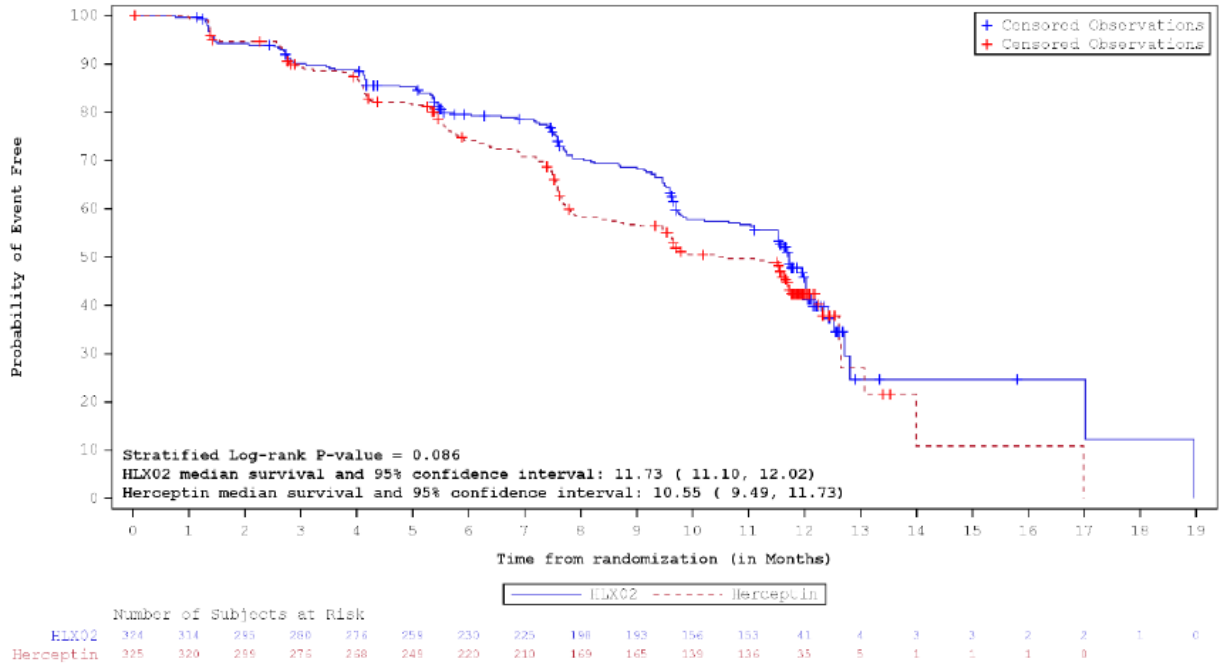


Figure 35: Analysis of PFS by Investigator – Overall (ITT Set) - (Second interim analysis – data cut-off: 10 Jul 2019)

Overall survival

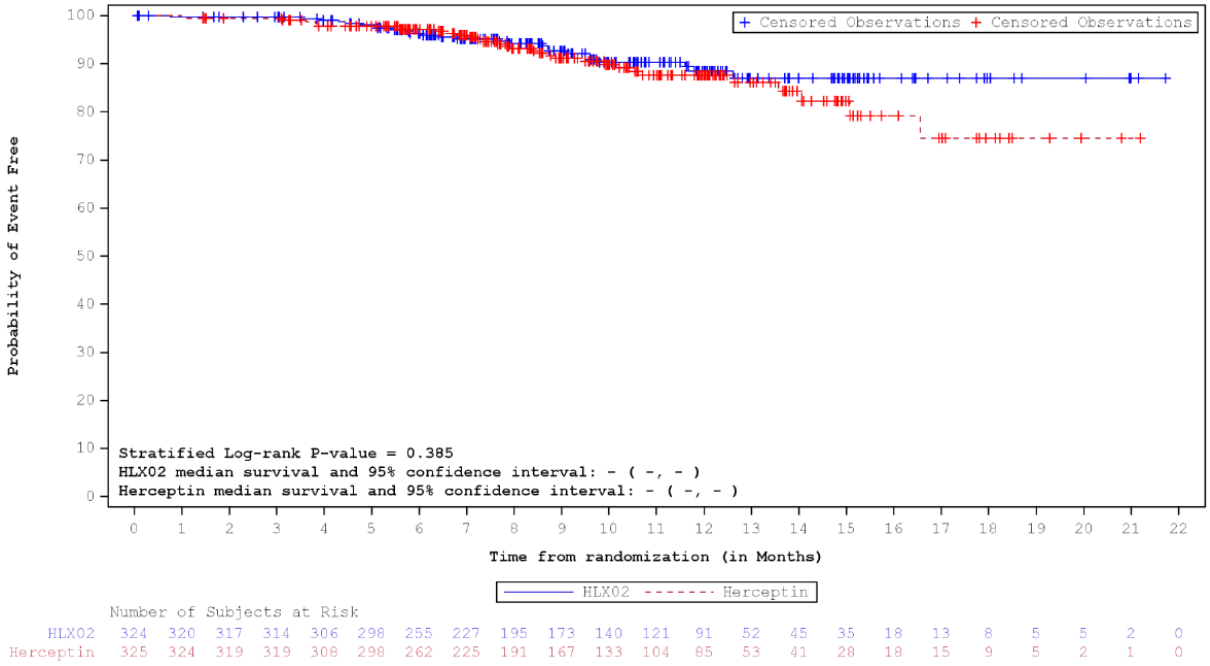


Figure 36: Kaplan-Meier Curve for OS -ITT - (First interim analysis- data cut-off: 23 Nov 2018)

Table 59: Analysis of OS (ITT set) - (First interim analysis- data cut-off: 23 Nov 2018)

Characteristics	HLX02 N=324	Herceptin N=325
Number of subjects with event, n(%)	26 (8.0)	32 (9.8)
Number of subjects censored, n(%)	298 (92.0)	293 (90.2)
Reason for censoring:		
Patients still followed without death as of cut-off date, the date last known to be alive is before the cut-off date, n(%)	298 (92.0)	293 (90.2)
Patients still followed without death as of cut-off date, the date last known to be alive is on or after the cut-off date, n(%)	0	0
OS (months)		
Median (95% CI)	- (-, -)	- (-, -)
HR (HLX02/Herceptin) (95% CI)	0.80 (0.48, 1.34)	
Stratified HR (HLX02/Herceptin) (95% CI)	0.79 (0.47, 1.34)	
p-value	0.385	
Event-free rate at:		
12 months, (%)	88.5	87.6
24 months, (%)	-	-
36 months, (%)	-	-

Source: Listing 16.2.6.1.4
- HR: Hazard Ratio. CI: Confidence Interval. %: Percentage of subjects in each category relative to the total number of subjects in the relevant analysis set.
- Stratity HR, its 95% CI is calculated from a stratified Cox proportional hazard model with hormone receptor status, prior neo-/adjuvant therapy with Herceptin, and ethnicity (Asian and non-Asian) as stratification factors. P-value (stratified) is calculated from logrank test.
- Overall survival at 12, 24, and 36 months, are defined as the probability of being alive 12, 24, and 36 months after randomization.
- Point estimator of Median and Event-free rate has generated by Kaplan-Meier estimates.

Table 60: Analysis of OS – Overall (ITT Set) - (Second interim analysis – data cut-off: 10 Jul 2019)

Characteristics	HLX02 N=324	Herceptin N=325
Number of patients with event, n (%)	57 (17.6)	65 (20.0)
Number of patients censored, n (%)	267 (82.4)	260 (80.0)
Reason for censoring:		
Patients still followed without death as of cut-off date, the date last known to be alive is before the cut-off date, n (%)	267 (82.4)	260 (80.0)
Patients still followed without death as of cut-off date, the date last known to be alive is on or after the cut-off date, n (%)	0	0
OS (months)		
Median (95% CI)	- (-, -)	28.45 (28.45, -)
HR (HLX02/Herceptin) (95% CI)	0.87 (0.61, 1.24)	
Stratified HR (HLX02/Herceptin) (95% CI)	0.85 (0.60, 1.22)	
P-value	0.388	
Event free rate at:		
12 months (%)	88.7	88.9
24 months (%)	73.5	71.8
36 months (%)	-	-

Abbreviations: CI = confidential interval; HR = Hazard Ratio; ITT = intention-to-treat; OS = overall survival.
Source: Table 14.2.6.1 and Listing 16.2.6.1.4
- HR: Hazard Ratio. CI: Confidence Interval. %: Percentage of patients in each category relative to the total number of patients in the relevant analysis set.
- Stratified HR, its 95% CI is calculated from a stratified Cox proportional hazard model with hormone receptor status, prior neo-/adjuvant therapy with Herceptin, and ethnicity (Asian and non-Asian) as stratification factors. P-value (stratified) is calculated from log-rank test.
- Overall survival at 12, 24, and 36 months, are defined as the probability of being alive 12, 24, and 36 months after randomization.
- Point estimator of Median and Event free rate has generated by Kaplan-Meier estimates.

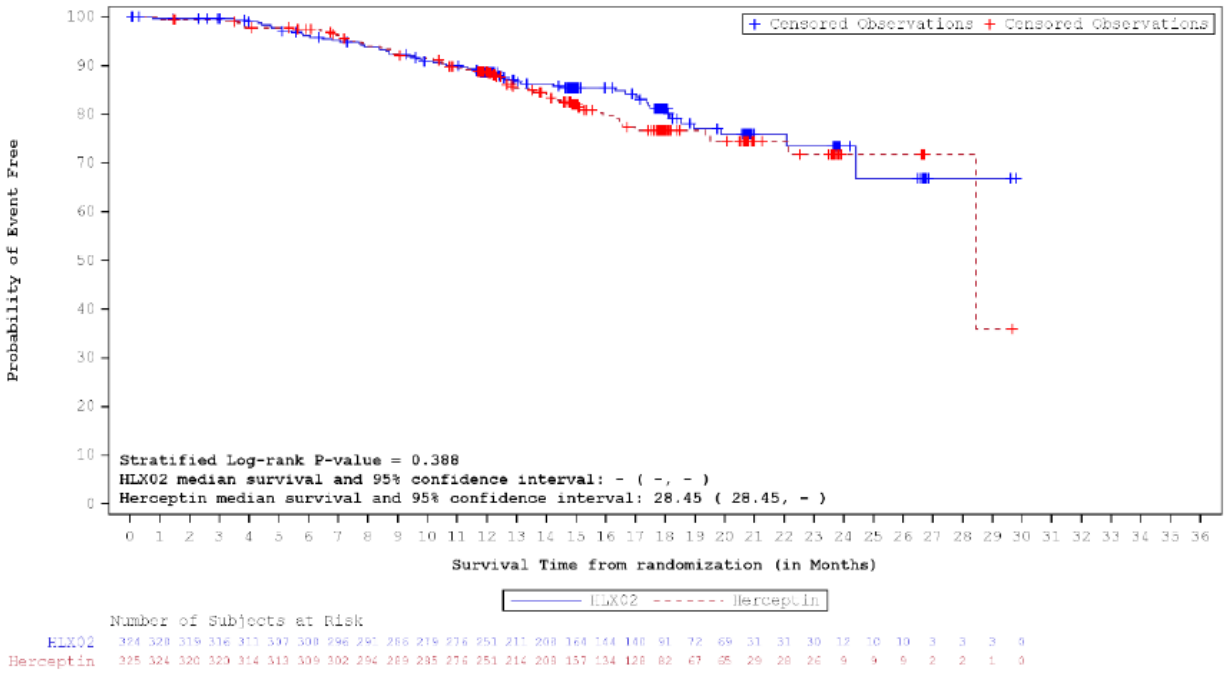


Figure 37*:* Analysis of OS – Overall (ITT Set) - (Second interim analysis – data cut-off: 10 Jul 2019)

Ancillary analyses

All the secondary endpoints have been analysed in the PP population and by subgroups Asian/non-Asian, Chinese/non-Chinese. The results in subgroups of Chinese/non-Chinese patients were consistent with those in Asian/non-Asian as only few Asian patients were recruited out of China.

Table 61: Analysis of Objective Response Rate (ORR) by Week by CIR - Asian and Non-Asian (ITT Set) - (First interim analysis- data cut-off: 23 Nov 2018)

Asian

Characteristic	HLX02 N=248	Herceptin N=251
Week 6		
Objective Response Rate (ORR)		
n(%)	118 (47.6)	103 (41.0)
Asymptotic 95% CI of the Rate	41.4, 53.8	35.0, 47.1
Difference and 95% CI	6.5 (-2.2, 15.2)	
CMH Test P-value	0.185	
Week 12		
Objective Response Rate (ORR)		
n(%)	147 (59.3)	136 (54.2)
Asymptotic 95% CI of the Rate	53.2, 65.4	48.0, 60.3
Difference and 95% CI	5.1 (-3.6, 13.8)	
CMH Test P-value	0.314	
Week 18		
Objective Response Rate (ORR)		
n(%)	154 (62.1)	143 (57.0)
Asymptotic 95% CI of the Rate	56.1, 68.1	50.8, 63.1
Difference and 95% CI	5.1 (-3.5, 13.7)	
CMH Test P-value	0.251	
Week 24		
Objective Response Rate (ORR)		
n(%)	150 (60.5)	134 (53.4)
Asymptotic 95% CI of the Rate	54.4, 66.6	47.2, 59.6
Difference and 95% CI	7.1 (-1.6, 15.8)	
CMH Test P-value	0.103	

Non-Asian

Characteristic	HLX02 N=76	Herceptin N=74
Week 6		
Objective Response Rate (ORR)		
n(%)	28 (36.8)	35 (47.3)
Asymptotic 95% CI of the Rate	26.0, 47.7	35.9, 58.7
Difference and 95% CI	-10.5 (-26.2, 5.3)	
CMH Test P-value	0.312	
Week 12		
Objective Response Rate (ORR)		
n(%)	43 (56.6)	51 (68.9)
Asymptotic 95% CI of the Rate	45.4, 67.7	58.4, 79.5
Difference and 95% CI	-12.3 (-27.7, 3.0)	
CMH Test P-value	0.161	
Week 18		
Objective Response Rate (ORR)		
n(%)	43 (56.6)	49 (66.2)
Asymptotic 95% CI of the Rate	45.4, 67.7	55.4, 77.0
Difference and 95% CI	-9.6 (-25.1, 5.9)	
CMH Test P-value	0.295	
Week 24		
Objective Response Rate (ORR)		
n(%)	43 (56.6)	41 (55.4)
Asymptotic 95% CI of the Rate	45.4, 67.7	44.1, 66.7
Difference and 95% CI	1.2 (-14.7, 17.1)	
CMH Test P-value	0.892	

Table 62: Analysis of Overall Response Rate (ORR) up to Week 24 by CIR – Asian and non-Asian (ITT Set) - (Second interim analysis – data cut-off: 10 Jul 2019)

Characteristics	HLX02	Herceptin
Asian	**N=248**	**N=251**
Best Overall Response		
Complete Response (CR), n (%)	16 (6.5)	8 (3.2)
Partial Response (PR), n (%)	163 (65.7)	169 (67.3)
non-Complete Response/non-Progressive Disease (non CR/non PD), n (%)	2 (0.8)	1 (0.4)
Stable Disease (SD), n (%)	34 (13.7)	51 (20.3)
Progressive Disease (PD), n (%)	18 (7.3)	14 (5.6)
Inevaluable (NE)	15 (6.0)	8 (3.2)
Objective Response Rate (ORR)		
n (%)	179 (72.2)	177 (70.5)
Risk Ratio and 90% CI	1.024 (0.932, 1.124)	
Asymptotic 95% CI of the Rate	66.6, 77.8	64.9, 76.2
Difference and 95% CI	1.7 (-6.3, 9.6)	
Stratified difference and 95% CI	1.4 (-6.6, 9.3)	
CMH Test P-value	0.736	
non-Asian	**N=76**	**N=74**
Best Overall Response		
Complete Response (CR), n (%)	1 (1.3)	4 (5.4)
Partial Response (PR), n (%)	51 (67.1)	51 (68.9)
non-Complete Response/non-Progressive Disease (non CR/non PD), n (%)	3 (3.9)	2 (2.7)
Stable Disease (SD), n (%)	14 (18.4)	14 (18.9)
Progressive Disease (PD), n (%)	6 (7.9)	2 (2.7)
Inevaluable (NE)	1 (1.3)	1 (1.4)
Objective Response Rate (ORR)		
n (%)	52 (68.4)	55 (74.3)
Risk Ratio and 90% CI	0.921 (0.776, 1.092)	
Asymptotic 95% CI of the Rate	58.0, 78.9	64.4, 84.3
Difference and 95% CI	-5.9 (-20.3, 8.5)	
Stratified difference and 95% CI	-4.3 (-18.7, 10.1)	
CMH Test P-value	0.565	

Abbreviations: CI = confidential interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; ITT = intention-to-treat; NE = Inevaluable; non CR/non PD = non-complete response/non-progressive disease; ORR= objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

Source: Table 14.2.2.2.2, CIR data

- CMH: Cochran-Mantel-Haenszel. %: Percentage of patients in each category relative to the total number of patients in the relevant analysis set for each treatment group.
- Objective Response = CR or PR.
- Stratified difference, its 95% CI and P-value are calculated from a stratified CMH with hormone receptor status, prior neo-/adjuvant therapy with Herceptin, and ethnicity (Asian and non-Asian) as stratification factors.

Immunogenicity results

A total of 4 (0.6%) patients [2 patients in each treatment arm] were observed at least one positive result for NAb during the study, who were considered to be overall NAb positive. Two of the 4 patients had an overall response of SD and 2 of PD. For patients with positive ADA ORR was 0% by both CIR and Investigator.

Summary of main study(ies)

The following table summarises 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 63: Summary of efficacy for trial HLX02-BC01

Title: Double-blind, Randomized, Multicenter, Phase III Clinical Study to Compare the Efficacy and to Evaluate the Safety and Immunogenicity of Trastuzumab Biosimilar HLX02 and EU-sourced Herceptin in Previously Untreated HER2 Overexpressing Metastatic Breast Cancer.				
Study identifier	**HLX02-BC01**			
Design	Parallel-group, active-controlled			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 cycles (~ 6 months) not applicable not applicable	
Hypothesis	Equivalence			
Treatments groups	HLX02		IV 8 mg/kg on Day 1 Cycle 1 (loading dose), 6 mg/kg every 3 weeks for up to a maximum of 12 months (17 cycles) +IV concurrent docetaxel 75mg/m2 every 3 weeks ~8 cycles (~ 6 months) N = 324	
	EU Herceptin		IV 8 mg/kg on Day 1 Cycle 1 (loading dose), 6 mg/kg every 3 weeks for up to a maximum of 12 months (17 cycles) +IV concurrent docetaxel 75mg/m2 every 3 weeks ~8 cycles (~ 6 months) N = 325	
Endpoints and definitions	Primary endpoint	ORR	CR or PR by week 24 as assessed by RECIST 1.1 (ICR), not confirmed	
	Secondary endpoint	ORR	ORR at Weeks 6, 12, 18, and 24	
		CBR	the proportion of patients who achieve CR, PR, or durable SD (SD ≥24 weeks)	
		DCR	the proportion of patients who achieve CR, PR, or SD of at least 12 weeks	
		DOR	time from date of the first documented objective tumour response (CR or PR) to the first documented progression of disease (PD) or to death due to any cause in the absence of documented PD	
		1 year PFS rate	Based on time from date of randomization to first PD or death due to any cause in the absence of documented PD.	
		1, 2, 3 year OS rate	Based on time from date of randomization to death due to any cause.	
Database lock	The date of the database lock was 29 December 2018. The data cut-off date for the interim analysis is 23 November 2018.			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT population, week 24			
Descriptive statistics and estimate variability	Treatment group	HLX02	EU Herceptin	
	Number of subject	324	325	
	ORR	230 (71%)	232 (71.4%)	
	95%-CI	(66.0%, 75.9%)	(66.5%, 76.3%)	
Effect estimate per comparison	ORR	Comparison groups	HLX02 vs. EU Herceptin	
		Risk difference	-0.4%	
		95%-CI	[-7.4%;6.6%]	
		Equivalence margin	(-13.5%; 13.5%)	
Notes	Sensitivity analyses (i.e. stratified analysis), analysis based on the PP population, as well as analyses using investigator-assessed ORR support the results of the primary endpoint analysis.			
Analysis description	**Secondary analyses**			
Analysis population and time point description	ITT population, week 24			
Descriptive statistics and estimate variability	Treatment group	HLX02	EU Herceptin	
	Number of subject	324	325	

	1 year PFS rate/median PFS (months)	43.0% /11.70	41.5%/9.69
	95%-CI	NA/(9.79, 12.16)	(NA/(8.34, 11.66)
	DOR median (months)	10.41	9.92
	95%-CI	(9.49, 11.47)	(8.31, 11.27)
	1 year OS rate	88.5%	87.6%
	95%-CI	NA	NA
Effect estimate per comparison		Comparison groups	HLX02 vs. EU Herceptin
	PFS (~40% maturity)	HR	0.83
		95%-CI	(0.65, 1.06)
	DOR	HR	0.75
		95%-CI	(0.55, 1.04)
	OS (~10% maturity)	HR	0.80
		95%-CI	(0.48, 1.34)
Notes	NA not available For the ORR at 6, 12, 18 and 24 weeks the data need confirmation. CBR and DCR results are supporting the results of the primary analysis.		

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

Not applicable. No meta-analysis neither pooled analysis have been submitted.

Clinical studies in special populations

No clinical studies in special populations were submitted (see discussion)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

HLX02 is proposed as a biosimilar to Herceptin. Herceptin is authorised in metastatic and early breast cancer settings as well as in gastric cancer. The applicant is applying for the same indications as Herceptin, even though from an efficacy point of view, the clinical development has been carried out on metastatic breast cancer.

The assessment of similarity in terms of efficacy between Zercepac (HLX02) and EU-sourced Herceptin is based on Study HLX02-BC01.

Study HLX02-BC01 is a double-blind, randomized, Phase 3, parallel-group clinical study evaluating the efficacy, safety, PK and immunogenicity of HLX02 in combination with docetaxel versus trastuzumab-EU with docetaxel in patients aged 18 years and over with HER2-positive metastatic breast cancer in the first-line treatment setting. Patients were stratified for estrogen receptor/progesterone receptor (ER/PgR) status, prior neo-/adjuvant therapy with EU-sourced Herceptin, and ethnicity (Asian and non-Asian). HLX02 and EU-Herceptin were both administered in combination with docetaxel for 8 cycles (24 weeks) and then continued as monotherapy for up to 17 cycles (about 12 months).

The evaluation of tumour response was measured according to RECIST 1.1. The Principal Investigator assessed the response every 6 weeks up to 24 weeks (regardless of the number of cycles actual given); thereafter, assessments were done every 9 weeks (after Cycles 11, 14, and 17) or earlier in the case of clinical signs of progression. Tumour response for the primary efficacy analysis were evaluated by central imaging review (CIR). No CIR was required after Week 24. All patients were to remain in the study until principal investigator-assessed disease progression, excessive toxicity, Investigator's judgment, withdrawal of consent, lost to follow-up, death, start of a new anticancer therapy, study termination by the sponsor, or for a maximum of 12 months of

treatment, whichever occurring first. The ORR difference between HLX02 and EU-Herceptin was analysed with a two-sided 95%CI. The equivalence would be declared if the 95% CI completely falls in an equivalence margin defined as (-13.5%; 13.5%).

This study is still ongoing. Data on a planned interim analysis when the primary efficacy data at Week 24 were available for all patients were submitted with the initial data package (cut-off date: 23 Nov 2018 and database lock: 29 Dec 2018). This interim analysis consisted of the primary efficacy analysis and analyses of evaluable secondary efficacy endpoints. By this cut-off date, 132 patients had completed, 215 were ongoing in the treatment and 302 had discontinued from the treatment.

The second planned interim analysis was performed when all efficacy data, as well as PK, safety/immunogenicity and survival data, up to 12 months were available for all patients (database lock: 16 Aug 2019; cut-off date: 10 Jul 2019). Up to the second interim analysis, a total of 292 (45.0%) patients completed the study treatment (155 [47.8%] in the HLX02 and 137 [42.2%] in the Herceptin); and 357 (55.0%) patients had discontinued the study treatment (169 [52.2%] in the HLX02 and 188 [57.8%] in the Herceptin); no patients were ongoing under treatment as of the cut-off date. Median total exposure duration was close to 1 year (312 days in the HLX02 and 292.0 days in the Herceptin). End of study is planned at 36 months after the last patient being randomized.

Dosing and concomitant therapy

Docetaxel was chosen for combination therapy with HLX02 or EU-Herceptin. This choice is supported from the comparability exercise perspective and would result in a more homogenous patient population. The dose of docetaxel used was 75 mg/m^2 paclitaxel with dose escalation to 100 mg/m^2 (as per Baselga et al, 2012; Swain et al, 2015, CLEOPARTA study) and not in line with the docetaxel label (100 mg/m^2). However, this dosage is widely used and have been justified by improved safety and tolerability. It is considered acceptable as the same dosing regimen was employed in two arms.

Target population and Eligibility criteria

As mentioned in the scientific advice, whilst the choice of patients' population for this clinical comparability is acceptable and is in line with the approved indication, the metastatic setting may not provide the most sensitive model out of all available choices. The choice of the metastatic breast cancer (mBC) over the early breast cancer (eBC) setting is not considered as the most optimal in terms of the expected homogeneity of patient population or its sensitivity to respond to HER2-targeting therapy that is generally used in first instance in the (neo-)adjuvant setting. The first line metastatic setting is nevertheless acceptable to address the clinical efficacy similarity. The choice of metastatic setting over early breast cancer setting was also determined by the fact that the neo-adjuvant setting is not approved for eBC in China, where the majority of patients were planned to be enrolled. HER2 targeted therapy is not widely used in China in (neo-) adjuvant setting and the availability of the currently recommended combination treatments in 1L metastatic setting may be limited. Therefore, the CHMP agreed with the selected MBC patient population.

Overall, the study population is considered representative of an approved therapeutic indication for Herceptin.

Key in- and exclusion criteria were discussed in the context of scientific advice. Inclusion of patients that have completed adjuvant or neo-adjuvant treatment > 12 months earlier was considered adequate. Inclusion of patients with stable / treated brain metastases was endorsed. However, inclusion of patients that have received prior 1st line anti-hormonal treatment for metastatic disease was not considered advisable. First line anti-hormonal treatment was mainly (only) applicable in case of limited disease or bone only metastatic disease (non-measurable and thus not applicable for this study) and when one chooses 1st line anti-hormonal treatment this was generally in combination with trastuzumab (Herceptin) which was not in agreement with the protocol.

Considering the limited number of patients included under modified disease-free interval criteria, the impact on results does not seem to be clinically relevant.

Limitation for the prior cumulative dose of anthracyclines is noted, seemingly only one patient in each arm had prior/concomitant doxorubicin exposure.

The central confirmation of HER2 overexpression status is supported and would improve sensitivity of the patient population. This status was assessed by central laboratory before randomisation to confirm eligibility using a FISH or IHC test, i.e. patients with a previous local IHC score of 2+ must have been tested centrally by FISH and those patients with a previous local IHC score of 3+ must be confirmed centrally by IHC.

Sample size and equivalence margin

The sample size calculations were based on the primary efficacy endpoint ORRwk24. This sample size calculation assumed a conservative ORR rate of 60% which was based on ORR results from 3 studies: Marty et al, 2005 (61%), CLEOPATRA (Baselga et al, 2012) (69%), and HERITAGE study with a biosimilar (Rugo et al, 2017) (69.6%).

Only two studies have been used for meta-analysis and the scientific advice have not been followed. The relevance of the two studies chosen for a meta-analysis (Phase 2 Study M77001 of Marty et al, 2005; Study H0648 reported in the FDA label for Herceptin) with the purpose of the equivalence margin calculation was also questioned at the time of the scientific advice in 2016.

The ORR difference was to be analysed with a two-sided 95%CI (alpha controlled ≤0.05). If the 95% CI completely falls in an equivalence region defined as (-13.5% to +13.5%), then the equivalence would be declared. The Applicant took into consideration the scientific advice recommendation and intermediate steps of the equivalence margin calculation were requested to be clarified.

The random-effect approach was used to define the difference in ORR and its 95%CI. This approach gives relatively wider CI than a fixed-effects approach, which appear nevertheless not much different based on the details that were provided on calculations on the metabin function of the meta library of the R language that was used to implement the calculated estimate and on the overall statistical methodology for the equivalence margin calculation.

Overall, the clinical relevance on this equivalence range was discussed and the overall approach is considered acceptable, although not optimal, to justify the chosen margins at this point.

It is acknowledged that under this approach, unpowered PFS and/or OS estimations would be likely obtained in the final analysis. Long-term data on PFS and OS were nevertheless requested. In the second interim analysis no significant difference was found between two treatment groups in terms of median DoR, PFS and OS despite of the immature data, which partly supported the primary results (see discussion further below).

It is noted that for equivalence study, PP population is usually recommended for primary analysis since low heterogeneity lead to increase the sensitivity of the study to identify any potential differences. However, as both ITT and PP populations have been calculated and powered, the applicant approach is accepted.

According to the applicant's report, there were no multiple comparison or multiplicity issues in this study as the primary comparison was between HLX02 and Herceptin treatment for the primary efficacy variable of ITT using a Chi-squared test and 95% Wald CIs.

Randomisation

The stratification factors included ER/PgR status and prior neo-/adjuvant therapy with Herceptin, to balance the prognostic variables between two treatment groups and also race (Asian and non-Asian). The stratification by tumour burden could have been considered.

Stratification of patients according to prior adjuvant therapy was considered adequate at the time of scientific advice as patients with metastatic breast cancer may have previously received Herceptin in the neo-/adjuvant setting and have baseline anti-drug antibodies (ADAs).

Primary and secondary endpoints

The overall response rate (ORR) is deemed as a sensitive endpoint to demonstrate the similarity between the biosimilar and reference product, as recommended by EMA guideline (EMA/CHMP/BMWP/403543/2010). The initial proposed ORR after 6 cycles (18 weeks) was not advisable per CHMP scientific advice because some patients need more cycles to respond based on the results of other trials. Therefore, ORR at 24 weeks (after 8 cycles) was recommended to confirm the response as the primary endpoint in the study. There was no provision for confirmation of responses and this point has not been discussed during scientific advice.

Proposed secondary endpoints included DoR, CBR, PFS, DCR and OS are considered acceptable. The analysis of the time to response is considered informative and the results have been provided with the updated efficacy report.

The primary assessment and sensitivity analyses were conducted in both Intent-to-treat (ITT) population and the Per-Protocol (PP) population. Since the predominant recruitment population are in Asia, subgroup analyses (non-Asian and Asian population) were also reported.

Conduct of the study

The study was initiated (first patient enrolled) on 11 November 2016. The first protocol amendment (version 3) was implemented previously to start the study (14 October 2016). Thus, these modifications do not seem to bias the study. In total, only 1.2% patients were excluded from the study due to major protocol deviations. The major protocol deviations leading to exclusion from ITT population appear slightly imbalanced, however absolute total numbers are low and have minor impact on the final results.

The blinded sample size re-estimation procedure was planned in the SAP after 300 patients have been evaluated for response at Week 24 to ensure at least 80% power (using the conditional power from the observed ORR difference and adjusting considering the actual dropout rate observed during this period). The procedure was overseen by a Data Monitoring Committee. It was concluded that there was no need for such re-estimation.

Baseline characteristics

Overall, the baseline characteristics of patients and disease were comparable between two arms. The majority of patients were Asian (mainly Chinese). This was not considered to be of concern at the time of the scientific advice. However, stratification by race has been encouraged.

Efficacy data and additional analyses

By the cut-off date (27 November 2018), the pivotal trial met the primary endpoint at the first interim analysis. The difference in ORR (HLX02 minus Herceptin) between the 2 treatments was -0.4 % with 95%CI of -7.4 % to 6.6%. The 95% CI was within the pre-specified equivalence margin of -13.5% to 13.5%.

The ORR up to 24 weeks in ITT set was 71.0% (230 of 324 patients) (95% CI, 66.0, 75.9) for HLX02 and 71.4% (232 of 325 patients) (95% CI, 66.5, 76.3) for Herceptin.

The results from primary analysis are supported by the results of several sensitivity analyses:

- The 95%CI of the risk difference in ORR adjusted for stratification factors was (-7.2%; 6.8%)
- Risk difference in ORR analysis in the PP population yielded the 95%CI of (-6.2% and 7.7%)
- Risk difference in ORR analysis based on investigator assessments resulted in 95%CI of (-4.4% and 9.8%)

The risk difference in ORR from all of the sensitivity analyses was therefore fully contained within the 95% CI boundaries of the pre-specified equivalence margin (-13.5%, 13.5%).

In Asian patients, the ORR difference was 1.7 % and the 95%CI of (-6.3%; 9.6%) was contained within the boundaries of the pre-defined margin of ±13.5%.

In the non-Asian subgroup, ORR up to 24 weeks in Herceptin arm (74.3%) was higher than that in HLX02 arm (67.1%), with a difference of -7.2%. The 95%CI was (-21.7%; 7.3%), thus the lower boundary of the reported 95%CI fell outside of the pre-defined margin of ±13.5%.

According to the published literature, efficacy profiles of HLX02 and Herceptin are not deemed to differ among different ethnicity including Asian and non-Asian population. Nevertheless, heterogeneity in ORR risk difference was observed in the subgroups by race. The subgroup of non-Asian patients is smaller (76 patients in the HLX02 arm, 74 patients in the Herceptin arm) what may explain the results.

The secondary efficacy analyses of CBR, DCR supported the primary analysis.

As to the secondary analysis of ORR by week 6, 12, 18 and 24 to assess the pattern of ORR changes, some discrepancies have been noticed in the provided analyses and were clarified. Furthermore, the change in the primary objective from ORR 'at Week 24' to ORR 'up to 24 weeks' that was implemented with protocol amendment 4 was only for clarification because the expression was misleading. Overall, the choice of the ORR 'up to week 24' instead of 'at week 24' was justified considering the occurrence of response all along the 24-week period instead of at one 24-week point would be more sensitive for detecting differences between arms.

Although the results from the concordance analysis indicated that there were no statistical significant differences between ORR at all time points assessed by CIR and by investigators, a trend of their risk difference beyond the pre-defined equivalence boundaries at week 18, 24 was reported. Furthermore, a statistically significant difference on the ORR assessed by the investigators at week 33 (corresponding to confirmation of the response) between the two treatment groups was also observed. For the subpopulation of non-Asian patients, the ORRwk24 difference assessed by CIR was -8.1% (95% CI: -22.5%, 6.3%) with the left side out of the lower boundary of the equivalence margin. It was 1.1% (-6.0%, 8.1%), which was well contained within the equivalence margin, when assessed by investigators. HRs for OS and PFS did not support this trend and were 0.84 (95% CI: 0.68, 1.04) and 0.91 (95% CI: 0.45, 1.82), respectively. The ORR assessed by CIR might be caused by systematic sampling error due to small sample size according to the applicant, but no definitive conclusion can be made in this regard.

Although the analysis of other secondary endpoints of PFS, DOR and OS needs to attain higher degree of maturity, for all of these points numerically better efficacy was observed for HLX02, with HRs being lower than 1 (0.75 for DOR, 0.83 for PFS and 0.80 for OS). There was a clear separation of KM curves for DOR and PFS, while for OS curves are superposing, but the data are still immature (about 10%). As these data were not

consistent with the primary endpoint, an updated analysis was considered necessary to see whether this trend in favour of HLX02 maintained at the long term.

Based on the results from the second interim analyses, a trend in favour of HLX02 was observed in the primary endpoint and ORR at week 33, 42 assessed by the investigators. No significant difference was found between two treatment groups in terms of median DoR, PFS and OS in the second interim analysis despite of the immature data, which partly supported the primary results. Of note, in subgroups analyses the patients at the age ≥50 in the HLX02 treatment group presented a favourable PFS trend compared with those in the Herceptin group. The estimated time for 24-month OS of last patient will be on 30 June 2020; the estimated time for 36-month OS of last patient will be on 30 June 2021. The applicant is recommended to provide the final CSR including data of 24-month and 36-month OS.

No studies were performed in special population which could be considered acceptable as no differences are expected from the reference drug.

Immunogenicity data are discussed under section 2.6.1.

Extrapolation

Extrapolation of indication has been justified by the applicant based on the fact that the mechanism of action of trastuzumab is the same in all three indications and the target receptor involved is also the same in MBC, EBC and MGC. The dosage is also similar for all three indications, and trastuzumab is administered by the same route in all indications. Hence, extrapolation in terms of efficacy is supported by the results of the physicochemical, structural and biological characterisation data, results from the comparative preclinical studies (*in vitro* functional tests) together with PK comparability data. Extrapolation is also considered acceptable from a safety perspective.

As only PK data on IV administration were submitted under this application (see clinical pharmacology section), only the IV route of administration can be authorised under this MA procedure (see SmPC section 4.2.). Medication errors due to subcutaneous administration have been classified as important identified risk in the RMP (see clinical safety).

2.5.4. Conclusions on the clinical efficacy

The pivotal study met its primary endpoint indicating similarity in term of efficacy between candidate biosimilar and the reference product. The provided sensitivity analyses supported the primary endpoint results. A trend in favour of HLX02 was observed in the primary endpoint and ORR at week 33, 42 assessed by the investigators. However, no significant difference was found between two treatment groups in terms of median DoR, PFS and OS in the second interim analysis despite of the immature data, partly supporting the primary results.

In conclusion, clinical efficacy between HLX02 and Herceptin is considered to be similar.

2.6. Clinical safety

Patient exposure

In the two trials which provided clinical safety data, the Phase II HLX02-HV01 and the Phase III HLX02-BC01 (hereafter referred to as HV01 and BC01 respectively), a total of 772 subjects were exposed at least once to

HLX02 or Herceptin (US- and EU-sourced in case of the HV01 trial, EU-sourced in case of the BC01 study). This translates to 373 patients having received HLX02, 37 having received US-sourced Herceptin and 362 having received EU-sourced Herceptin.

In part 1 of the HV01 trial, 12 patients received doses of 2, 4, 6, and 8 mg/kg HLX02 (3 subjects per dose level) and in part 2, subjects were exposed as follows: 37 received HLX02, 37 received US-sourced Herceptin and 37 received EU-sourced Herceptin.

All subjects whom had received at least one administration of investigational medicinal product (IMP) or comparator were included in the respective HV01 part1, HV02 part2 and BC01 safety sets.

All patients in the both HV01 safety sets were of Chinese ethnicity, male and between 18 and 45 years of age. In contrast, all patients in the BC01 trial were of female gender, with ages ranging from 26 to 76 years of age (mean age = 50 y.o.a.) and 72,9% were of Chinese ethnicity, 4,0% of Non-Chinese Asian ethnicity and 23,1% of Caucasian ethnicity.

In the BC01 trial, as of 23 November 2018, both treatment groups (HLX02 and EU-Herceptin) underwent about the same mean number of treatment cycles, but the HLX02 group had a higher mean total exposure (238.4 days versus 228.8 days in the Herceptin group) and consequently a higher cumulative dose exposure (median 4550.5 mg versus 4200.0 mg respectively).

By the second interim analysis (data cut-off date as of 10 July 2019), in the 649 SAS population (324 patients received HLX02 and 325 received Herceptin), the median number of cycles completed by patients was similar in the HLX02 treatment group (15) and the Herceptin treatment group (14). The total drug exposure duration of HLX02 group and Herceptin group was 264.6 (114.76) days and 253.4 (114.29) days.

Overall and relative dose intensity were similar in both the treatment groups. The median cumulative dose of the study medication was 5488.5 mg (for HLX02) and 4945.0 mg (for Herceptin) treatment groups, respectively. Dose reduction was reported in 1 patient in Herceptin treatment group. Dose delay was reported in 55 patients in HLX02 treatment group and 46 patients in Herceptin treatment group. Dose interruption was reported in a total of 21 and 16 patients from the HLX02 and Herceptin treatment groups, respectively.

Table 64: Exposure to Study Treatment -Overall (Safety Analysis Set) in Study HLX02-BC01 (DCO 10 July 2019)

Characteristic	HLX02 N=324	Herceptin N=325	Total N=649
Number of cycle completed			
n (missing)	324(0)	325(0)	649(0)
Mean (SD)	12.4(5.43)	11.8(5.38)	12.1(5.41)
Median	15.0	14.0	14.0
Q1, Q3	8.0, 17.0	7.0, 17.0	8.0, 17.0
Min, Max	1, 17	1, 17	1, 17
Number of cycle has completed N, n(%)			
Cycle 1	9 (2.8)	3 (0.9)	12 (1.8)
Cycle 2	20 (6.2)	21 (6.5)	41 (6.3)
Cycle 3	3 (0.9)	4 (1.2)	7 (1.1)
Cycle 4	13 (4.0)	20 (6.2)	33 (5.1)
Cycle 5	5 (1.5)	5 (1.5)	10 (1.5)
Cycle 6	17 (5.2)	24 (7.4)	41 (6.3)
Cycle 7	3 (0.9)	6 (1.8)	9 (1.4)
Cycle 8	19 (5.9)	21 (6.5)	40 (6.2)
Cycle 9	8 (2.5)	7 (2.2)	15 (2.3)
Cycle 10	8 (2.5)	8 (2.5)	16 (2.5)
Cycle 11	23 (7.1)	33 (10.2)	56 (8.6)
Cycle 12	5 (1.5)	7 (2.2)	12 (1.8)
Cycle 13	9 (2.8)	3 (0.9)	12 (1.8)
Cycle 14	18 (5.6)	18 (5.5)	36 (5.5)
Cycle 15	5 (1.5)	5 (1.5)	10 (1.5)
Cycle 16	4 (1.2)	2 (0.6)	6 (0.9)
Cycle 17	155 (47.8)	138 (42.5)	293 (45.1)
Total exposure duration (days)			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	264.6 (114.76)	253.4 (114.29)	259.0 (114.57)
Median	312.0	292.0	297.0
Q1, Q3	171.5, 358.0	165.0, 358.0	169.0, 358.0
Min, Max	21, 408	21, 417	21, 417
Injection times			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	12.4 (5.43)	11.8 (5.38)	12.1 (5.41)
Median	15.0	14.0	14.0
Q1, Q3	8.0, 17.0	7.0, 17.0	8.0, 17.0
Min, Max	1, 17	1, 17	1, 17
Total exposure intensity (mg/day)			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	19.12 (3.811)	18.78 (3.768)	18.95 (3.791)
Median	18.39	18.11	18.23
Q1, Q3	16.42, 21.13	16.27, 20.47	16.35, 20.77
Min, Max	12.2, 33.9	11.1, 37.1	11.1, 37.1

Characteristic	HLX02 N=324	Herceptin N=325	Total N=649
Relative dose intensity			
n (missing)	324 (0)	325 (0)	649 (0)
Mean (SD)	99.95 (0.661)	100.01 (1.099)	99.98 (0.907)
Median	100.00	100.00	100.00
Q1, Q3	100.00, 100.00	100.00, 100.00	100.00, 100.00
Min, Max	93.3, 103.0	88.9, 110.8	88.9, 110.8
Dose reduced of IP, n (%)	0	1 (0.3)	1 (0.2)
Dose delayed of IP, n (%)	55 (17.0)	46 (14.2)	101 (15.6)
Dose interrupted of IP, n (%)	21 (6.5)	16 (4.9)	37 (5.7)

Source: Table 12-1, Listing 16.2.5.1.1.1, Table 14.1.10.1 and Table 14.1.10.4 of HLX02-BC01 CSR
- Percentages were based on the number of patients in the safety set. Subgroup percentages were based on the number of patients in the subgroup safety set.
- Investigational Product: HLX02 or Herceptin.
- Total exposure duration (days) = last study drug date – first study drug date + 21.
- Actual dose intensity = Actual total dose/ Total exposure duration (days)
- Planned dose intensity = Planned total dose/ Total exposure duration (days)
- Relative Dose Intensity (RDI) = (Actual dose intensity)/(Planned dose intensity)×100

Adverse events

Adverse event classification was done in a standard way and utilised MEdDRA v18.0 (HV01)/MEdDRA v21.1 (BC01) and CTCAE v4.03.

Adverse events of special interest (AESI) were defined as being IRR (Infusion-related reactions) and cardiac toxicities in both studies HV01 and BC01, and additionally allergic-like reactions/hypersensitivity and haematological events in study BC01.

Study HV01

HV01-Part 1:

Across the 4 treatment groups, a total of 8 subjects (66.7%) experienced AEs/TEAEs: 2 subjects in the 2 mg/kg group (66.7%), 3 subjects in the 4 mg/kg group (100.0%), 1 subject in the 6 mg/kg group (33.3%), and 2 subjects in the 8 mg/kg (66.7%).

Table 65: Overview of adverse events (Safety set 1) in study HLX02-HV01

Category	2mg/kg (N=3) n (%)	4mg/kg (N=3) n (%)	6mg/kg (N=3) n (%)	8mg/kg (N=3) n (%)	Total (N=12) n (%)
AE	2 (66.7)	3 (100.0)	1 (33.3)	2 (66.7)	8 (66.7)
TEAE	2 (66.7)	3 (100.0)	1 (33.3)	2 (66.7)	8 (66.7)
AE leading to discontinuation	0	0	0	0	0
TEAE leading to discontinuation	0	0	0	0	0
SAE	0	0	0	0	0
TESAE	0	0	0	0	0
TEAE leading to death	0	0	0	0	0
ADR [1]	2 (66.7)	3 (100.0)	0	2 (66.7)	7 (58.3)
Death	0	0	0	0	0

Source: Table 12-1 of HLX02-HV01 CSR

Note: TE=Treatment Emergent; AE=Adverse Event; SAE=Serious Adverse Event; TESAE=Treatment Emergent Serious Adverse Event ADR=Adverse Drug Reaction; N = number of subjects in the analysis population; n = number of subjects in the specified category.
[1] ADR is defined as TEAE with probable, possible or not assessable/unclassifiable relationship with study medication. An adverse event is considered treatment-emergent if it first occurs or worsens following the start of treatment from the time of injection to the end of study (day 57 ± 1 day).

The most common TEAEs were in the Investigations system organ class (SOC), with 6 events in total.

Table 66: All Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set 1) in study HLX02-HV01

System Organ Class Preferred term	2mg/kg (N=3) n (%)	4mg/kg (N=3) n (%)	6mg/kg (N=3) n (%)	8mg/kg (N=3) n (%)	Total (N=12) n (%)
Subject with at least one TEAE	**2 (66.7)**	**3 (100.0)**	**1 (33.3)**	**2 (66.7)**	**8 (66.7)**
Cardiac disorders	1 (33.3)	0	0	1 (33.3)	2 (16.7)
Dilatation ventricular	1 (33.3)	0	0	0	1 (8.3)
Left atrial dilatation	0	0	0	1 (33.3)	1 (8.3)
General disorders and administration site conditions	0	2 (66.7)	0	0	2 (16.7)
Asthenia	0	2 (66.7)	0	0	2 (16.7)
Investigations	2 (66.7)	2 (66.7)	1 (33.3)	1 (33.3)	6 (50.0)
Alanine aminotransferase increased	0	1 (33.3)	0	1 (33.3)	2 (16.7)
Aspartate aminotransferase increased	0	0	0	1 (33.3)	1 (8.3)
Blood bilirubin increased	1 (33.3)	0	0	0	1 (8.3)
Blood triglycerides increased	0	0	1 (33.3)	0	1 (8.3)
Ejection fraction decreased	1 (33.3)	0	0	0	1 (8.3)
Globulins decreased	0	1 (33.3)	0	0	1 (8.3)
Nervous system disorders	0	3 (100.0)	0	0	3 (25.0)
Dizziness	0	2 (66.7)	0	0	2 (16.7)
Somnolence	0	2 (66.7)	0	0	2 (16.7)
Respiratory, thoracic and mediastinal disorders	0	1 (33.3)	0	0	1 (8.3)
Cough	0	1 (33.3)	0	0	1 (8.3)

Source: Table 12-2 of HLX02-HV01 CSR

Note: TEAE=Treatment Emergent Adverse Event; N = number of subjects in the analysis population; n = number of subjects in the specified category. An adverse event is considered treatment-emergent if it first occurs or worsens following the start of treatment from the time of injection to the end of study (day 57 ± 1 day). Based on MedDRA version 18.0. Percentage is based on number of subjects in each group, not number of events. Sorted in descending order of incidence by system organ class and preferred term.

Six subjects (50%) experienced TEAEs of mild severity (1 subject from the 2 mg/kg group, 3 subjects from the 4 mg/kg group, 1 subject from the 6 mg/kg group, and 1 subject from the 8 mg/kg group). Overall, at least 1 TEAE of moderate severity was reported for 2 subjects (16.7%), 1 subject each in the 2 mg/kg group and 8 mg/kg group.No AEs with CTCAE Grade ≥4 haematological toxicity, Grade ≥3 non-haematological toxicity (including IRRs) or serious unexpected AEs were reported.

AEs of special interest

AEs of special interest included IRR and cardiac toxicity. A total of 2 subjects experienced at least one TEAE of special interest associated with cardiac toxicity: 1 subject (33.3%) in the 2 mg/kg group experienced dilatation ventricular (mild in severity) and ejection fraction decreased (moderate in severity), and one subject (33.3%) in the 8 mg/kg group experienced left atrial dilatation (mild in severity). No TEAEs of special interest associated with IRR were reported.

ADRs

An ADR was defined as a TEAE with a probable, possible, or not assessable/unclassifiable relationship with study drug.

Table 67: Summary of all Drug Related Treatment-Emergent Adverse Events (ADR) by System Organ Class and Preferred Term (Safety Set 1) in study HLX02-HV01

System Organ Class Preferred Term	2mg/kg (N=3) n (%)	4mg/kg (N=3) n (%)	6mg/kg (N=3) n (%)	8mg/kg (N=3) n (%)	Total (N=12) n (%)
Subject with at least one TEAE	2 (66.7)	3 (100.0)	0	2 (66.7)	7 (58.3)
Cardiac disorders	1 (33.3)	0	0	1 (33.3)	2 (16.7)
Dilatation ventricular	1 (33.3)	0	0	0	1 (8.3)
Left atrial dilatation	0	0	0	1 (33.3)	1 (8.3)
General disorders and administration site conditions	0	2 (66.7)	0	0	2 (16.7)
Asthenia	0	2 (66.7)	0	0	2 (16.7)
Investigations	2 (66.7)	2 (66.7)	0	1 (33.3)	5 (41.7)
Alanine aminotransferase increased	0	1 (33.3)	0	1 (33.3)	2 (16.7)
Aspartate aminotransferase increased	0	0	0	1 (33.3)	1 (8.3)
Blood bilirubin increased	1 (33.3)	0	0	0	1 (8.3)
Ejection fraction decreased	1 (33.3)	0	0	0	1 (8.3)
Globulins decreased	0	1 (33.3)	0	0	1 (8.3)
Nervous system disorders	0	3 (100.0)	0	0	3 (25.0)
Dizziness	0	2 (66.7)	0	0	2 (16.7)
Somnolence	0	2 (66.7)	0	0	2 (16.7)

Source: Table 12-5 of HLX02-HV01 CSR
Note: TEAE=Treatment Emergent Adverse Event; N = number of subjects in the analysis population; n = number of subjects in the specified category. An adverse event is considered treatment-emergent if it first occurs or worsens following the start of treatment from the time of injection to the end of study (day 57 ± 1 day). Based on MedDRA version 18.0. Percentage is based on number of subjects in each group, not number of events. Sorted in descending order of incidence by system organ class and preferred term. Drug Related Treatment-Emergent Adverse is defined as TEAE with Probable, Possible or Not assessable/unclassifiable relationship with study medication

Phase 1 HLX02-HV01-Part 2:

Across the 3 treatment groups, 86 subjects (77.5%) experienced a total of 283 AEs/276 TEAEs. Of these, 28 subjects (75.7%) in the HLX02 group experienced 94 AEs/94 TEAEs, 32 subjects (86.5%) in the CN-sourced Herceptin group experienced 107 AEs/103 TEAEs, and 26 subjects (70.3%) in the EU-sourced Herceptin group experienced 82 AEs/79 TEAEs. A higher percentage of subjects in the CN-sourced Herceptin group had at least one TEAE compared with the HLX02 group and the EU-sourced Herceptin group. No deaths or SAEs were reported. No subjects were discontinued due to TEAEs.

Table 68: Overview of adverse events (Safety set 2) in study HLX02-HV01

Category	HLX02 (N=37) n (%), Event	CN-sourced Herceptin (N=37) n (%), Event	EU-sourced Herceptin (N=37) n (%), Event	Total (N=111) n (%), Event
AE	28 (75.7), 94	32 (86.5), 107	26 (70.3), 82	86 (77.5), 283
TEAE	28 (75.7), 94	32 (86.5), 103	26 (70.3), 79	86 (77.5), 276
AE leading to discontinuation	0	0	0	0
TEAE leading to discontinuation	0	0	0	0
SAE	0	0	0	0
TESAE	0	0	0	0
TEAE leading to death	0	0	0	0
ADR [1]	27 (73.0), 76	27 (73.0), 83	18 (48.6), 44	72 (64.9), 203
Death	0	0	0	0

Source: Table 12-7 of HLX02-HV01 CSR

Note: TE=Treatment Emergent; AE=Adverse Event; SAE=Serious Adverse Event; TESAE=Treatment Emergent Serious Adverse Event; ADR=Adverse Drug Reaction; N = number of subjects in the analysis population; n = number of subjects in the specified category.

[1] ADR is defined as TEAE with probable, possible or not assessable/unclassifiable relationship with study medication. An adverse event is considered treatment-emergent if it first occurs or worsens following the start of treatment from the time of injection to the end of study (day 57 ± 1 day.)

In the overall 3 treatment groups, the most frequently reported TEAEs by PT (≥5% of subjects) were ALT increased, blood triglycerides increased (27.9% each), AST increased (23.4%), neutrophil count increased, white blood cell count increased (16.2% each), N-terminal prohormone brain natriuretic peptide increased (9.0%), gamma-glutamyltransferase increased, white blood cells urine positive (7.2% each), blood bilirubin increased, blood glucose increased, and glucose urine present (5.4% each).

The following TEAEs were reported at a ≥10% frequency in the HLX02 group compared with the CN-sourced Herceptin group and the EU-sourced Herceptin group: neutrophil count increased (27.0% versus 16.2% and 5.4%), white blood cell count increased (27.0% versus 16.2% and 5.4%), ALT increased (24.3% versus 37.8% and 21.6%), blood triglycerides increased (21.6% versus 29.7% and 32.4%), AST increased (18.9% versus 29.7% and 21.6%), and N-terminal prohormone brain natriuretic peptide increased (10.8% versus 8.1% and 8.1%).

In the overall 3 treatment groups, the most frequently reported TEAEs by SOC were investigations (69.4%), general disorders and administration site conditions and gastrointestinal disorders (4.5% each), and cardiac

disorders and skin and subcutaneous tissue disorders (3.6% each). In the HLX02 group, the most frequently reported TEAEs by SOC were investigations (73.0%) and gastrointestinal disorders (5.4%); in the CN-sourced Herceptin group, the most frequently reported TEAEs by SOC were investigations (70.3%), gastrointestinal disorders (5.4%), and general disorders and administration site conditions (5.4%); in the EU-Sourced Herceptin group, the most frequently reported TEAEs by SOC were investigations (64.9%), cardiac disorders (5.4%), general disorders and administration site conditions (5.4%), and skin and subcutaneous tissue disorders (5.4%).

Table 69: All Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Set 2) in study HLX02-HV01

System Organ Class Preferred Term	HLX02 (N=37) n (%)	CN-sourced Herceptin (N=37) n (%)	EU-sourced Herceptin (N=37) n (%)	Total (N=111) n (%)
Subject with at least one TEAE	**28 (75.7)**	**32 (86.5)**	**26 (70.3)**	**86 (77.5)**
Blood and lymphatic system disorders	1 (2.7)	1 (2.7)	0	2 (1.8)
Anaemia	1 (2.7)	0	0	1 (0.9)
Neutropenia	0	1 (2.7)	0	1 (0.9)
Thrombocytopenia	0	1 (2.7)	0	1 (0.9)
Cardiac disorders	1 (2.7)	1 (2.7)	2 (5.4)	4 (3.6)
Left atrial dilatation	1 (2.7)	0	0	1 (0.9)
Palpitations	0	0	1 (2.7)	1 (0.9)
Sinus bradycardia	0	1 (2.7)	0	1 (0.9)
Tricuspid valve incompetence	0	0	1 (2.7)	1 (0.9)
Eye disorders	1 (2.7)	0	1 (2.7)	2 (1.8)
Conjunctival haemorrhage	0	0	1 (2.7)	1 (0.9)
Eye pain	1 (2.7)	0	0	1 (0.9)
Gastrointestinal disorders	2 (5.4)	2 (5.4)	1 (2.7)	5 (4.5)
Diarrhoea	1 (2.7)	2 (5.4)	1 (2.7)	4 (3.6)
Nausea	1 (2.7)	0	0	1 (0.9)
Vomiting	1 (2.7)	0	0	1 (0.9)
General disorders and administration site conditions	1 (2.7)	2 (5.4)	2 (5.4)	5 (4.5)
Chills	1 (2.7)	1 (2.7)	0	2 (1.8)
Pyrexia	0	1 (2.7)	1 (2.7)	2 (1.8)
Chest discomfort	0	0	1 (2.7)	1 (0.9)
Temperature intolerance	0	1 (2.7)	0	1 (0.9)
Infections and infestations	0	1 (2.7)	0	1 (0.9)
Otitis media acute	0	1 (2.7)	0	1 (0.9)
Investigations	27 (73.0)	26 (70.3)	24 (64.9)	77 (69.4)
Alanine aminotransferase increased	9 (24.3)	14 (37.8)	8 (21.6)	31 (27.9)
Blood triglycerides increased	8 (21.6)	11 (29.7)	12 (32.4)	31 (27.9)
Aspartate aminotransferase increased	7 (18.9)	11 (29.7)	8 (21.6)	26 (23.4)
Neutrophil count increased	10 (27.0)	6 (16.2)	2 (5.4)	18 (16.2)
White blood cell count increased	10 (27.0)	6 (16.2)	2 (5.4)	18 (16.2)
N-terminal prohormone brain natriuretic peptide increased	4 (10.8)	3 (8.1)	3 (8.1)	10 (9.0)
Gamma-glutamyltransferase increased	3 (8.1)	4 (10.8)	1 (2.7)	8 (7.2)
White blood cells urine positive	2 (5.4)	2 (5.4)	4 (10.8)	8 (7.2)
Blood bilirubin increased	3 (8.1)	3 (8.1)	0	6 (5.4)

Investigations(continued)	27 (73.0)	26 (70.3)	24 (64.9)	77 (69.4)
Blood glucose increased	3 (8.1)	2 (5.4)	1 (2.7)	6 (5.4)
Glucose urine present	2 (5.4)	0	4 (10.8)	6 (5.4)
Electrocardiogram T wave amplitude decreased	3 (8.1)	1 (2.7)	1 (2.7)	5 (4.5)
Globulins decreased	3 (8.1)	1 (2.7)	0	4 (3.6)
Blood creatine phosphokinase increased	2 (5.4)	0	1 (2.7)	3 (2.7)
Haemoglobin increased	1 (2.7)	1 (2.7)	1 (2.7)	3 (2.7)
Urine leukocyte esterase positive	0	1 (2.7)	2 (5.4)	3 (2.7)
Electrocardiogram QT prolonged	0	1 (2.7)	1 (2.7)	2 (1.8)
Electrocardiogram T wave amplitude increased	1 (2.7)	1 (2.7)	0	2 (1.8)
Electrocardiogram T wave inversion	2 (5.4)	0	0	2 (1.8)
Electrocardiogram abnormal	0	1 (2.7)	1 (2.7)	2 (1.8)
Lymphocyte count decreased	0	1 (2.7)	1 (2.7)	2 (1.8)
Lymphocyte percentage decreased	0	1 (2.7)	1 (2.7)	2 (1.8)
Mononuclear cell count abnormal	0	2 (5.4)	0	2 (1.8)
Neutrophil count decreased	0	1 (2.7)	1 (2.7)	2 (1.8)
Protein urine present	0	0	2 (5.4)	2 (1.8)
Red blood cells urine positive	1 (2.7)	0	1 (2.7)	2 (1.8)
Bacterial test positive	0	0	1 (2.7)	1 (0.9)
Blood alkaline phosphatase increased	1 (2.7)	0	0	1 (0.9)
Blood urine present	0	0	1 (2.7)	1 (0.9)
Crystal urine present	0	0	1 (2.7)	1 (0.9)
Lymphocyte count increased	0	0	1 (2.7)	1 (0.9)
Mean platelet volume increased	0	1 (2.7)	0	1 (0.9)
White blood cell count decreased	0	1 (2.7)	0	1 (0.9)
Metabolism and nutrition disorders	1 (2.7)	0	0	1 (0.9)
Hyperkalaemia	1 (2.7)	0	0	1 (0.9)
Musculoskeletal and connective tissue disorders	1 (2.7)	0	0	1 (0.9)
Myalgia	1 (2.7)	0	0	1 (0.9)
Nervous system disorders	0	1 (2.7)	0	1 (0.9)
Headache	0	1 (2.7)	0	1 (0.9)
Renal and urinary disorders	1 (2.7)	0	1 (2.7)	2 (1.8)
Haematuria	1 (2.7)	0	1 (2.7)	2 (1.8)
Skin and subcutaneous tissue disorders	1 (2.7)	1 (2.7)	2 (5.4)	4 (3.6)
Dermatitis	0	1 (2.7)	0	1 (0.9)
Eczema	1 (2.7)	0	0	1 (0.9)
Pruritus	0	0	1 (2.7)	1 (0.9)
Rash	0	0	1 (2.7)	1 (0.9)

Source: Table 12-8 of HLX02-HV01 CSR
Note: TEAE=Treatment Emergent Adverse Event; N = number of Subjects in the analysis population;
n = number of Subjects in the specified category.
Percentage is based on the number of subjects in the analysis population.
An adverse event is considered as treatment-emergent if it first occurs or worsens following the start of treatment from the time of injection to the end of study (day 57 ± 1 day).
Based on MedDRA version 18.0. Sorted alphabetically for SOC and by descending frequency at PT level within SOC.

Most TEAEs in each treatment group were mild (56.8% in the HLX02 group, 59.5% in the CN-sourced Herceptin group, and 48.6% in the EU-sourced Herceptin group, respectively) or moderate (18.9% in the HLX02 group, 18.9% in the CN-sourced Herceptin group, and 21.6% in the EU-sourced Herceptin group, respectively). Three subjects in the CN-sourced Herceptin group experienced at least 1 severe TEAE; no severe TEAEs were reported in the other 2 groups.

No AEs with CTCAE Grade ≥4 hematological toxicity or serious unexpected AEs were reported. A total of 5 subjects (4.5%) experienced at least one AE of CTCAE Grade ≥3 non-hematological toxicity (including IRRs; 2 subjects experienced IRRs: 1 subject in CN-sourced Herceptin group and 1 subject in EU-sourced Herceptin group): 4 subjects (10.8%) in the CN-sourced Herceptin group and 1 subject (2.7%) in the EU-sourced Herceptin group.

TEAEs of special interest

A total of 25 subjects (22.5%) experienced at least 1 TEAE of special interest. Similar results were seen in the HLX02 group (9 subjects, 24.3%), the CN-sourced Herceptin group (8 subjects, 21.6%), and the EU-sourced Herceptin group (8 subjects, 21.6%).

In the overall 3 treatment groups, the most frequently reported TEAEs of special interest associated with cardiac toxicity (>2.0%) were N-terminal prohormone brain natriuretic peptide increased (10 subjects, 9.0%) and electrocardiogram T wave amplitude decreased (5 subjects, 4.5%), followed by all other TEAEs of special interest related with cardiac toxicity with a frequency of less than 2.0%. The TEAEs of special interest related with IRR were chill and pyrexia (2 subjects each, 1.8%).

ADRs

Table 70: Summary of all Drug Related Treatment-Emergent Adverse Events (ADR) by System Organ Class and Preferred Term (Safety Set 2) in study HLX02-HV01

System Organ Class Preferred Term	HLX02 (N=37) n (%)	CN-sourced Herceptin (N=37) n (%)	EU-sourced Herceptin (N=37) n (%)	Total (N=111) n (%)
Subject with at least one TEAE	**27 (73.0)**	**27 (73.0)**	**18 (48.6)**	**72 (64.9)**
Blood and lymphatic system disorders	1 (2.7)	1 (2.7)	0	2 (1.8)
Anaemia	1 (2.7)	0	0	1 (0.9)
Neutropenia	0	1 (2.7)	0	1 (0.9)
Thrombocytopenia	0	1 (2.7)	0	1 (0.9)
Cardiac disorders	1 (2.7)	0	2 (5.4)	3 (2.7)
Left atrial dilatation	1 (2.7)	0	0	1 (0.9)
Palpitations	0	0	1 (2.7)	1 (0.9)
Tricuspid valve incompetence	0	0	1 (2.7)	1 (0.9)
Eye disorders	1 (2.7)	0	0	1 (0.9)
Eye pain	1 (2.7)	0	0	1 (0.9)
Gastrointestinal disorders	2 (5.4)	2 (5.4)	1 (2.7)	5 (4.5)
Diarrhoea	1 (2.7)	2 (5.4)	1 (2.7)	4 (3.6)
Nausea	1 (2.7)	0	0	1 (0.9)
Vomiting	1 (2.7)	0	0	1 (0.9)
General disorders and administration site conditions	1 (2.7)	2 (5.4)	2 (5.4)	5 (4.5)
Chills	1 (2.7)	1 (2.7)	0	2 (1.8)
Pyrexia	0	1 (2.7)	1 (2.7)	2 (1.8)
Chest discomfort	0	0	1 (2.7)	1 (0.9)
Temperature intolerance	0	1 (2.7)	0	1 (0.9)
Investigations	24 (64.9)	23 (62.2)	15 (40.5)	62 (55.9)
Alanine aminotransferase increased	9 (24.3)	14 (37.8)	8 (21.6)	31 (27.9)
Aspartate aminotransferase increased	7 (18.9)	11 (29.7)	8 (21.6)	26 (23.4)
Neutrophil count increased	10 (27.0)	5 (13.5)	2 (5.4)	17 (15.3)
White blood cell count increased	10 (27.0)	5 (13.5)	2 (5.4)	17 (15.3)
N-terminal prohormone brain natriuretic peptide increased	4 (10.8)	3 (8.1)	3 (8.1)	10 (9.0)
Gamma-glutamyltransferase increased	3 (8.1)	4 (10.8)	1 (2.7)	8 (7.2)
Blood bilirubin increased	3 (8.1)	3 (8.1)	0	6 (5.4)
Blood triglycerides increased	1 (2.7)	4 (10.8)	0	5 (4.5)

Electrocardiogram T wave amplitude decreased	3 (8.1)	1 (2.7)	1 (2.7)	5 (4.5)
Globulins decreased	3 (8.1)	1 (2.7)	0	4 (3.6)
Blood creatine phosphokinase increased	2 (5.4)	0	1 (2.7)	3 (2.7)
Haemoglobin increased	1 (2.7)	1 (2.7)	1 (2.7)	3 (2.7)
Blood glucose increased	1 (2.7)	1 (2.7)	0	2 (1.8)
Electrocardiogram QT prolonged	0	1 (2.7)	1 (2.7)	2 (1.8)
Electrocardiogram T wave amplitude increased	1 (2.7)	1 (2.7)	0	2 (1.8)
Electrocardiogram T wave inversion	2 (5.4)	0	0	2 (1.8)
Electrocardiogram abnormal	0	1 (2.7)	1 (2.7)	2 (1.8)
Glucose urine present	0	0	2 (5.4)	2 (1.8)
Lymphocyte count decreased	0	1 (2.7)	1 (2.7)	2 (1.8)
Mononuclear cell count abnormal	0	2 (5.4)	0	2 (1.8)
Neutrophil count decreased	0	1 (2.7)	1 (2.7)	2 (1.8)
Mean platelet volume increased	0	1 (2.7)	0	1 (0.9)
White blood cell count decreased	0	1 (2.7)	0	1 (0.9)
Metabolism and nutrition disorders	1 (2.7)	0	0	1 (0.9)
Hyperkalaemia	1 (2.7)	0	0	1 (0.9)
Musculoskeletal and connective tissue disorders	1 (2.7)	0	0	1 (0.9)
Myalgia	1 (2.7)	0	0	1 (0.9)
Nervous system disorders	0	1 (2.7)	0	1 (0.9)
Headache	0	1 (2.7)	0	1 (0.9)
Renal and urinary disorders	1 (2.7)	0	1 (2.7)	2 (1.8)
Haematuria	1 (2.7)	0	1 (2.7)	2 (1.8)
Skin and subcutaneous tissue disorders	1 (2.7)	1 (2.7)	1 (2.7)	3 (2.7)
Dermatitis	0	1 (2.7)	0	1 (0.9)
Eczema	1 (2.7)	0	0	1 (0.9)
Rash	0	0	1 (2.7)	1 (0.9)

Source: Table 12-14 of HLX02-HV01 CSR
Note: TEAE=Treatment Emergent Adverse Event; N = number of Subjects in the analysis population; n = number of Subjects in the specified category.
Percentage is based on the number of subjects in the analysis population.
An adverse event is considered as treatment-emergent if it first occurs or worsens following the start of treatment from the time of injection to the end of study (day 57 ± 1 day).
Based on MedDRA version 18.0.
Sorted alphabetically for SOC and by descending frequency at PT level within SOC.

Study BC01

Of the 649 patients in the study, 641 (98.8%) patients were reported at least one AE (HLX02: 320 of 324 [98.8%] patients; Herceptin: 321 of 325 [98.8%]). All of these patients also reported TEAEs. A similar number of AEs (HLX02=6975 vs Herceptin=7144) and TEAEs (HLX02=6828 and Herceptin=7002) were reported in the 2 treatment groups. There were similar number of pre-treatment AEs reported in both the treatment groups.

Table 71: Summary of All Adverse Events – Overall (Safety Analysis Set) in Study HLX02-BC01

Number of patients experiencing	HLX02 N=324 n (%) E	Herceptin N=325 n (%) E	Total N=649 n (%) E
No adverse event	4 (1.2)	4 (1.2)	8 (1.2)
Any adverse events (AEs)	320 (98.8) 6975	321 (98.8) 7144	641 (98.8) 14119
Pre-treatment AEs	62 (19.1) 131	66 (20.3) 124	128 (19.7) 255
Treatment emergent adverse events (TEAEs)	320 (98.8) 6828	321 (98.8) 7002	641 (98.8) 13830
Severity			
Grade 1	3 (0.9) 3065	7 (2.2) 3230	10 (1.5) 6295
Grade 2	39 (12.0) 1872	33 (10.2) 1992	72 (11.1) 3864
Grade 3	84 (25.9) 1245	95 (29.2) 1201	179 (27.6) 2446
Grade 4	191 (59.0) 643	180 (55.4) 571	371 (57.2) 1214
Grade 5	3 (0.9) 3	6 (1.8) 8	9 (1.4) 11
TEAE Relationship with IP			
Related	236 (72.8) 2295	233 (71.7) 2547	469 (72.3) 4842
Not related	84 (25.9) 4533	88 (27.1) 4455	172 (26.5) 8988
TEAE Relationship with Non-IP			
Related	314 (96.9) 5515	320 (98.5) 5721	634 (97.7) 11236
Not related	6 (1.9) 1313	1 (0.3) 1281	7 (1.1) 2594
Adverse events of special interest (AESI)	260 (80.2) 3059	258 (79.4) 2875	518 (79.8) 5934
TEAEs of special interest	260 (80.2) 3045	258 (79.4) 2864	518 (79.8) 5909
Severity			
Grade 1	10 (3.1) 716	9 (2.8) 695	19 (2.9) 1411
Grade 2	22 (6.8) 856	31 (9.5) 877	53 (8.2) 1733
Grade 3	53 (16.4) 914	62 (19.1) 816	115 (17.7) 1730
Grade 4	175 (54.0) 559	156 (48.0) 476	331 (51.0) 1035
Relationship with IP			
Related	142 (43.8) 997	136 (41.8) 986	278 (42.8) 1983
Not related	118 (36.4) 2048	122 (37.5) 1878	240 (37.0) 3926
Relationship with Non-IP			
Related	249 (76.9) 2909	252 (77.5) 2738	501 (77.2) 5647
Not related	11 (3.4) 136	6 (1.8) 126	17 (2.6) 262

Treatment emergent adverse events (TEAEs)			
Dose Changed	30 (9.3) 32	29 (8.9) 29	59 (9.1) 61
TEAEs leading to IP Drug Interrupted	20 (6.2) 20	18 (5.5) 18	38 (5.9) 38
TEAEs leading to IP Drug Withdrawn	10 (3.1) 12	11 (3.4) 11	21 (3.2) 23
Dose not changed	314 (96.9) 6384	319 (98.2) 6594	633 (97.5) 12978
Not applicable	142 (43.8) 405	147 (45.2) 367	289 (44.5) 772
Unknown	3 (0.9) 7	6 (1.8) 11	9 (1.4) 18

Number of patients experiencing	HLX02 N=324 n (%) E	Herceptin N=325 n (%) E	Total N=649 n (%) E
Serious adverse events (SAEs)	78 (24.1) 166	82 (25.2) 145	160 (24.7) 311
Serious TEAEs	77 (23.8) 163	81 (24.9) 143	158 (24.3) 306
Severity			
Grade 1	0 (0.0) 3	1 (0.3) 4	1 (0.2) 7
Grade 2	12 (3.7) 27	7 (2.2) 14	19 (2.9) 41
Grade 3	22 (6.8) 53	31 (9.5) 57	53 (8.2) 110
Grade 4	40 (12.3) 77	36 (11.1) 60	76 (11.7) 137
Grade 5	3 (0.9) 3	6 (1.8) 8	9 (1.4) 11
Relationship with IP			
Related	32 (9.9) 71	31 (9.5) 55	63 (9.7) 126
Not related	45 (13.9) 92	50 (15.4) 88	95 (14.6) 180
Relationship with Non-IP			
Related	63 (19.4) 137	62 (19.1) 117	125 (19.3) 254
Not related	14 (4.3) 26	19 (5.8) 26	33 (5.1) 52
Death	3 (0.9) 3	6 (1.8) 8	9 (1.4) 11

Source: Table 12-3 and Listing 16.2.7.1.1 of HLX02-BC01 CSR
- E: Frequency of adverse events.
- Adverse events were coded to system organ class and preferred term using the MedDRA Version 21.1 coding dictionary.
- Severity assessment was done in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) V4.03.
- Percentages were based on the number of patients in the safety set.
- If a patient had multiple events of the same severity or relationship, then they were counted only once in that severity or relationship. If a patient had multiple events with different severity or relationship, then the patient was counted only once for more severe adverse event or related adverse event.
- Patients with missing severity or relationship were counted for both categories with maximum severity or relationship and missing category.
- IP: Investigational Product (HLX02 or Herceptin); Non-IP: Non-Investigational Product (Docetaxel).
-Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first administration date of study medication and no later than 30 (+2) days after the last administration date on study of study medication

Similar incidence of TEAEs was noted for total Asian (99.0%) and non-Asian (98.0%) populations, as well as for Chinese (98.9%), and non-Chinese (98.3%). The two treatment groups within the Asian and non-Asian populations, and within the Chinese and non-Chinese populations had similar incidence of the TEAEs.

The most commonly reported SOCs were investigations (HLX02: 299 [92.3%] patients; Herceptin: 303 [93.2%] patients); skin and subcutaneous tissue disorders (HLX02: 208 [64.2%] patients; Herceptin: 204 [62.8%]

patients); and blood and lymphatic system disorders (HLX02: 182 [56.2%] patients; Herceptin: 205 [63.1%] patients).

The most commonly reported TEAEs by PT were WBC decreased (HLX02: 267 [82.4%] patients; Herceptin: 276 [84.9%]), neutrophil count decreased (HLX02: 266 [82.1%] patients; Herceptin: 268 [82.5%]), alopecia (HLX02: 180 [55.6%] patients; Herceptin:174 [53.5%] patients) and anaemia (HLX02: 167 [51.5%] patients; Herceptin: 187 [57.5%] patients). In general, the incidence of TEAEs in HLX02 or Herceptin treated patients and frequency of occurrence was similar among both the treatment groups in overall population.

Table 72: Incidence of Treatment Emergent Adverse Events Occurring in ≥5% of Patients by treatment group – Overall (Safety Analysis Set) in Study HLX02-BC01

System organ class Preferred term	HLX02 N=324 n (%) E	Herceptin N=325 n (%) E	Total N=649 n (%) E
Number of patients experiencing at least one TEAE	**320 (98.8) 6828**	**321 (98.8) 7002**	**641 (98.8) 13830**
Investigations	299 (92.3) 3710	303 (93.2) 3584	602 (92.8) 7294
White blood cell decreased	267 (82.4) 1495	276 (84.9) 1486	543 (83.7) 2981
Neutrophil count decreased	266 (82.1) 1468	268 (82.5) 1385	534 (82.3) 2853
Aspartate aminotransferase increased	82 (25.3) 131	74 (22.8) 115	156 (24.0) 246
Alanine aminotransferase increased	75 (23.1) 143	69 (21.2) 106	144 (22.2) 249
Weight increased	48 (14.8) 60	50 (15.4) 70	98 (15.1) 130
Gamma-glutamyltransferase increased	37 (11.4) 52	33 (10.2) 42	70 (10.8) 94
Platelet count decreased	31 (9.6) 61	33 (10.2) 55	64 (9.9) 116
Blood alkaline phosphatase increased	26 (8.0) 34	19 (5.8) 23	45 (6.9) 57
Weight decreased	18 (5.6) 22	16 (4.9) 16	34 (5.2) 38
Skin and subcutaneous tissue disorders	208 (64.2) 348	204 (62.8) 388	412 (63.5) 736
Alopecia	180 (55.6) 181	174 (53.5) 174	354 (54.5) 355
Rash	32 (9.9) 43	27 (8.3) 42	59 (9.1) 85
Palmar-plantar erythrodysaesthesia syndrome	17 (5.2) 17	20 (6.2) 21	37 (5.7) 38
Nail discolouration	13 (4.0) 13	19 (5.8) 19	32 (4.9) 32
Blood and lymphatic system disorders	182 (56.2) 529	205 (63.1) 599	387 (59.6) 1128
Anaemia	167 (51.5) 450	187 (57.5) 494	354 (54.5) 944
Bone marrow failure	20 (6.2) 53	24 (7.4) 72	44 (6.8) 125
Febrile neutropenia	16 (4.9) 18	20 (6.2) 21	36 (5.5) 39
General disorders and administration site conditions	180 (55.6) 411	166 (51.1) 444	346 (53.3) 855
Oedema peripheral	63 (19.4) 84	54 (16.6) 69	117 (18.0) 153
Pyrexia	54 (16.7) 71	46 (14.2) 69	100 (15.4) 140
Asthenia	31 (9.6) 50	40 (12.3) 76	71 (10.9) 126
Fatigue	29 (9.0) 53	30 (9.2) 55	59 (9.1) 108
Malaise	30 (9.3) 42	27 (8.3) 58	57 (8.8) 100
Peripheral swelling	23 (7.1) 29	21 (6.5) 28	44 (6.8) 57
Face oedema	18 (5.6) 18	13 (4.0) 14	31 (4.8) 32

Gastrointestinal disorders	143 (44.1) 489	151 (46.5) 488	294 (45.3) 977
Diarrhoea	75 (23.1) 161	75 (23.1) 120	150 (23.1) 281
Nausea	48 (14.8) 85	58 (17.8) 94	106 (16.3) 179
Vomiting	31 (9.6) 39	34 (10.5) 47	65 (10.0) 86
Constipation	27 (8.3) 47	23 (7.1) 30	50 (7.7) 77
Stomatitis	18 (5.6) 30	21 (6.5) 36	39 (6.0) 66
Abdominal pain upper	12 (3.7) 13	20 (6.2) 28	32 (4.9) 41

System organ class Preferred term	**HLX02 N=324 n (%) E**	**Herceptin N=325 n (%) E**	**Total N=649 n (%) E**
Number of patients experiencing at least one TEAE	**320 (98.8) 6828**	**321 (98.8) 7002**	**641 (98.8) 13830**
Metabolism and nutrition disorders	131 (40.4) 398	132 (40.6) 457	263 (40.5) 855
Hypoalbuminaemia	40 (12.3) 66	45 (13.8) 87	85 (13.1) 153
Decreased appetite	33 (10.2) 45	35 (10.8) 40	68 (10.5) 85
Hypocalcaemia	29 (9.0) 61	39 (12.0) 68	68 (10.5) 129
Hypokalaemia	26 (8.0) 42	30 (9.2) 40	56 (8.6) 82
Hyperglycaemia	29 (9.0) 47	18 (5.5) 42	47 (7.2) 89
Hyperuricaemia	16 (4.9) 23	29 (8.9) 46	45 (6.9) 69
Hypertriglyceridaemia	12 (3.7) 17	21 (6.5) 31	33 (5.1) 48
Infections and infestations	120 (37.0) 202	140 (43.1) 251	260 (40.1) 453
Urinary tract infection	53 (16.4) 76	61 (18.8) 100	114 (17.6) 176
Upper respiratory tract infection	30 (9.3) 41	35 (10.8) 51	65 (10.0) 92
Respiratory, thoracic and mediastinal disorders	82 (25.3) 149	74 (22.8) 143	156 (24.0) 292
Cough	33 (10.2) 57	31 (9.5) 41	64 (9.9) 98
Musculoskeletal and connective tissue disorders	70 (21.6) 121	78 (24.0) 160	148 (22.8) 281
Pain in extremity	17 (5.2) 22	19 (5.8) 29	36 (5.5) 51
Arthralgia	11 (3.4) 20	19 (5.8) 28	30 (4.6) 48
Back pain	10 (3.1) 11	18 (5.5) 24	28 (4.3) 35
Nervous system disorders	76 (23.5) 121	69 (21.2) 117	145 (22.3) 238
Headache	20 (6.2) 21	14 (4.3) 23	34 (5.2) 44
Dizziness	18 (5.6) 26	12 (3.7) 13	30 (4.6) 39
Cardiac disorders	51 (15.7) 78	63 (19.4) 113	114 (17.6) 191
Injury, poisoning and procedural complications	52 (16.0) 61	38 (11.7) 44	90 (13.9) 105
Infusion related reaction	42 (13.0) 48	32 (9.8) 36	74 (11.4) 84
Vascular disorders	34 (10.5) 40	32 (9.8) 45	66 (10.2) 85
Psychiatric disorders	24 (7.4) 38	33 (10.2) 45	57 (8.8) 83
Insomnia	23 (7.1) 33	27 (8.3) 35	50 (7.7) 68
Eye disorders	22 (6.8) 28	24 (7.4) 34	46 (7.1) 62
Hepatobiliary disorders	18 (5.6) 26	17 (5.2) 22	35 (5.4) 48
Renal and urinary disorders	16 (4.9) 23	18 (5.5) 20	34 (5.2) 43

ource: Table 12-6 of HLX02-BC01 CSR.
E: Frequency of adverse events.
Percentages were based on the number of patients in the safety set.
System organ classes (SOCs) were sorted in descending order of patient frequency in total; preferred terms were sorted within system organ class in descending order of patient frequency in total. If the frequency of the preferred term was tied, the preferred terms were sorted alphabetically.
Adverse events were coded to system organ class and preferred term using the MedDRA Version 21.1 coding dictionary.
Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first administration date of study medication and no later than 30 (+2) days after the last administration date on study of study medication.

Table 73: Treatment Emergent Adverse Events by System Organ Class and Severity by CTCAE Grade-Overall (Safety Analysis Set) events – Overall (Safety Analysis Set) in Study HLX02-BC01

System organ class	CTCAE Grade	HLX02 N=324 n (%) E	Herceptin N=325 n (%) E	Total N=649 n (%) E
Number of patients experiencing at least one TEAE	Overall	320 (98.8) 6828	321 (98.8) 7002	641 (98.8) 13830
	Grade 1	3 (0.9) 3065	7 (2.2) 3230	10 (1.5) 6295
	Grade 2	39 (12.0) 1872	33 (10.2) 1992	72 (11.1) 3864
	Grade 3	84 (25.9) 1245	95 (29.2) 1201	179 (27.6) 2446
	Grade 4	191 (59.0) 643	180 (55.4) 571	371 (57.2) 1214
	Grade 5	3 (0.9) 3	6 (1.8) 8	9 (1.4) 11
Investigations	Overall	299 (92.3) 3710	303 (93.2) 3584	602 (92.8) 7294
	Grade 1	10 (3.1) 997	17 (5.2) 958	27 (4.2) 1955
	Grade 2	32 (9.9) 999	30 (9.2) 1029	62 (9.6) 2028
	Grade 3	74 (22.8) 1100	85 (26.2) 1055	159 (24.5) 2155
	Grade 4	183 (56.5) 614	171 (52.6) 542	354 (54.5) 1156
Skin and subcutaneous tissue disorders	Overall	208 (64.2) 348	204 (62.8) 388	412 (63.5) 736
	Grade 1	48 (14.8) 167	50 (15.4) 198	98 (15.1) 365
	Grade 2	150 (46.3) 171	150 (46.2) 184	300 (46.2) 355
	Grade 3	10 (3.1) 10	4 (1.2) 6	14 (2.2) 16
Blood and lymphatic system disorders	Overall	182 (56.2) 529	205 (63.1) 599	387 (59.6) 1128
	Grade 1	69 (21.3) 320	70 (21.5) 333	139 (21.4) 653
	Grade 2	70 (21.6) 145	85 (26.2) 201	155 (23.9) 346
	Grade 3	27 (8.3) 43	35 (10.8) 45	62 (9.6) 88
	Grade 4	16 (4.9) 21	15 (4.6) 20	31 (4.8) 41
General disorders and administration site conditions	Overall	180 (55.6) 411	166 (51.1) 444	346 (53.3) 855
	Grade 1	106 (32.7) 308	110 (33.8) 356	216 (33.3) 664
	Grade 2	67 (20.7) 96	46 (14.2) 77	113 (17.4) 173
	Grade 3	7 (2.2) 7	7 (2.2) 8	14 (2.2) 15
	Grade 5	0 (0.0) 0	3 (0.9) 3	3 (0.5) 3
Gastrointestinal disorders	Overall	143 (44.1) 489	151 (46.5) 488	294 (45.3) 977
	Grade 1	77 (23.8) 352	77 (23.7) 341	154 (23.7) 693
	Grade 2	54 (16.7) 121	65 (20.0) 136	119 (18.3) 257
	Grade 3	12 (3.7) 16	9 (2.8) 11	21 (3.2) 27
Metabolism and nutrition disorders	Overall	131 (40.4) 398	132 (40.6) 457	263 (40.5) 855
	Grade 1	84 (25.9) 327	80 (24.6) 373	164 (25.3) 700
	Grade 2	35 (10.8) 54	35 (10.8) 58	70 (10.8) 112
	Grade 3	10 (3.1) 14	14 (4.3) 23	24 (3.7) 37
	Grade 4	2 (0.6) 3	2 (0.6) 2	4 (0.6) 5
	Grade 5	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1

System organ class	CTCAE Grade	HLX02 N=324 n (%) E	Herceptin N=325 n (%) E	Total N=649 n (%) E
Infections and infestations	Overall	120 (37.0) 202	140 (43.1) 251	260 (40.1) 453
	Grade 1	42 (13.0) 85	47 (14.5) 101	89 (13.7) 186
	Grade 2	55 (17.0) 90	68 (20.9) 121	123 (19.0) 211
	Grade 3	21 (6.5) 25	21 (6.5) 25	42 (6.5) 50
	Grade 4	0 (0.0) 0	4 (1.2) 4	4 (0.6) 4
	Grade 5	2 (0.6) 2	0 (0.0) 0	2 (0.3) 2
Respiratory, thoracic and mediastinal disorders	Overall	82 (25.3) 149	74 (22.8) 143	156 (24.0) 292
	Grade 1	48 (14.8) 104	44 (13.5) 106	92 (14.2) 210
	Grade 2	26 (8.0) 36	25 (7.7) 32	51 (7.9) 68
	Grade 3	6 (1.9) 7	4 (1.2) 4	10 (1.5) 11
	Grade 4	1 (0.3) 1	0 (0.0) 0	1 (0.2) 1
	Grade 5	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Musculoskeletal and connective tissue disorders	Overall	70 (21.6) 121	78 (24.0) 160	148 (22.8) 281
	Grade 1	52 (16.0) 88	51 (15.7) 124	103 (15.9) 212
	Grade 2	16 (4.9) 31	25 (7.7) 34	41 (6.3) 65
	Grade 3	2 (0.6) 2	1 (0.3) 1	3 (0.5) 3
	Grade 5	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Nervous system disorders	Overall	76 (23.5) 121	69 (21.2) 117	145 (22.3) 238
	Grade 1	54 (16.7) 92	47 (14.5) 86	101 (15.6) 178
	Grade 2	20 (6.2) 27	18 (5.5) 26	38 (5.9) 53
	Grade 3	2 (0.6) 2	3 (0.9) 4	5 (0.8) 6
	Grade 5	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Cardiac disorders	Overall	51 (15.7) 78	63 (19.4) 113	114 (17.6) 191
	Grade 1	33 (10.2) 58	38 (11.7) 80	71 (10.9) 138
	Grade 2	13 (4.0) 15	20 (6.2) 28	33 (5.1) 43
	Grade 3	2 (0.6) 2	2 (0.6) 2	4 (0.6) 4
	Grade 4	3 (0.9) 3	2 (0.6) 2	5 (0.8) 5
	Grade 5	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Injury, poisoning and procedural complications	Overall	52 (16.0) 61	38 (11.7) 44	90 (13.9) 105
	Grade 1	24 (7.4) 29	18 (5.5) 24	42 (6.5) 53
	Grade 2	23 (7.1) 25	18 (5.5) 18	41 (6.3) 43
	Grade 3	4 (1.2) 6	2 (0.6) 2	6 (0.9) 8
	Grade 4	1 (0.3) 1	0 (0.0) 0	1 (0.2) 1
Vascular disorders	Overall	34 (10.5) 40	32 (9.8) 45	66 (10.2) 85
	Grade 1	14 (4.3) 17	13 (4.0) 22	27 (4.2) 39
	Grade 2	18 (5.6) 21	14 (4.3) 17	32 (4.9) 38
	Grade 3	2 (0.6) 2	5 (1.5) 6	7 (1.1) 8
Psychiatric disorders	Overall	24 (7.4) 38	33 (10.2) 45	57 (8.8) 83
	Grade 1	14 (4.3) 26	27 (8.3) 39	41 (6.3) 65
	Grade 2	10 (3.1) 12	6 (1.8) 6	16 (2.5) 18

Eye disorders	Overall	22 (6.8) 28	24 (7.4) 34	46 (7.1) 62
	Grade 1	18 (5.6) 24	19 (5.8) 28	37 (5.7) 52
	Grade 2	4 (1.2) 4	5 (1.5) 6	9 (1.4) 10
Hepatobiliary disorders	Overall	18 (5.6) 26	17 (5.2) 22	35 (5.4) 48
	Grade 1	12 (3.7) 19	12 (3.7) 15	24 (3.7) 34
	Grade 2	4 (1.2) 5	3 (0.9) 5	7 (1.1) 10
	Grade 3	2 (0.6) 2	2 (0.6) 2	4 (0.6) 4
Renal and urinary disorders	Overall	16 (4.9) 23	18 (5.5) 20	34 (5.2) 43
	Grade 1	14 (4.3) 20	14 (4.3) 16	28 (4.3) 36
	Grade 2	2 (0.6) 3	2 (0.6) 2	4 (0.6) 5
	Grade 3	0 (0.0) 0	2 (0.6) 2	2 (0.3) 2
Immune system disorders	Overall	13 (4.0) 24	15 (4.6) 19	28 (4.3) 43
	Grade 1	5 (1.5) 13	5 (1.5) 7	10 (1.5) 20
	Grade 2	8 (2.5) 11	8 (2.5) 9	16 (2.5) 20
	Grade 3	0 (0.0) 0	1 (0.3) 2	1 (0.2) 2
	Grade 4	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Overall	9 (2.8) 10	10 (3.1) 11	19 (2.9) 21
	Grade 1	4 (1.2) 4	7 (2.2) 8	11 (1.7) 12
	Grade 2	3 (0.9) 4	1 (0.3) 1	4 (0.6) 5
	Grade 3	2 (0.6) 2	2 (0.6) 2	4 (0.6) 4
Reproductive system and breast disorders	Overall	7 (2.2) 10	10 (3.1) 11	17 (2.6) 21
	Grade 1	3 (0.9) 5	7 (2.2) 8	10 (1.5) 13
	Grade 2	1 (0.3) 1	2 (0.6) 2	3 (0.5) 3
	Grade 3	3 (0.9) 4	1 (0.3) 1	4 (0.6) 5
Ear and labyrinth disorders	Overall	6 (1.9) 7	3 (0.9) 5	9 (1.4) 12
	Grade 1	5 (1.5) 6	3 (0.9) 5	8 (1.2) 11
	Grade 3	1 (0.3) 1	0 (0.0) 0	1 (0.2) 1
Endocrine disorders	Overall	2 (0.6) 3	2 (0.6) 2	4 (0.6) 5
	Grade 1	2 (0.6) 3	2 (0.6) 2	4 (0.6) 5
Social circumstances	Overall	1 (0.3) 1	0 (0.0) 0	1 (0.2) 1
	Grade 1	1 (0.3) 1	0 (0.0) 0	1 (0.2) 1

Source: Table 12-7, Listing 16.2.7.1.3 of HLX02-BC01 CSR
- TEAE: Treatment Emergent Adverse Event; E: Frequency of TEAE.
- Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first administration date of study medication and no later than 30 (+2) days after the last administration date on study of study medication; E: Frequency of TEAE.
- Percentages were based on the number of patients in the safety set. Subgroup Percentages were based on the number of patients in the Subgroup safety set.
- System organ classes (SOCs) were sorted in descending order of patient frequency in total; preferred terms were sorted within system organ class in descending order of patient frequency. If the frequency of the preferred term was tied, the preferred terms were sorted alphabetically.
- Adverse events were coded to system organ class and preferred term using the MedDRA Version 21.1 coding dictionary.

TEAEs of special interest

A total of 518 (260 in HLX02 and 258 in Herceptin treatment group) patients were reported with 5934 AESIs. The most commonly reported SOCs were investigations (HLX02: 234 [72.2%] patients; Herceptin: 232 [71.4%] patients); and blood and lymphatic system disorders (HLX02: 141 [43.5%] patients; Herceptin: 155 [47.7%] patients). Most commonly reported AESIs were WBC decreased (HLX02: 225 [69.4%] patients; Herceptin: 224 [68.9%] patients), neutrophil count decreased (HLX02: 214 [66.0%] patients; Herceptin: 209 [64.3%] patients); and anaemia (HLX02: 122 [37.7%] patients; Herceptin: 133 [40.9%] patients). In general, the

incidence of AESIs in HLX02 or Herceptin treated patients and frequency of occurrence was similar among both the treatment groups in overall population. After the 1st database lock (29 December 2018), the incidence of Grade 4 AESIs in the HLX02 group was nearly 10% higher than that in the EU-Herceptin group. But after the 2nd database lock (16 August 2019), as the follow-up time increased, the difference between 2 groups was reduced (6%).

As of cut-off date (10 July 2019), the longest time to special interest TEAE was observed in Herceptin treatment group for SOCs of metabolism and nutrition disorders (mean [SD] time taken was 16.93 [1.313] weeks) and respiratory, thoracic, and mediastinal disorders (mean 16.71 weeks). There was no special interest TEAE for these SOCs observed in HLX02 treatment group at the time of this report. In Herceptin treatment group, the shortest time (0.14 weeks) to special interest TEAE observed was for SOC of general disorders and administration site conditions. In HLX02 treatment group, the longest time to special interest TEAE observed was for SOC of cardiac disorders (20.07 [15.402] weeks); the shortest time (0.56 [1.042] weeks) to special interest TEAE was observed for injury, poisoning and procedural complications. For overall population in both the treatment groups, longest time to special interest TEAEs (in weeks) was observed for cardiac disorders (overall=17.93 [13.747] weeks), in which the HLX02 treatment group (20.07 [15.402] weeks) had a longer duration for time to special interest TEAEs than the Herceptin treated patients (16.04 [12.269] weeks)

The incidence of AESIs was higher in Asian population than the non-Asian population in both the treatment groups. A total of 478/499 Asian (HLX02: 238; Herceptin: 240) and 40/150 non-Asian (HLX02: 22; Herceptin: 18) patients were reported with 5640 and 294 AESIs, respectively. The most commonly reported AESIs in Asian population were WBC decreased (HLX02: 208 [83.9%] patients; Herceptin: 214 [85.3%] patients), neutrophil count decreased (HLX02: 195 [78.6%] patients; Herceptin: 196 [78.1%] patients), and anaemia (HLX02: 117 [47.2%] patients; Herceptin: 130 [51.8%] patients). In general, the incidence of AESIs in HLX02 or Herceptin treated patients and frequency of occurrence was similar among both the treatment groups in Asian patients. The most commonly reported AESIs in non-Asian population were neutrophil count decreased (HLX02: 19 [25.0%] patients; Herceptin: 13 [17.6%] patients), WBC decreased (HLX02: 17 [22.4%] patients; Herceptin: 10 [13.5%] patients). In general, the incidence of AESIs in HLX02 or Herceptin treated patients was similar among both the treatment groups in non-Asian patients.

Both the Asian and non-Asian populations had the longest time to special interest TEAE observed for cardiac disorders and shortest time to special interest TEAE observed for injury, poisoning and procedural complications, respectively. Time to special interest TEAEs for cardiac disorders were similar between the 2 treatment groups in the Asian population; however, in the non-Asian population, the HLX02 treated patients (30.95 [14.844] weeks) had a very longer time taken for special interest TEAEs than the Herceptin treatment group (14.00 [20.162] weeks).

A total of 455 Chinese (HLX02: 228; Herceptin: 227) and 63 non-Chinese (HLX02: 32; Herceptin: 31) patients were reported with 5488 and 446 AESIs, respectively. The most commonly reported AESIs in Chinese population were WBC count decreased (HLX02: 203 [85.7%] patients; Herceptin: 203 [86.0%] patients), neutrophil count decreased (HLX02: 190 [80.2%] patients; Herceptin: 185 [78.4%] patients); and anaemia (HLX02: 115 [48.5%] patients; Herceptin: 123 [52.1%] patients).

The most commonly reported AESIs in non-Chinese population were neutrophil count decreased (HLX02: 24 [27.6%] patients; Herceptin: 24 [27.0%] patients), WBC decreased (HLX02: 22 [25.3%] patients; Herceptin: 21 [23.6%] patients). In general, the incidence of AESIs was similar among HLX02 and Herceptin treatment groups in both Chinese and non-Chinese populations.

Time to special interest TEAEs showed a similar result pattern within the 2 treatment groups with Chinese population resembling the results of Asian and non-Chinese populations matching with results for non-Asian population. Cardiac disorders took longest time (16.96 [12.520] weeks in Chinese population and 20.82 [17.582] weeks in non-Chinese population) to special interest TEAE and injury, poisoning and procedural complications (1.49 [5.054] in Chinese population and 1.12 [2.529] weeks in non-Chinese population) reported the shortest time in both the populations.

Serious adverse events and deaths

Study HV01

No deaths occurred and no serious adverse events were reported in either of the two parts of this study.

Study BC01

A total of 9 deaths occurred in the study BC01, 3 in the HLX02 group and 6 in the EU-Herceptin group. The highest number of deaths (3 patients in Herceptin treatment group) were due to general disorders and administration site conditions. One patient (0.3%) each died due to dyspnoea in both treatment groups. Other deaths were due to lung infection and pneumonia (1 [0.3%] patient each in HLX02 treatment group), cardiovascular disease, electrolyte imbalance, arthralgia and altered consciousness (1 [0.3%] patient each in Herceptin treatment group).

Compared to 8 patients in the Asian population (HLX02: 3 patients; Herceptin: 5 patients) only 1 patient (in Herceptin group) died due to a TEAE in the non-Asian population. Most of the deaths (total 4 = 3 in Asian and 1 non-Asian patient, all in Herceptin group) were due to general disorders and administration site conditions. Compared to 8 patients in the Chinese population only 1 patient died due to a TEAE in the non-Chinese population. The results observed for Chinese population was same as Asian and non-Chinese was same as the non-Asian population.

Table 74: Treatment Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term – Overall Safety Analysis Set, in Study HLX02-BC01

System organ class Preferred term	HLX02 N=324 n (%) E	Herceptin N=325 n (%) E	Total N=649 n (%) E
Number of patients experiencing at least one adverse event*	**3 (0.9) 3**	**6 (1.8) 8**	**9 (1.4) 11**
General disorders and administration site conditions	0 (0.0) 0	3 (0.9) 3	3 (0.5) 3
Death	0 (0.0) 0	3 (0.9) 3	3 (0.5) 3
Infections and infestations	2 (0.6) 2	0 (0.0) 0	2 (0.3) 2
Lung infection	1 (0.3) 1	0 (0.0) 0	1 (0.2) 1
Pneumonia	1 (0.3) 1	0 (0.0) 0	1 (0.2) 1
Respiratory, thoracic and mediastinal disorders	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Dyspnoea	1 (0.3) 1	1 (0.3) 1	2 (0.3) 2
Cardiac disorders	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Cardiovascular disorder	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Metabolism and nutrition disorders	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Electrolyte imbalance	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Musculoskeletal and connective tissue disorders	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Arthralgia	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Nervous system disorders	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1
Altered state of consciousness	0 (0.0) 0	1 (0.3) 1	1 (0.2) 1

Source: Table 12-13 of HLX02-BC01 CSR

*Incidence of deaths due to TEAE

E: Frequency of adverse events.

Percentages were based on the number of patients in the safety set.

System organ classes (SOCs) were sorted in descending order of patient frequency in total; preferred terms were sorted within system organ class in descending order of patient frequency in total. If the frequency of the preferred term was tied, the preferred terms were sorted alphabetically.

Adverse events were coded to system organ class and preferred term using the MedDRA Version 21.1 coding dictionary.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first administration date of study medication and no later than 30 (+2) days after the last administration date on study of study medication.

Laboratory findings

Study HV01

In part 1 no clinically significant changes from baseline to post-baseline occurred in any of the dosing groups for haematology markers, serum markers of myocardial injury or urinalysis results.

A total of 8 shifts with clinical significance were noted for abnormal blood bilirubin, ALT, blood triglycerides and AST.

No abnormalities were detected regarding serum markers of myocardial injury, urinalysis, haematology, vital signs, physical examinations, 12-lead ECGs and chest X-rays.

In Part 2 of the study, assessments of most of the haematology, biochemistry, and urinalysis parameters as well as serum markers of myocardial injury were either normal, or abnormal but not clinically significant and none of the abnormalities were reported as SAE.

No abnormalities were detected regarding vital signs.

Study BC01

Haematology parameters in both the treatment groups barely shifted from the baseline values and were almost same for overall, Asian and non-Asian, Chinese and non-Chinese populations, and no trends could be observed. Herceptin patients did however have an overall slightly higher decrease in haematology parameters compared to HLX02 subjects.

Likewise, minimal change was recorded in blood chemistry parameters from baseline and no trend seems to exist.

Coagulation factor analysis and urinalysis did not reveal any untoward changes or differences between treatment groups, both from an overall population perspective as in a stratified analysis along the Asian/non-Asian/Chinese/non-Chinese axes.

Generally, changes in vital signs and physical examinations were minimal and did not have any observed trends. The shifts from baseline to EOS showed that the values remained normal for most of the patients.

With regards to ECG parameters there was no general significant shift from baseline measurements and the incidence rate was similar in both treatment groups and similar findings were found in the Asian/Chinese/non-Asian/non-Chinese stratified analysis. Abnormal shifts in heart rate did occur in 2 HLX02 treated patients versus 8 Herceptin treated patients.

Likewise, no marked shifts in LVEF could be found for the majority of the patient population and treatment group differences were neither noted.

ECOG performance scores remained stable throughout the study (all patients having ECOG PS 0 or 1), with only one patient in each treatment group shifting to a PS of 3 by end of study. At safety follow-up 3 HLX02 and 3 Herceptin patients had shifted to an ECOG PS of 2, while one Herceptin patient presented with a PS of 3.

Safety in special populations

No specific safety analysis based on age, sex, height, weight or body mass were provided. Neither were extrinsic factors such as medical environment, use of other drugs, use of tobacco, use of alcohol, and food habits subjected to a safety analysis.

There was a single pregnancy-related incidence in study HV01 reported as possible pregnancy due to unprotected intercourse during the active study period. No further information was provided or available, except for the notice that the pregnancy was eventually terminated.

Immunological events

In both clinical studies, a multi-tiered strategy was used to detect, confirm and titrate anti-drug ADA. Several bioanalytical methods were used for the determination of anti-drug antibodies (ADAs) from the serum samples of healthy volunteers (study HLX02-HV01) and from patients with HER2 positive, recurrent or previously untreated metastatic breast cancer (study HLX02-BC01). In addition, two different approaches were used to detect, confirm and titer ADA in the comparative immunogenicity assessment: a one- and a two-assay approach for the study HLX02-BC01 and the study HLX02-HV01, respectively. Neutralising antibody (NAb) detection was to be performed for all confirmed positive ADA samples. Further discussion on the immunogenicity assays is provided in the section 2.6.1.

Study HLX02-HV01

No ADA positive results, and subsequently no NAb development, were observed in either part of the study.

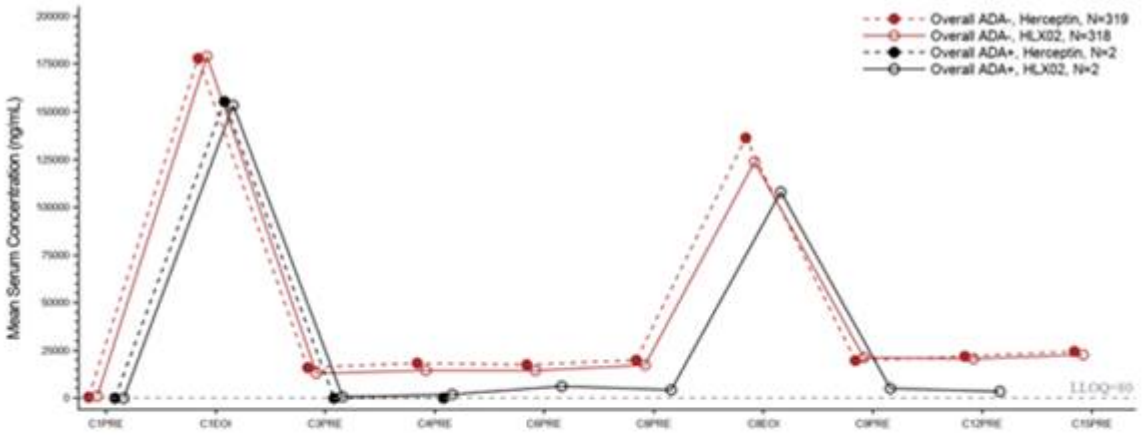
Study HLX02-BC01

The results for the neutralizing capacity of the samples confirmed as ADA positive in study HLX02-BC01 were provided at the time of the second interim analysis. ADA positivity was protocol defined as presenting with an ADA positive result at any visit post-screening over the course of treatment until 30 days post-last treatment.

A total of 23 (3.6%) patients (6 [1.9%] in HLX02 and 17 [5.3%] in Herceptin group) tested positive for ADA at Screening (prior to first IMP infusion). However, following the protocol definition of ADA positivity in relation to study treatment these patients were not considered ADA^+ in the immunogenicity analysis.

During the study a total of 4 patients (0.6%), 2 in each treatment arm, tested ADA positive at one or more time-points, and this possibly resulted in a lower mean trastuzumab serum concentration than ADA^- patients (see Figure 38). In the second interim analysis no new ADA+ cases were identified, though the four subjects that were found to be positive were now also confirmed to all have developed neutralizing antibodies.

Consistent safety results were observed between the 4 ADA positive patients. None of the 4 patients were reported with any SAE and 1 patient in Herceptin group experienced IRR. A range of 7 to 24 TEAEs were reported. The sample size was too small to draw any conclusion on statistical significance.



Abbreviations: C = cycle; EOI =end of infusion; LLOQ = lower limit of quantification; PRE = predose.
Source: Figure 11-7 of HLX02-BC01 CSR
Due to the limitation of graphic display, standard deviations (SD) are not included in the curve, which is inconsistent with pharmacokinetic statistical analysis plan.
Antibody stratification was based on the overall status. Overall ADA status: a subject was considered positive if ADA positive result was observed at any visit over the course of treatment until 30 days post-last treatment.
Missing ADA result was treated as negative for determination of overall ADA status.
The lines are translated with +/-0.05 unit to make the Serum Concentration curve clearer.

Figure 38: Mean trastuzumab serum concentration-time profiles for both treatments (stratified by overall antidrug antibody status, linear scale) - pharmacokinetic analysis set

Drug Interruption/Withdrawal and Discontinuation due to AES

Study HLX02-HV01

No SD interruptions/withdrawals or discontinuations due to AEs were reported in this study.

Study HLX02-BC01

Dose reduction was reported in 1 patient in Herceptin treatment group. Dose delay was reported in 55 patients in HLX02 treatment group and 46 patients in Herceptin treatment group. Dose interruption was reported in a total of 21 and 16 patients from the HLX02 and Herceptin treatment groups, respectively.

Overall, 59/649 (9.1%) patients experienced a TEAE leading to study drug interruption or withdrawal during the active treatment period. There was a similar incidence of patients who had TEAEs leading to study drug interruption or withdrawal in the HLX02 and Herceptin treatment groups. The majority of withdrawal events occurred due to infusion related reactions.

A higher number of patients reported drug interruption or drug withdrawn due to a TEAE in the Asian [53 (10.6%)] and Chinese [51 (10.8%)] populations compared with the non-Asian [6 (4.0%)], and the non-Chinese [(8 (4.5%)]) populations.

Post marketing experience

Not Applicable.

2.6.1. Discussion on clinical safety

The current safety analysis is based on data gathered from study HLX02-HV01 and the pivotal HLX02-BC01. Study HLX02-HV01 was a Phase II PK and dose-assessment study which recruited only healthy Chinese males and consisted of two parts. In part 2, the subjects were 1:1:1 randomized to HLX02/US-Herceptin/EU-Herceptin treatment. Study HLX02-BC01 was a Phase III equivalence study comparing HLX02 versus the active comparator Herceptin which recruited females only and for which the ethnic make-up was approximately 77% Asian/Chinese patients and around 23% Caucasian (EU) patients.

The cut-off date for the first analysis was the date on which W24 data was available for all patients (23 November 2018). Overall, 215 patients (116 and 99 in the HLX02 and Herceptin arm, respectively) were still under treatment at this data cut-off. Both treatment groups (HLX02 and EU-Herceptin) underwent about the same mean number of treatment cycles, but the HLX02 group had a higher mean total exposure (238.4 days versus 228.8 days in the Herceptin group) and consequently a higher cumulative dose exposure (median 4550.5 mg versus 4200.0 mg respectively. This difference was driven by the Caucasian subpopulation where HLX02 subjects were exposed 9.3 days longer than the Herceptin ones, whereas no such exposure difference was noted in the Asian/Chinese subpopulations. In contrast, Asian/Chinese patients had more dose interruptions/withdrawals (without apparent difference between treatment groups) compared to Caucasians.

At the 23 November 2018 cut-off date, about 98.8% of all patients experienced at least one TEAE event, and overall the incidence profile was well balanced between the two treatment groups. Nonetheless, most events including AESIs, were Grade ≥4 in both groups. ADRs were experienced by approximately 23% of patients in both treatment groups. About twice as much EU-Herceptin patients discontinued study participation (2.2% versus 1.2% in the HLX02 group), despite the number of TESAEs and SADRs being similar in both arms.

Generally, the types of reported TESAEs were fairly evenly distributed between both treatment groups, with neutrophil count decreased (10.2% of HLX02 patients; 7.4% of Herceptin patients), WBC decreased (4.9% and 3.7% respectively), and febrile neutropenia (3.4% in both groups) being the most reported events.

A total of 5261 AESIs were reported by 248 HLX02 subjects and 232 EU-Herceptin subjects, with a broadly similar incidence and event profile between the two groups. The most reported events in both groups were

neutrophil/WBC decrease and anaemia. When stratified along severity grades it was shown that HLX02 patients had more grade 4 AESIs compared to the EU-Herceptin subjects.

Treatment Emergent Adverse Events (TEAE) leading to death occurred in both groups, with twice as many incidents in the EU-Herceptin group (6 fatalities versus 3 in the HLX02 group), but the overall very low number of deaths precludes any confirmative analysis on this observation.

As advised during in the CHMP Scientific Advice, the Applicant also investigated all the safety parameters in a stratified analysis, with the stratification axes being Asian/non-Asian and Chinese/non-Chinese. This gave rise to three sub-populations: Chinese (73%), non-Chinese Asian (4%) and Caucasian subjects (23%). The stratified analysis led to the observation that the Asian population (including Chinese and non-Chinese Asian subjects) had a far greater incidence of AESIs and SAEs compared to the Caucasian subjects, with the same observation apparent in the Chinese versus non-Chinese subjects and Asian versus non-Asian stratification analyses.

ADRs and severity graded TEAEs were balanced between the treatment arms in the non-Asian/Asian/non-Chinese/Chinese stratified analyses, although when compared in a stratified manner it seems that the Asian population had a higher incidence of treatment related anaemia.

Given that sensitivity to anaemia is intricately linked with body weight, an analysis of the safety parameters stratified according to body weight was requested to check whether this may possibly be the underlying reason for the Asian/Chinese/Other ethnicities discordances noted above. Patients with a weight up to 60 kg were found to be generally more predisposed towards anaemia-related adverse events. The analysis was hampered by the fact that relatively few non-Asians fell in a weight category below 60 kg. Nonetheless, the results indicate that Asians with a body weight comparable to the relatively heavier non-Asian subjects did not differ in anaemia and anaemia-related adverse event frequencies, whereas patients with lower body weights were more affected.

Proportionally more subjects in the Asian/Chinese subgroups reported TESAEs (28%) than in the non-Asian subgroup (6%), with the most common events being neutrophil count decreased and WBC decreased in all subgroups, while the Asian subjects also had a relatively high incidence of febrile neutropenia.

In regards to drug-related TESAEs (TESADRs), there was an overall balance in incidence and types of events between the HLX-02 and EU-Herceptin groups overall, but when stratified according to subpopulations it was clear that the pattern of higher incidence in Asian subjects, as noticed for overall TESAEs, was also apparent for TESADRs.

Drug interruptions or withdrawals happened in 7% of patients overall with no appreciable difference between the two treatment groups. However, non-Chinese Asian/Chinese subjects had a 3- and 2.5-fold higher rate of drug interruptions and withdrawals based on the performed analyses.

As a minimum of 1 year of median treatment exposure is considered necessary to allow a sufficiently rigorous safety evaluation, the applicant provided the results from a second interim analysis with the cut-off date 10 July 2019. It is noted that the median exposure duration with this second interim analysis did not reach the requested one year of duration (median duration of 312 days). Nonetheless, based on the safety and immunogenicity data available in the second interim analysis which did not show worrisome divergences between treatment groups, this is considered acceptable. Also, it is unlikely that the 1.8-month difference in exposure would expose a divergence between treatment groups in either safety or immunogenic aspects. Furthermore, the applicant will provide the final safety analysis together with the final CSR. However, it is clear that the threshold of 1 year of exposure data will not be met due to the large number of patients that have already exited the study at the second interim analysis.

In the second interim report, the numbers of exposed patients and the demographic characteristics remained the same as in the first interim analysis. A total of 292 (45.0%) patients had completed the 12-month study treatment (47.8% in the HLX02 treatment group and 42.2% in the Herceptin treatment group). In the overall population, the difference in median cumulative dose exposure between the HLX02 and the Herceptin arms remained visible despite relatively equal treatment cycle numbers: 5488.5 mg for HLX02 and 4945.0 mg for Herceptin. Although the exposure duration difference between different treatment groups has further increased, this has not resulted in an appreciable effect on the safety profile comparison.

Generally, the overall adverse event profile remained unchanged, with a small number of TEAEs being reclassified from 'unrelated' to 'related' without any impact on the overall similarity of safety profiles between HLX02 and Herceptin. No new deaths were reported in either treatment group.

Renal and urinary disorders have now also been observed, but overall the treatment groups are balanced in regard to frequency and severity. The vast majority of events in this SOC were mild in nature and no Grade 4 events occurred.

With regards to AESIs, HLX02 subjects experienced an about ten percent higher incidence of grade 4 severity adverse events of special interest in the first analysis and a difference in Grade 4 severity AESI still exists in the second interim analysis (6%). However, the fact that longer term data led to a decrease of the gap between treatment groups indicates that this may have been caused by immature data. The difference is considered too small to ascribe cause to the observations.

Slightly higher incidence of AEs of special interest were reported with HLX02 for investigations, especially for white blood cell decreased, neutrophil count decreased and infusion related reactions (12.0% for HLX02 vs 8.3% for Herceptin, DCO 28 November 2018). Results from the second interim analysis were in line with those observed in the first interim analysis. Overall, even if incidence is slightly higher for HLX02, differences are small enough to be considered a chance finding.

Imbalance in the SOC of cardiac disorders (7.7% in the HLX02 arm and 13.2% in the Herceptin arm) was requested to be discussed. Neither cardiac events nor overall LVEF had large changes or discrepancies noted throughout both interim analyses, and moreover no clinically meaningful differences between treatment groups are apparent at this timepoint. Based on the data provided HLX02 does not appear to induce untoward more cardiac abnormalities during the treatment duration as achieved in the pivotal trial.

Although being more a question about the overall safety profile rather than differences between HLX02 and Herceptin groups, the higher rate of dose interruptions in Asian version Non-Asian remained noticeable at the second interim analysis: 18 in the Asian HLX02 and 16 in the Asian Herceptin groups versus 3 and 0 in non-Asian subjects respectively.

Numerically more Asian patients had discontinuations due to AEs in both arms, although the numbers were low: 6 patients (2.4%) in the HLX02 arm and 8 patients (3.2%) in the Herceptin arm in Asian patients and respectively, 3 patients (3.9%) and 0 patients in the non-Asian subpopulation.

Differences in the incidence of treatment-related anaemia between Asian and non-Asian subjects were also present. Notably, between Asian and non-Asian stratified groups a large gap remained in the proportion of AESIs (95.8% vs 26.7%), both with HLX02 and Herceptin.

Although it is true that in the pivotal phase III trial, proportionally, more than three times as much subjects were Asian versus Non-Asian (N = 499 versus 150 respectively), the differences in safety outcomes seen are too large to be explainable by sheer numerical skewing.

Although it is acknowledged that different populations exhibit different sensitivities and safety to different anti-tumour therapies and that other factors may also influence outcomes, the differences seen are of such magnitude that it makes it unlikely that extrinsic factors could be the cause, leaving the possibility that an ethnogenetic difference in response to the treatment could be a reasonable cause for the observed differences in safety. It can be argued that possibly docetaxel may be the culpable factor at play here, and that Asian populations may be more sensitive to haematological/neutropenic toxicities for this compound (Yano 2013, Kenmotsu 2015). Chemotherapies tend to have more haematotoxic impact on Asian patients, which may be in part due to the general lower body weight of these people.

It is indeed acknowledged that docetaxel is known to be able to cause haematological adverse events such as neutropenia and leukopenia, but on the other hand so does trastuzumab (febrile neutropenia, anaemia, neutropenia, leukopenia and thrombocytopenia are all listed as very common side effects in the Herceptin SmPC). What is also clear however is that in the trastuzumab monotherapy HLX02-HV01 study, encompassing 123 subjects over both study phases, haematologic disorders were very rare (affecting only around 2% of subjects). This finding in combination with the published data referred above does led some credence to the argument that it may indeed be the docetaxel component of the pivotal trial treatment which is causing the large difference in certain adverse events between the Asian and non-Asian study populations. Differential prior exposure to chemotherapy might also explain the observed differences in safety profile.

In study HV01, only Chinese subjects were enrolled which was discussed in the CHMP Scientific Advice in which it was noted that no ethnogenetic effects on outcomes would reasonably be expected but that a stratified analysis in the Phase III trial was considered prudent for certainty's sake. However, this approach would also imply that if said stratified analysis would find indication of clinically relevant differences between Chinese/non-Chinese subjects in regards to outcomes, the acceptability of the Phase II study in regards to dose definition, safety guidance and PK towards non-Chinese subjects could become a point of scrutiny. However, the observed differences in safety profile between Asian and non-Asian populations were thoroughly discussed, and adequately supported with possible clarifications, such that the acceptability of the phase II study in support of the application could be reasonably accepted.

In study part I, there was generally even balance between the incidence of TEAEs and ADRs between the three treatment groups, and no untoward adverse event findings were apparent in the different dose groups. In neither of the study parts SAEs or deaths were noted and the majority of events were mild to moderate in intensity.

In part 2 the most reported TEAEs were in the SOCs investigations, gastrointestinal disorders, general disorders and administration site conditions and (only in the US-Herceptin group) cardiac disorders. In terms of Preferred Term TEAEs that occurred in more than 5 % of patients, these were noted as being ALT increased, Blood triglycerides increased, AST increased, Neutrophil count increased, WBC count increased, N-terminal prohormone brain natriuretic peptide increased, GGT increased, WBC urine positive, Blood bilirubin increased, Blood glucose increased, and Glucose urine present.

On further analysis it seems that more incidents of neutrophil count increased and WBC count increased occurred in the HLX02 patients compared to both Herceptin groups (differences noted between 10 and 20%) whereas the US Herceptin patients had more incidences of liver injury markers (differences of up to 10%). As the neutrophil and WBC count increased events were usually evaluated as ADR this also implied that in combination with the ECG T-Wave observations more ADRs were noted in the HLX02 and US-Herceptin patients.

Given that no severity analyses were undertaken, it is difficult to ascribe clinical relevancy to these findings. However, considering that these observations were not replicated in the larger Phase III HLX02-BC01 trial, it is likely that these observations are chance findings.

With regards to immunogenicity, a two-antigen assay approach with one assay using reagents that detect ADA against the biosimilar product HLX02 and one assay using reagents that detect ADA against the reference product was used in the study HLX02-HV01. With the exception of the binding reagents (biotinylated-drug and ruthenylated-drug), the same electrochemiluminescence (ECL) bridging format with a prior ELISA extraction phase using the respective drug was performed (HLX02 or CN-Herceptin manufactured in US). The suitability of using US Herceptin-labeled reagents to detect antibodies against both EU Herceptin and US Herceptin was investigated in a number of experiments. Overall, a number of limitations have been identified for the immunogenicity assays used in the study HLX02-HV01. Because the comparative immunogenicity exercise between the originator and the biosimilar is largely made by the analysis of ADA data generated from study HLX02-BC01, these issues are not further pursued.

In the study HLX02-BC01, a single-antigen approach using biotinylated- and ruthenylated-HLX02 in an another ECL bridging assay has been applied to detect, confirm and titer ADA. The 24 months long-term stability data for the ADA samples tested with this method are recommended to be provided (recommendation).

A neutralising assay based on a direct competitive ligand binding approach using HLX02 as binding and detection reagent and including an acid dissociation step has been developed and validated. Although some parameters were not selected as recommended in the current state-of the-art-practices, it is expected that it would not change the comparative immunogenicity assessment considering the clinical data and the low risk of immunogenicity for trastuzumab products in the intended treatment populations.

Since no ADA were detected in the study HLX02-HV01, no NAb analysis was carried out and no validation activities for the associated analytical method were completed. In clinical study HLX02-BC01, a number of patients were found ADA positive (see below). Neutralising antibody (NAb) detection was to be performed for all confirmed positive ADA samples. The final bioanalytical reports (ADA and NAb assays) are recommended to be provided (see recommendation).

It is noted that all 4 ADA+ patients were also NAb+, with an observed impact on serum availability of the study treatments. No immediate effect was noted on the safety parameters, while in regards to efficacy two of the four patients were found to suffer progressive disease and two had stable disease at the end of treatment. The available data does not seem to indicate that a difference between originator and biosimilar in this regard exists, but on the other hand the numbers observed are too low to allow drawing any statistically meaningful conclusion from these observations. Given that no more patients are currently undergoing treatment it is expected that finalised immunogenicity data will be forthcoming in the final report (recommendation), though given the paucity of nAB+ subjects new insights are not expected.

Furthermore, in the HLX02-BC01 trial 23 subjects were tested positive for ADA at screening, presumably due to trastuzumab exposure >12 months prior if adherent to the inclusion criteria, and a further four shifted from ADA-negative to ADA–positive status during the trial. Only these latter 4 were considered as ADA-positive subjects for the immunogenicity analysis. However, it was considered necessary to also analyse the response of the ADA+-at-screening subjects in order to form a more complete image of the immunogenic profile of HLX02 versus Herceptin. This analysis was provided in response and generally no effect on safety could be detected. Likewise, the ADA+-at-screening patients did not seem to have an ORR that diverged from the overall ORR findings (data not shown). However, it is difficult to draw any solid conclusion on these observations given the extremely low sample size.

Overall, there were some hints that ADA positivity may influence response but the number of subjects with ADA and/or NAb positive were too limited to be able to draw any conclusion.

Medication errors due to subcutaneous administration have been classified as important identified risk in the RMP for this biosimilar based on its seriousness, but the benefit risk defined in the SmPC is not impacted. Whereas Zercepac is presented as a lyophilised formulation for intravenous infusion, the reference medicinal Herceptin is available in two presentations for both intravenous and subcutaneous administration. It is therefore possible that a mistake could be made and Zercepac could be administered subcutaneously which could lead to patient harm through over dosing, under dosing or treatment toxicity. However, the risk is greater with the reference medicinal product Herceptin, than for trastuzumab biosimilars which have been approved with a single route of administration. Herceptin has now been used for several years as standard practice with successful risk strategies.

2.6.2. Conclusions on the clinical safety

Overall the safety of HLX02 does not seem to deviate from the safety profile of the Herceptin comparator. Some differences in certain safety parameters were observed in the analysis conducted with Asian/non-Asian and Chinese/non-Chinese the Asian/Chinese/non-Asian/non-Chinese as stratification axes. However, this could be due to the difference in docetaxel toxicity which exists between Asian and non-Asian patients. Furthermore, ADRs and severity graded TEAEs were balanced between the treatment arms in these subpopulations.

Despite the shortfall of one month of exposure, the totality of evidence generated at this point sufficiently indicates that the investigational medicinal product, HLX02 is biosimilar to the reference product from a safety perspective. Updated safety data, including immunogenicity data, are recommended to be provided with the final CSR of study HLX02-BC01.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Cardiac dysfunction • Hypersensitivity • Oligohydramnios
Important potential risks	Medication error (subcutaneous administration)
Missing information	None

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

Safety concern	Risk minimisation measures
Cardiac dysfunction	Routine risk minimisation measures: Warning in section 4.4 of the SmPC concerning the risk of cardiac dysfunction and the need for caution in patients with increased cardiac risk. Recommendations concerning cardiac assessment and monitoring before, during and after treatment with trastuzumab. Criteria for discontinuing or interrupting treatment with trastuzumab based on LVEF. The need to institute CHF treatment. Cardiac undesirable effects listed in section 4.8 of the SmPC including Ejection fraction decreased, Cardiac failure congestive, Cardiogenic shock, Acute pulmonary oedema, Pulmonary oedema and Orthopnoea. Legal Status: Prescription only medicine
Hypersensitivity	Section 4.2 of the SmPC describes the correct method of administration for the first and subsequent infusions and the recommended observation times following these infusions. The need to be prepared for managing anaphylaxis and possible actions including interrupting or slowing the infusion rate if hypersensitivity reactions occur are also described. Section 4.4 warns about the risk of hypersensitivity reactions and informs that patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. This section also provides information concerning pre-medication and treatment for these reactions and warns about the possibility of delayed reactions. Section 4.8 of the SmPC lists the following undesirable effects: Infusion related reaction, Erythema, Rash, Swelling face, Wheezing, Dyspnoea, Cough and Lip swelling, Hypersensitivity, Maculopapular rash, Pruritus, Asthma and Hypotension, Urticaria, Anaphylactic reaction, Anaphylactic shock, Angioedema, Respiratory distress, Respiratory failure, Bronchospasm and Laryngeal oedema. Legal Status: Prescription only medicine

Safety concern	Risk minimisation measures
Oligohydramnios	Section 4.6 of the proposed SmPC warns about the risk of oligohydramnios and foetal harm and advises that women of childbearing potential should use effective contraception during treatment and for 7 months after treatment with trastuzumab. The SmPC also states that trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. If a pregnant woman is treated with trastuzumab, or if a patient becomes pregnant while receiving trastuzumab or within 7 months following the last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable. Section 4.8 of the proposed SmPC lists the following undesirable effects: Oligohydramnios, pulmonary hypoplasia and renal hypoplasia. Legal Status: Prescription only medicine
Medication error (subcutaneous administration).	Routine risk minimisation measures: Warning in section 4.2 'Posology and method of administration' of the SmPC concerning the administration of Zercepac, such that Zercepac intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only. In addition product will only be administered by healthcare professionals. Text is also included to prevent medication errors, re checking the vial labels to ensure that the medicinal product being prepared and administered correctly. Legal Status: Prescription only medicine

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Herceptin and Solifenacin succinate. The bridging report submitted by the applicant has been found acceptable.

2.9.2. Additional monitoring

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

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

HLX02 (Zercepac) has been developed as a biosimilar to the reference product Herceptin (INN: trastuzumab) for intravenous use. Subcutaneous use is not applied for. The proposed indications for HLX02 are the same as those currently authorised for the reference medicinal product:

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

To assess the biosimilarity of HLX02 to the reference medicinal product Herceptin from a quality perspective, the applicant has performed an extensive head-to-head analytical study and an overall similarity study using multiple batches of HLX02 and Herceptin. An array of orthogonal analytical methods has been used to assess the primary and high order structure, the purity and impurity profile of the molecule, the extent of post translational modifications and the biological activity of the molecule.

For the *in vitro* non-clinical biosimilarity assessment several assays were conducted, including the binding kinetics of HLX02 to HER2, inhibition of the proliferation, ADCC, ADCP, CDC, apoptosis, C1q binding and FcγR and FcRn-receptor affinity assays. In all the studies performed, HLX02 was manufactured according to two manufacturing processes and comparisons were conducted against several batches of EU-sourced Herceptin. *In vivo* studies including pharmacology, pharmacokinetics and toxicology determinations were carried out with HLX02 following a prior manufacturing process and compared to China-sourced Herceptin. Data provided is compliant with applicable EMA guidance although *in vivo* studies are not considered essential for MAA according to current relevant EMA guidelines. The *in vitro* primary pharmacodynamics data provided concluded on biosimilarity between HLX02 and the reference medicinal product trastuzumab (Herceptin).

The clinical development programme to demonstrate PK comparability and clinical efficacy/safety similarity between HLX02 and reference medicinal product trastuzumab (Herceptin), consisted of two trials:

PK similarity: Phase 1, two-parts [Part 1 – open-label, single dose-ascending study evaluating safety, tolerability, immunogenicity and PK at different doses of HLX02; Part 2 - randomised, double-blind, 3-arm parallel-controlled, single-dose study comparing the PK, safety, tolerability and immunogenicity comparability of HLX02 and two reference medicinal product trastuzumab (EU-sourced Herceptin manufactured in Germany and CN-sourced Herceptin manufactured in the US)) clinical trial in healthy male subjects (Study HLX02-HV01).

Clinical efficacy and safety comparability: Phase 3, randomised, double-blind, 2-arm parallel-controlled, multi-national confirmatory study evaluating the efficacy and safety of HLX02 versus EU-sourced Herceptin in patients with HER2-overexpressing recurrent or previously-untreated metastatic breast cancer (Study HLX02-BC01).

3.2. Results supporting biosimilarity

From a quality perspective, the available data from the analytical similarity assessment demonstrates that HLX02 is highly similar to Herceptin. The amino acid sequence is identical, and primary and higher order structures including secondary, tertiary structure are similar. The purity and heterogeneities between HLX02 and Herceptin assessed by SEC, CE-SDS, CEX, icIEF and UPLC-FLR glycan profiling are highly similar, with similar profiles of size and charge variants and glycan moieties. Minor differences in relative abundance of charge variants and glycan moieties were observed and have been appropriately justified. A series of functional assays relevant to MoA, efficacy and safety were conducted to evaluate the biological activity. In response to a major objection raised, satisfactory data was provided to confirm high similarity between HLX02 and EU Herceptin with regard to ADCC activity. The forced degradation studies involving high temperature, illumination, acidity, alkalinity, oxidation and shaking showed that HLX02 and Herceptin-EU had similar degradation behaviours and degradation trends.

The data provided regarding the *in vitro* primary pharmacodynamics studies support similarity between Herceptin and HLX02 (Zercepac) from a non-clinical perspective.

By the cut-off date (27 November 2018), the pivotal trial met the primary endpoint at the interim analysis. The difference in ORR (HLX02 minus Herceptin) between the 2 treatments was -0.4 % with 95%CI of -7.4 % to 6.6%. The 95% CI was within the pre-specified equivalence margin of -13.5% to 13.5%. The ORR up to 24 weeks in ITT set was 71.0% (230 of 324 patients) (95% CI, 66.0, 75.9) for HLX02 and 71.4% (232 of 325 patients) (95% CI, 66.5, 76.3) for Herceptin.

The results from primary analysis were supported by the results of several sensitivity analyses. With the second interim analyses (10 Jul 2019), a trend in favour of HLX02 was observed in the primary endpoint and ORR at week 33, 42 assessed by the investigators. However, no significant difference was found between two treatment groups in terms of median DoR, PFS and OS in the second interim analysis despite of the immature data, which partly supported the primary results.

In the pivotal study Study HLX02-BC01, the safety of HLX02 did not seem to deviate from the safety profile of the Herceptin comparator. Some differences in certain safety parameters were observed in the analysis conducted with Asian/non-Asian and Chinese/non-Chinese the Asian/Chinese/non-Asian/non-Chinese as stratification axes. However, this could be due to the difference in docetaxel toxicity which exists between Asian and non-Asian patients. Furthermore, ADRs and severity graded TEAEs were balanced between the treatment arms in these subpopulations.

With regards to immunogenicity, the number of subjects with ADA and/or NAb positive results were too limited to be able to draw any clinically meaningful conclusion.

Overall, biosimilarity of HLX02 to the reference medicinal products can be concluded from a PK/PD, immunogenicity, safety and efficacy perspective.

3.3. Uncertainties and limitations about biosimilarity

The median exposure duration with the second interim analysis did not reach the requested one year of duration (median duration of 312 days). Nonetheless, based on the safety and immunogenicity data available in the second interim analysis which did not show worrisome divergences between treatment groups, this is considered acceptable. Also, it is unlikely that the 1.8-month difference in exposure would expose a divergence between treatment groups in either safety or immunogenic aspects. Furthermore, the applicant is recommended to provide updated safety analysis, including immunogenicity data, in the final CSR.

3.4. Discussion on biosimilarity

From a quality perspective, an extensive comparability exercise has been performed between HLX02 and EU Herceptin and the results confirm a high level of similarity from a quality point of view.

Biosimilarity of HLX02 to the reference medicinal product Herceptin is supported from a non-clinical perspective based on the *in vitro* pharmacology data.

From a PK/PD, efficacy and safety perspective, biosimilarity of HLX02 to the reference medicinal products can be concluded. Despite the shortfall of one month of exposure, the totality of evidence generated at this point sufficiently indicates that the investigational medicinal product, HLX02 is biosimilar to the reference product from a safety perspective.

Therefore, based on the totality of data, biosimilarity between HLX02 and Herceptin has been demonstrated.

3.5. Extrapolation of safety and efficacy

Extrapolation of indication has been justified by the applicant based on the fact that the mechanism of action of trastuzumab is the same in all three indications and the target receptor involved is also the same in MBC, EBC and MGC. The dosage is also similar for all three indications, and trastuzumab is administered by the same route in all indications. Hence, extrapolation in terms of efficacy is supported by the results of the physicochemical, structural and biological characterisation data, results from the comparative preclinical studies (in vitro functional tests) together with PK comparability data. Extrapolation is also considered acceptable from a safety perspective.

3.6. Additional considerations

It has also to be considered that medication errors (subcutaneous administration) have been included as identified risk, due to the marketed formulation from the reference medicinal product. In this regard, measures are in place to mitigate this risk (routine risk communication as well as routine risk minimisation activities), which are sufficient in order to minimise the risks of the product in the proposed indications.

3.7. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Outcome

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

"Breast cancer

Metastatic breast cancer

Zercepac 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

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

Zercepac 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

Zercepac 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.

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

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

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

Not applicable.

These conditions fully reflect the advice received from the PRAC.