Amsterdam, 26 February 2026
EMA/69263/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Poherdy

International non-proprietary name: Pertuzumab

Procedure No. EMEA/H/C/006583/0000

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
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AEX	Anion Exchange Chromatography
AUC	Area under the curve
AV	Atrioventricular
bpCR	Breast pathologic complete response
BSA	Body surface area
C	Cycle
CAT	Committee for Advanced Therapies
CBE	Clinical breast exam
CHO	Chinese Hamster Ovary
CI	Confidence Interval
cIPC	Critical In-process Control
Cmax	Maximum serum concentration
CMH	Cochran-Mantel-Haenszel
CPP	Critical Process Parameter
CR	Complete Response
CSR	Clinical Study Report
DB	Double-blind
DFS	Disease-free survival
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Estrogen Receptor
GCP	Good Clinical Practice
HER2	Human epidermal growth factor receptor 2
HLX11	Poherdy
HR	Hormone receptor
HR	Hazard Ratio
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IPC	In-process Control
IPT	In-process Test
IRC	Independent review committee

IRT	Interactive Response System
ISH	In Situ Hybridization
ITT	Intent-to-treat
IV	Intravenous
LVEF	Left ventricular ejection fraction
MUGA	Multiple Gated Acquisition
NA	Not Applicable
Nab	Neutralizing antibodies
NE	Not Evaluable
NYHA	New York Heart Association
ORR	Overall response rate
PD	Pharmacodynamics
PD	Progressive Disease
PES	Polyethersulfone
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
PPS	Per-Protocol Set
PR	Progesterone Receptor
PR	Partial Response
PRAC	Pharmacovigilance Risk Assessment Committee
Q3W	Every 3 weeks
RD	Randomised
RD	Risk Difference
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk management plan
RR	Risk Ratio
SD	Standard Deviation
SD	Stable Disease
SmPC	Summary of Product Characteristics
t1/2	Elimination half-life
TNM	Tumour Node Metastasis
tpCR	Total pathologic Complete Response
UPB	Unprocessed Bulk
VCD	Viable Cell Density

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	POHERDY
Active substance	Pertuzumab
INN or common name	Pertuzumab
Applicant	Organon N.V. Kloosterstraat 6 5349 AB Oss NETHERLANDS
EMA product number	EMEA/H/C/006583
ATC code and pharmacotherapeutic group	L01FD02 MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES HER2 (Human Epidermal Growth Factor Receptor 2) inhibitors
Pharmaceutical form(s) and strength (s)	Concentrate for solution for infusion 420 mg
Packaging	Vial (glass)
Package size(s)	1 vial
Route of administration	Intravenous use
Device or diagnostic	Not applicable
Orphan designation	Not applied for
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 10(4) of Directive 2001/83/EC
Final indication	<u>Early breast cancer</u> Poherdy is indicated for use in combination with trastuzumab and chemotherapy in: • the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence • the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence <u>Metastatic breast cancer</u> Poherdy is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.
New active substance status	Not applied for

1.2. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	Topic (quality / non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
11 November 2021	Quality, Clinical	EMA/SA/0000068461	The Scientific advice pertained to the following quality and clinical aspects: • Impact of differences observed in the preliminary analytical similarity comparison of HLX11 and EU-Perjeta on clinical efficacy and safety. • The design of a randomized, double-blind clinical study to compare efficacy, safety, and immunogenicity of HLX11 versus EU-sourced Perjeta in patients with early or locally advanced HER2 positive and HR-negative breast cancer including study population, inclusion/exclusion criteria, choice of background therapy, its dose, and dose adjustment criteria, primary and secondary endpoints, stratification factors, treatment duration, sample size and statistical approach, crossover design. • Extrapolation of clinical efficacy and safety data to the other authorized indication of Perjeta provided that analytical, non-clinical, and clinical PK studies demonstrate biosimilarity.

1.3. Eligibility to the centralised procedure

The applicant Henlius Europe GmbH submitted on 28 February 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Poherdy (Pertuzumab), through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Early breast cancer

HLX11 is indicated for use in combination with trastuzumab and chemotherapy in:

- the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence.
- the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.

Metastatic breast cancer

HLX11 is indicated for use in combination with trastuzumab and docetaxel in adult patients

with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

During the procedure, the applicant has changed from Henlius Europe GmbH to N.V. Organon Relevant documents for the change of applicant have been provided, validated and agreed.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, and 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 European Union provisions in force for not less than 8 years in the EEA:

Product name, strength, pharmaceutical form:	Perjeta, 420 mg, Concentrate for solution for infusion
Marketing authorisation holder:	Roche Registration GmbH
Date of authorisation:	04 March 2013
Marketing authorisation granted by:	European Union
Marketing authorisation number:	EU/1/13/813/001

1.5. Information on paediatrics

Not applicable.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

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

1.7. Steps taken for the assessment of the product

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

Rapporteur:	Jan Mueller-Berghaus
Co-rapporteur:	Outi Mäki-Ikola

The rapporteur and Co-rapporteur appointed by the PRAC were:

PRAC rapporteur:	Marie Louise Schougaard Christiansen
PRAC Co-rapporteur:	N/A

The application was received by the EMA on	28 February 2025
The procedure started on	27 March 2025
The CHMP rapporteur's first assessment report was received on	16 June 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	18 June 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	30 June 2026
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	2 October 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	17 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP list of outstanding issues on	27 January 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	11 February 2026
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 Poherdy on	26 February 2026

1.8. CHMP outcome

1.8.1. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.8.2. Opinion

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

Early breast cancer

Poherdy is indicated for use in combination with trastuzumab and chemotherapy in:

- the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence (see section 5.1)

- the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence (see section 5.1)

Metastatic breast cancer
Poherdy is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

1.8.3. Conclusions on biosimilarity and benefit risk balance

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

1.8.4. Conditions or restrictions regarding supply and use

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

1.8.5. Other conditions and requirements of the marketing authorisation

1.8.5.1. 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.

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

1.8.6.1. Risk management plan (RMP)

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

An updated RMP should be submitted:

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

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

Not applicable.

2. Introduction

2.1. Therapeutic context

Not applicable.

2.2. Aspects of development

Poherdy is being developed as a proposed biosimilar to EU-Perjeta.

The clinical development program to demonstrate PK similarity and clinical comparability between Poherdy and EU-Perjeta consists of the following two trials:

- PK similarity (study HLX11-001): a randomized, double-blind, intravenous single-dose, parallel, four-arm phase I clinical study to compare pharmacokinetics, safety, and immunogenicity of HLX11 vs. Perjeta (US, EU, and CN-sourced) in healthy Chinese male subjects.
- Clinical comparability (study HLX11-BC301): a multicenter, randomized, double-blind, parallel-controlled phase III clinical study to evaluate the efficacy and safety of pertuzumab biosimilar HLX11 vs. EU-Perjeta in the neoadjuvant therapy of HER2-positive and HR-negative early-stage or locally advanced breast cancer.

2.3. Description of the product

Poherdy has been developed by Shanghai Henlius Biotech, Inc. as a proposed biosimilar of Perjeta. Poherdy contains the active substance pertuzumab.

Pertuzumab is a recombinant humanised IgG1 monoclonal antibody that specifically targets the extracellular dimerization domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby, blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signalling through two major signal pathways, mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of these signalling pathways can result in cell growth arrest and apoptosis, respectively. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

The proposed indications for Poherdy are the same as those approved for Perjeta:

Early breast cancer

Poherdy *is indicated for use in combination with trastuzumab and chemotherapy in:*

- *the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence;*
- *the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.*

Metastatic breast cancer

Poherdy *is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.*

One 14 ml vial of concentrate contains 420 mg of pertuzumab at a concentration of 30 mg/ml. This is the same amount and concentration of drug substance as the reference medicinal product.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required. EU-GMP certificate is available in EudraGMPD: BE/GMP/2025/038

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

2.4.3. Good clinical practice (GCP) inspection(s)

No inspection required.

3. Quality aspects

3.1. Introduction

Poherdy is a proposed biosimilar to the reference medicinal product (RMP) Perjeta (EMEA/H/C/002547).

The active substance pertuzumab (INN), also referred to as HLX11, is a humanised IgG1 monoclonal antibody (MAb) produced in mammalian Chinese hamster ovary (CHO) cells by recombinant DNA technology. It specifically targets the extracellular dimerisation domain (subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), and thereby, blocks ligand-dependent heterodimerisation of HER2 with other HER family members, including EGFR, HER3 and HER4.

The active substance is formulated with L-Histidine, L-Histidine hydrochloride monohydrate, sorbitol, polysorbate 20 (PS20) and water for injections.

The finished product is presented as a 420 mg concentrate for solution for infusion in a 14 mL vial (concentration of 30 mg/mL).

3.2. Active Substance

3.2.1. General Information

HLX11 is a humanised IgG1 kappa MAb. This glycosylated MAb consists of two identical heavy chains (HCs) and 2 identical light chains (LCs) covalently linked by disulfide bonds. Each heavy chain has 448 amino acids, while each light chain has 214 amino acids. The antibody contains four pairs of interchain disulfide bonds and 12 pairs of intrachain disulfide bonds. Each heavy chain contains one N-glycosylation site (N299). The major glycans identified are G0, G0F, G1F and G2F. HLX11 molecular weight is approximately 145 kDa excluding N-glycan contribution weight.

3.2.2. Manufacture, process controls and characterisation

Description of the manufacturing Process

HLX11 active substance is manufactured and tested for release by Shanghai Henlius Biologics Co., Ltd. (SJ1) at Building 1, No. 182 Wenjun Road, Songjiang District, Shanghai, China. A Certificate of GMP compliance is provided. All sites involved in manufacturing and control of the active substance operate in accordance with EU GMP.

Cell culture process

The active substance is produced by transfected CHO cells through a fed-batch process. Single-use technology is used in the active substance manufacturing process. The upstream process begins with the thawing of a working cell bank (WCB) vial, which is then expanded in shake flasks and seed bioreactors and eventually in a final production bioreactor.

The bioreactor harvest undergoes clarification, followed by downstream purification steps. The test and the acceptable limit are indicated in the description of the manufacturing process.

Purification process

The downstream process includes chromatography steps, orthogonal virus clearance steps. Subsequently, buffer exchanged through diafiltration. The active substance is formulated, filtered and dispensed into bottles. A risk-based approach to ensure appropriate microbiological control throughout the process. A tiered in-process control strategy is implemented.

Reprocessing is permitted for certain steps under specific condition.

Control of Materials

Raw materials

A list of raw materials used in active substance manufacturing process is provided. The formula of the buffers used in the downstream process is provided as well. All the non-compendial raw materials are tested and released for manufacturing based on the in-house specifications. The compendial methods are following both Ph. Eur. and USP.

Generation of cell substrate

The amino acid sequences of the variable regions of the HLX11 heavy and light chains were obtained from the US patent titled "Uses for and article of manufacture including Her2 dimerisation inhibitor pertuzumab" (Patent number: US20130095172A1). The expression vectors were transfected into CHO cells and cell line was selected based on cell growth and antibody expression level.

Both the MCB and the WCB were characterised and tested according to the ICH Q5A guideline. Testing results of MCB and WCB met their corresponding acceptance criteria. The study of LIVCA has been conducted. The resulting intervening passage number for LIVCA between MCB vial thaw and the EOPC was determined and PDL was determined. The stability of MCB and WCB will be tested according to the established cell bank storage stability protocol for MCB and WCB. Future WCBs will be established within a GMP cell banking facility. All future WCBs will be characterised and released in accordance with well-established tests, which are provided with the documentation.

Control of critical steps and intermediates

Active substance manufacturing process includes defined process parameters and IPCs/IPTs for each unit step. Process parameters are classified as CPP or non-CPP. CPPs are critical for maintaining the critical quality attributes (CQAs), and acceptable ranges for these CPPs have been established. A tiered

in-process control strategy is implemented. These categories are distinguished based on their impacts on patient safety, product quality and process consistency.

The proposed manufacturing process control strategy is considered adequate.

Process validation

Process performance qualification (PPQ) runs on consecutive commercial scale active substance batches were successfully executed. All results for consecutive PPQ batches met the pre-defined acceptance criteria.

At different stages throughout the manufacturing process, holds of process intermediates are proposed in some unit operations. Process intermediate hold time studies were conducted to support the proposed hold time during manufacturing process.

Lifetime studies of reusable resins were conducted using small-scale models qualified for downstream process characterisation. Lifetime studies for resins and membranes will further be executed on at-scale batches as part of a concurrent validation exercise which is accepted. Reprocessing is permitted for certain steps in case of failure of post-use filter integrity test.

In the active substance and finished product manufacturing processes, numbers of single-use components were utilised throughout the upstream process, downstream process, filling, and packaging stages. The risk assessment performed on these components is acknowledged.

An extractable study was conducted.

Overall, the manufacturing process for the active substance is considered adequately validated.

Manufacturing process development

A quality target product profile (QTPP) was developed based on expected efficacy and safety outcomes for the product. From initial potential CQAs (pCQAs), HLX11 CQAs were determined from the QTPP based on a risk assessment. An additional risk assessment was conducted to identify process parameters that may impact CQAs. The identification of active substance related CQAs and key performance attributes (KPAs) is part of defining the key output variables linked to the process parameters which are studied, e.g. glycosylation most likely affected by the cell culture process. Process characterisation study for each unit operation was conducted using various methods, including univariate studies (e.g. One Factor at a Time (OFAT) analysis), multivariate studies (e.g. Design of experiment (DoE)), and extreme case studies. Overall, the approach is acceptable. The upstream unit operation process characterisation studies include vial thaw, cell expansion in shake flasks, cell expansion in 50 L WAVE bioreactor, a 500 L bioreactor, and cell production in a 2000 L bioreactor. The process characterisation study for CEX was conducted using a DoE approach on the qualified small-scale model. Within the studied range for load density, a significant impact was observed on acidic peaks and yield; however, the results remained within the PC AC. A process characterisation study was conducted for the last manufacturing step (Step 13), i.e. active substance formulation, filtration, aliquoting and storage, and no CPPs have been identified. Several CQAs, such as osmolality, polysorbate 20 and protein content are directly affected by addition of excipients in the formulation step. Since HLX11 active substance and finished product have the same formulation composition and content, i.e. no further formulation step is included in the finished product manufacturing process, the addition of excipients should be considered critical. A CPP impacting on a CQA cannot be downgraded as non-critical based on detectability and/or well-established control. Therefore, addition of excipients and buffer in the active substance formulation step are considered as CPPs. A downstream removal capability study was conducted for process-related impurities, confirming their effective removal during the downstream process.

Three manufacturing processes were developed for HLX11 active substance and used for the production of clinical study, PPQ, and commercial batches. The product quality comparability assessment between different processes was performed in accordance with the ICH Q5E guideline. The comparison of physico-chemical properties, post-translational modifications (PTMs) (excluding glycosylation), impurities, biological activities, thermal stability and IPC results indicates mainly comparable quality. In conclusion, comparability has been sufficiently demonstrated.

Characterisation

Elucidation of structure

A characterisation study was performed using four PPQ batches produced from active substance commercial process. The characterisation of HLX11 active substance includes the analyses of primary structure, higher-order structure, post-translational modifications, size variants, charge heterogeneity, glycosylation, biological activities, and immunochemical properties using state-of-art and orthogonal methods. The methods have been either validated or verified for release and stability testing, or qualified for structural, physicochemical and biological characterisation. Data indicate that HLX11 had the same structure and function as Pertuzumab.

Impurities

Regarding product-related impurities, HLX11 should have the same purity profile as Perjeta and thus, the issue is further discussed in the biosimilarity section. In general, relevant product-related impurities are covered by the overall control strategy including specifications and adequate limits.

The proposed commercial purification process is capable for process-related impurity clearance. Clearance study is concluded as low safety risk for patient in regards to process-related impurities.

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

Specifications and justification of proposed limits

Specifications are set in accordance with ICH Q6B and include control of identity, purity and impurities, potency and other general tests.

The proposed acceptance criteria for identity, appearance, pH, osmolality, polysorbate 20, protein content, purity and impurities, potency, bacterial endotoxins and bioburden are appropriately justified and acceptable.

The Applicant has outlined their strategy for setting of release and stability acceptance criteria. For quantitative testing items without compendial requirement and relevant development data, an appropriate approach was used.

Analytical methods

Sufficiently detailed descriptions of analytical methods are provided. Compendial methods are tested according to the current Ph. Eur monographs.

Analytical methods developed in house were validated according to recommendations of ICH Q2 guideline and were confirmed as suitable for use. Pharmacopoeia methods were verified based on Ph. Eur. Monographs. Certain in-house methods were investigated with regard to stability indicating properties. These seem rather harsh conditions and only moderate changes to the quality attributes are obvious. But their stability indicating potential is acknowledged. Both methods for endotoxin detection were validated and also tested for interference. Low endotoxin recovery (LER) was evaluated on the active substance and finished product. The Applicant is encouraged to consider the feasibility of

transitioning to Ph. Eur. 2.6.32 Test for bacterial endotoxins using recombinant cascade reagent method (rCR-based method), eliminating the need for horseshoe crab derived material.

Batch analysis

The batch analysis data for HLX11 active substance is provided. These batches were tested according to the test methods and specifications applicable at the time of the testing and release. All results met the acceptance criteria.

Reference Standards or Materials

A brief, but sufficient description of these reference standards and their characterisation is included.

The Applicant briefly outlines the strategy on replacement of future reference standards in case the current primary reference standard or working reference standard depletes. Regarding the potency assignment of future reference standards, the Applicant has elaborated on the potency requalification requirement of future reference standards. The defined acceptance criteria and number of tests are considered sufficient to avoid a potential drift in potency to future reference standards and hence is accepted. In addition, the risk of drifting can be mitigated by implementing a two-tiered system for reference standards. The Applicant confirmed that the primary reference standard will only be used for the qualification and requalification of the working reference standard or new primary reference standard, and the working reference standard is to be used for routine QC purposes and supporting the requalification of primary reference standard if needed.

Regarding stability, the Applicant indicates that the primary reference standard has been requalified from preparation date and an appropriate period since the first working reference standard released. The requalification requirements of reference standards are provided. The Applicant clarified that the working reference standard is newly prepared and has not yet reached the stability testing period, so there are no requalification results of the working reference standard included. Working reference standards will be requalified at regular intervals after their preparation.

Container closure system

The container closure system (CCS) for HLX11 active substance is PC bottle from Nalgene Nunc International, a part of Thermo Fisher Scientific. PC bottle for active substance is made of biological compatible materials and passed the test of USP Class VI. Extractable and leachable studies were conducted on aseptic PC bottle and the available results were considered safe.

3.2.4. Stability

Stability studies were conducted in accordance with the requirements of ICH Q5C. Long-term and accelerated stability studies were conducted on HLX11 active substance produced by different processes. Freeze-thaw stability was conducted with one batch. Three batches of active substance were selected for a stress stability study. On the basis of the data provide, it is considered acceptable to claim a shelf life of 24 months when stored at -40 ± 5℃, protected from light for HLX11 active substance.

3.3. Finished Medicinal Product

3.3.1. Description of the product and Pharmaceutical Development

Description of the product

HLX11 finished product (Poherdy) is provided as a sterile liquid solution for intravenous infusion at a concentration of 30.0 mg/mL in 420 mg (14 mL) in single dose vials. Each vial of HLX11 finished product contains 420 mg HLX11 (pertuzumab). Other ingredients are L-histidine, L-histidine hydrochloride monohydrate, sorbitol, polysorbate 20, and water for injections, with a pH of 6.0. All excipients are compendial. No excipients of human or animal origin or novel excipients are used.

The formulation of HLX11 is different from the reference medicinal product EU-Perjeta formulation. Sucrose has been replaced with sorbitol and histidine acetate with histidine hydrochloride.

Pharmaceutical development

The pharmaceutical development of Poherdy is in general adequately described.

During development the manufacturing process was optimised resulting in three processes. The main changes introduced are up-scales and facility adaptations. Two ICH Q5E compliant comparability studies were performed, one for each process change. The studies included comparisons of in-process tests, release tests additional characterisation and for the first study (P1.0 to P2.0) degradation behaviour under forced degradation conditions. This is considered acceptable, taking the changes made into account. In general, the materials from the processes are considered comparable.

The development of the control strategy of Poherdy finished product is based on the QTPP. A risk assessment to define the CQAs has been performed using two factors: impact and uncertainty of that impact. To identify site-specific CPPs and non-CPPs, a failure mode and effects analysis (FMEA) approach was used. This analysis relied on prior process knowledge, historical manufacturing, formulation development and process characterisation data. The approach has been sufficiently described. Process characterisation studies have been performed to establish acceptable ranges of process parameters which do not affect CQAs.

The HLX11 finished product CCS consists of a 20 mL middle borosilicate glass vial (type I glass), a 20 mm chlorobutyl rubber stopper, and a 20mm aluminium-plastics combination cap. The glass vial and rubber stopper comply with Ph. Eur. Extractable and Leachable studies were performed which showed no compounds above safety levels. An elemental impurity assessment in line with ICH Q3D revealed no concern. An inverted stability study using long-term and accelerated conditions showed no differences in trends on quality attributes in comparison to upright stability data indicating that the primary packaging materials are compatible with the product.

HLX11 is intended to be administered by intravenous infusion. Compatibility studies were performed using IV bags made of PVC or polypropylene (PP) material of construction with target concentration between 1.5 mg/ml and 3 mg/ml after dilution with 0.9% sodium chloride solution. The study demonstrates that the diluted product remains stable for 48 hours at 2-8℃ and 24 hours at 30℃ under ambient light.

A microbial challenge study was performed for up to 48 hours using diluted product samples. The study results indicate that the maximum acceptable storage time after dilution is up to 48 hours at 2-8°C. Considering a 2-fold safety margin it is recommended in the SmPC from a microbial point of view that the diluted product be stored at 2-8°C for up to 24 hours if not used immediately after preparation.

3.3.2. Manufacture of the product and process controls

Manufacture

The finished product manufacturing, primary and secondary packaging take place at Shanghai Henlius Biologics. Final EU batch release is performed at Eurofins PHAST GmbH. All sites involved in manufacturing and controls of the finished product operate in accordance with EU GMP.

The finished product manufacturing process consists of thawing of active substance, active substance mixing, sterile filtration, aseptic filling, 100% inspection and release sampling of filled vials. The filled vials are assembled with a stopper and capped.

The batch formula of finished product was provided, including formula for a minimum and maximum batch sizes.

A brief description of each step has been included, which is considered adequate. IPCs are indicated and the processing times stated.

Process controls

The process control strategy has been briefly described. Control strategy parameters CPP, IPC have been defined. Process parameters are classified based on the criticality of each process parameter as either a CPP or a non-CPP. A tiered in-process control strategy has been adopted.

All process control elements are managed in the quality system and routine monitoring of process and product performance.

Reprocessing of a manufacturing step is not mentioned and therefore not permitted.

The control strategy has been briefly described. The process parameters and IPC limits, as well as process time and intermediate hold-time conditions and limits are supported by process characterisation and PPQ-batch data.

Process validation

PPQ batches manufactured from the commercial process were included into the process validation. The data provided including additional validation tests complied with the predefined acceptance criteria.

Hold time qualification studies were performed investigating all manufacturing steps.

Aseptic process (media fill) simulations (APS) have been performed. Sterilisation of equipment and packaging components has been directly validated. This is considered sufficient.

Shipping validation has been done. The data do not raise concerns.

3.3.3. Product specification, analytical procedures, batch analysis

Specifications

The specifications have been set based the principles of ICH Q6B and include control of identity, appearance, pH, osmolality, polysorbate 20, protein content, purity and impurities, potency, bacterial endotoxins and sterility, and other general tests. Acceptance criteria were developed considering clinical evidence, compendial requirements, relevant development studies, reference product quality range, manufacturing process variability, and analytical method variability.

Analytical procedures

The methods used for finished product testing are either compendial test methods or are identical to the methods used for active substance testing, with the exception of the visible particles, sterility, container closure integrity assay, and extractable volume. The test methods are sufficiently described.

Compendial methods including colour, clarity, bacterial endotoxins, sterility, pH, osmolality, visible and subvisible particles, extractable volume and protein content are based on respective Ph. Eur. monographs. The verification results for sterility tests (membrane filtration) presented in the dossier confirms the suitability of the method for its intended use. The level of endotoxins was determined using the kinetic turbidimetric assay (KTA). Limulus amebocyte lysate (LAL) is used as substrate. Appropriate verification results were provided for turbidimetric endotoxin method.

For product formulations that contain a combination of a surfactant (e.g. polysorbate) and a chelator (e.g. EDTA, citrate, phosphate, histidine), studies investigating LER should be submitted in the marketing authorisation application (MAA) dossier. The Applicant provided sufficient information (see active substance section).

Non-compendial analytical methods for the finished product of HLX11 are mainly same than those used for active substance and include SEC-HPLC, CEX-HPLC, CE-SDS (reduced), CE-SDS (non-reduced), protein content, cell-based anti-proliferation assay, HER2 binding activity (ELISA), PS20 content, identity by peptide mapping. Method validation is provided.

Batch analysis

Batch release data are provided for HLX11 finished product manufactured commercial manufacturing process at Shanghai Henlius Biologics Co., Ltd. (SJ1). Furthermore, development batch data from process manufactured at Shanghai Henlius Biopharmaceutical Co., Ltd. (YS) were also provided. All test results are within specifications.

Reference standards or materials

For information on reference standards, reference is made to corresponding active substance section, which is considered adequate, as the same materials are used for active substance and finished product. The information provided is considered sufficient.

Characterisation of impurities

In regard to potential finished product impurities, reference is in general made to corresponding active substance section, which is considered adequate as no new impurities are expected.

A risk assessment concerning nitrosamines in line with the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products 03 August 2020 EMA/409815/2020 has been provided in Module 1. No risk has been identified and no dedicated control is considered necessary, which is endorsed.

Elemental impurities were investigated in accordance with ICH Q3D and specific information on all extractable and leachable studies is presented. In summary the risk of elemental impurities is negligible.

Container closure system

The HLX11 finished product CCS consists of a 20 mL Type I borosilicate glass vial, a 20 mm chlorobutyl rubber stopper, and a 20 mm aluminium-plastic combination cap (flip-off aluminium cap). The glass vial and stopper are in immediate contact with the finished product and comply with applicable compendial requirements. The quality control testing is briefly described. Certificates of analysis have been provided for the glass vials, rubber stoppers as well as the aluminium caps used. The technique

used for sterilisation have been stated (sterilisation by vial washer and depyrogenation tunnel for vials and heat inactivation by autoclave for rubber stoppers). Sterility assurance levels (SAL) of 10^{-6} are stated.

Overall, the CCS is considered to provide sufficient finished product protection against microbial contamination and adequate for long-term storage as supported by stability studies performed with identical CCS materials. The control strategy in place for the CCS qualification is sufficient.

3.3.4. Stability of the product

Stability studies were conducted in accordance with the requirements of ICH Q5C. Long-term and accelerated stability studies were conducted on HLX11 finished product produced by different processes. Three batches of finished product were selected for a stress stability study. On the basis of the data provided, the shelf life of 36 months when stored at 2ºC – 8ºC, protected from light for HLX11 finished product is acceptable.

The provided post-approval stability protocol is considered sufficient. The Applicant commits that all stability studies will be completed, one batch will be placed to stability, and in case of confirmed OOS or out-of-trend (OOT) results the competent authority will be informed, which is acknowledged.

After dilution, the chemical and physical in-use stability of Poherdy has been demonstrated for 48 hours at 2°C to 8°C followed by 24 hours at 30°C protected from light. From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2℃ to 8℃, unless dilution has taken place in controlled and validated aseptic conditions.

3.3.5. Biosimilarity

The biosimilarity exercise on quality aspects for the proposed biosimilar HLX11 with its EU reference medicinal products Perjeta followed the recommendations as laid down in EMA/CHMP/BWP/247713/2012. For establishment of the similarity criteria for the biosimilarity evaluation of HLX11 with its reference medicinal products a statistical approach was used.

Extensive structural and functional characterisations are applied using sensitive and state-of-the-art orthogonal methods to determine not only similarities but also potential differences in quality attributes. Any differences detected in the quality attributes will be appropriately justified with regard to their potential impact on safety and efficacy. In addition, the forced degradation and accelerated stability studies were also conducted. The product degradation is also evaluated to reflect the potential differences between HLX11 and EU-Perjeta.

In summary, the conclusion that biosimilarity versus the reference medicinal product has been sufficiently demonstrated, can be agreed.

Table 2: Summary of analytical similarity assessment results between HLX11 and EU-Perjeta

Test Category	Quality Attribute	Similarity Assessment Results
Primary structure	Amino acid sequence	Identical
	Molecular weight (MW)	Minor differences, which do not impact the efficacy and safety.
	Disulfide linkage	Identical
	Glycosylation site	Identical
	Post-translational modifications (PTM)	Minor differences, which do not impact the efficacy and safety.
	Free thiols	Similar
Higher order structure	Secondary and tertiary structures	Similar
Charge heterogeneity	Acidic peaks	Minor differences, which do not impact the efficacy of the product.
	Main peak	Minor differences, which do not impact the efficacy of the product.
	Basic peaks	Minor differences, which do not impact the efficacy of the product.
	Isoelectric point	Identical
Glycan distribution	Total Afuc	Slightly lower total Afuc were observed in HLX11, and the difference is not clinically significant
	Total High mannose	Slightly higher total HM were observed in HLX11, which did not cause differences in ADCC activities and clinical PK
	Total Gal	Similar
	Sialylation	Similar
	Sialic acid	Similar
Size Variants	Aggregates and monomer	Similar
		Similar
		Similar
	IgG	Minor differences, which do not impact the efficacy of the product.
	HC+LC	Minor differences, which do not impact the efficacy of the product.
	Non-glycosylated heavy chain (NGHC)	Similar
Protein content		Similar
Immunochemical properties	FcγRIa	Similar
	FcγRIIa-R	Similar
	FcγRIIa-H	Similar
	FcγRIIb/c	Minor differences, which do not impact the efficacy of the product.
	FcγRIIIa-V	Minor differences, which do not impact the efficacy of the product.
	FcγRIIIa-F	Minor differences, which do not impact the efficacy of the product.
	FcγRIIIb	Minor differences, which do not impact the efficacy of the product.
	FcRn	Similar

Test Category	Quality Attribute	Similarity Assessment Results
	C1q Binding	Similar
Bioactivity	HER2 binding	Similar
		Similar
	Anti-Proliferation	Similar
	ADCC	Slightly higher ADCC activity were observed in HLX11, and the difference is not clinically significant
	CDC	Negative
Accelerated stability study		Same degradation pathway and similar degradation trend
Forced degradation study		Same degradation pathway and similar degradation trend

3.3.6. Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated. The active substance is produced in a serum-free culture medium. No risk material of bovine origin is added during fermentation. The MCB and WCB which has been established is free from TSE-risk substances.

Virus safety

The fermentation process of the monoclonal antibody is in a serum-free medium. This minimises a possible contamination for adventitious viruses. The cells used for production of Poherdy have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the cell bank with the exception of A-type and C-type retroviral particles, which are well known to be present in in rodent cells. This is acceptable since there is sufficient capacity within the manufacturing procedure for reduction of this type of viral particles. The purification process includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated. The removal capacity of small non-enveloped viruses (MVM) is mainly based on several steps having some effectiveness. During the manufacture of active substance, column chromatography resins are used during purification. The viral clearance studies were performed with new and aged (AEX) chromatographic resins and column regeneration has been investigated.

In summary, the virus safety of Poherdy is expected to be sufficiently demonstrated.

3.4. Discussion and conclusion on chemical, pharmaceutical and biological aspects

Module 3 provided in support of the MAA for Poherdy is well structured and includes essential information. No major issued were identified.

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the active substance and finished product.

The analytical biosimilarity study showed good comparability between the proposed biosimilar and its RMP Perjeta. Poherdy is considered biosimilar to EU-Perjeta from a quality point of view.

Overall, the quality of this product is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical

performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the MAA for Poherdy is considered approvable from the quality point of view.

3.5. Recommendation(s) for future quality development

None.

4. Non-clinical aspects

4.1. Introduction

HLX11 (pertuzumab) is a humanized IgG1 kappa monoclonal antibody that targets the extracellular dimerization domain (subdomain II) of HER2, preventing its dimerization with other HER family proteins (HER1, HER3 and HER4). This inhibition blocks downstream signalling pathways, thereby suppressing tumour cell proliferation. In addition, HLX11 mediates antibody-dependent cell-mediated cytotoxicity (ADCC) through its Fc region.

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

No individual non-clinical studies were performed and considered necessary. In vitro assays (including functional assays) were conducted during the analytical comparability exercise which is acceptable. Based on the totality of evidence data of analytical, functional and clinical comparative studies no further non-clinical in vivo data are needed.

4.2. Pharmacology

4.2.1. Pharmacodynamics

4.2.1.1. Primary pharmacodynamic studies

To demonstrate biosimilarity of HLX11 to its RMP EU-Perjeta a comprehensive panel of in vitro methods were employed including physicochemical and functional assays. The in vitro PD study data were included in the quality part of the submission of the dossier and evaluated in the quality assessment report (Section 3.).

Based on the analytical comparability data and in line with EMA guideline on similar biological medicinal products containing monoclonal antibodies – nonclinical and clinical issues (EMA/CHMP/BMWP/403543/2010) no additional non-clinical in vivo studies are deemed necessary.

4.2.1.2. Secondary pharmacodynamic studies

No secondary PD studies are required for biological medicinal products.

4.2.1.3. Safety pharmacology programme

Safety pharmacology studies are not required for similar biological medicinal products.

4.2.1.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies are required for similar biological medicinal products.

4.2.2. Pharmacokinetics

No non-clinical PK or TK studies were considered necessary. This is in line with EMA guideline on similar biological medicinal products containing monoclonal antibodies – nonclinical and clinical issues (EMA/CHMP/BMWP/403543/2010).

4.3. Toxicology

Not applicable.

4.3.1. 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 Rev. 1) 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 pertuzumab is not expected to pose a risk to the environment due to its nature.

4.1. Overall discussion and conclusions on non-clinical aspects

4.1.1. Discussion

HLX11 has been developed as a biosimilar to the European Medicines Agency (EMA) approved reference product (RMP) EU-Perjeta. Relevant EMA guidelines were followed in the development of biosimilar medical product.

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

To demonstrate biosimilarity of Poherdy to its RMP EU-Perjeta a comprehensive panel of in vitro methods were employed including physicochemical and functional assays. The in vitro PD study data were included in quality part of the dossier and evaluated in the quality assessment report. Therefore, the biosimilarity assessment is not repeated/included in the non-clinical assessment report and reference is made to the quality/biosimilar assessment in the quality assessment report.

4.1.2. Conclusion on non-clinical aspects

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

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

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

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

The Applicant confirms that both clinical studies were performed in accordance with the International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP), the Declaration of Helsinki, and other relevant regulations.

5.1.2. Tabular overview of clinical trials

Table 3: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 1 - PK/PD study					
HLX11-001	RD, DB, 4-arm, single-dose	Single dose of IV 420 mg of HLX11, US-Perjeta, EU-Perjeta, or CN-Perjeta over 60 ± 10 minutes	Healthy male Chinese subjects	PK similarity, safety, tolerability, immunogenicity. Primary endpoint: C_{max} with the observed value collected AUC_{0-t} $AUC_{0-\infty}$	160 randomised and treated
Phase 3 Therapeutic confirmatory					

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
HLX11-BC301	Multicentre, RD, DB, 2-arm	Neoadjuvant: trastuzumab: Q3W, 8 mg/kg IV C1 → 6 mg/kg IV C2-4; + HLX11/EU-Perjeta: Q3W, 840 mg IV C1 → 420 mg IV C2-4; + docetaxel: Q3W, 75 mg/m² IV C1-C4 Adjuvant: Doxorubicin: Q3W, 60 mg/m² IV C5-C8 followed by: Trastuzumab: Q3W, 8 mg/kg IV C9 → 6 mg/mg IV C10-21 + HLX11/EU-Perjeta: Q3W, 840 mg IV C9 → 420 mg IV C10-21	Subjects with early-stage or locally advanced, HER2-positive and HR-negative breast cancer with a primary tumor diameter > 2 cm	To demonstrate that HLX11 and EU-Perjeta have similar clinical efficacy To compare the safety, PK, and immunogenicity of HLX11 vs. EU-Perjeta . Primary endpoint: tpCR rate, as assessed by IRC	908 enrolled and randomised (454 HLX11, 454 EU-Perjeta); Completed study: 101 (HLX11: 51, Perjeta-HLX11: 25, Perjeta-Perjeta: 25)

RD = randomised; DB = double blind; Q3W = every 3 weeks; IV = intravenous

5.2. Clinical pharmacology

5.2.1. Methods

Methods for the determination of HLX11 and Perjeta in human serum for both clinical studies are ELISA-based. Method validation was performed in accordance with the CHMP Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and evaluated the quantification range, accuracy, precision, selectivity and matrix effect, interference and specificity, hemolysis and lipemic effects, dilution linearity, hook effect, and stability

The method for ADA detection utilizes the bridging principle to detect anti-HLX11 antibodies in human serum based on biotin- and ruthenium-labelled HLX11. Ruthenium in the "Biotin-HLX11-Anti- HLX11 Antibody-HLX11-Ruthenium" complex excites a light signal at 620 nm, which is captured by an MSD instrument. The captured signal intensity is directly proportional to the titer of ADAs.

Anti-HLX11 NAb were detected from ECL immunoassay using the MSD MESO QuickPlex SQ 120 platform. In this assay, human serum samples were co-incubated with Bio-HLX11 to form immune complexes. The immune complexes were then captured by streptavidin-coated magnetic beads. After washing free Bio-HLX11 away, the ADA (including NAb) were eluted off the beads by acid treatment.

These eluted samples were incubated with Ru-HLX11 and then transferred to HER2-coated MSD plate. Anti-drug antibodies with NAb blocked binding of HER2 with Ru- HLX11, which caused inhibition of the ECL signal. Samples with a mean signal intensity less than or equal to the assay cut point were positive for the presence of anti-HLX11 Nab.

During validation of methods for detection of ADAs and NAb in study HLX11-BC301 reagent interchangeability of the labelling reagent HLX11-Biotin with EU-Perjeta -Biotin was demonstrated.

Overall, it is concluded that the methods for ADA/NAb detection utilized in the two clinical studies were suitable for the indented purpose and sufficiently robust and sensitive.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Study HLX11-001 was performed to demonstrate the PK similarity between the proposed biosimilar HLX11 and its reference product Perjeta. Clinical pharmacology data to support a demonstration of biosimilarity to a reference product include the PK parameters maximum serum concentration (C_{max}), area under the concentration time- curve from time 0 to time of the last quantifiable concentration (AUC_{0-t}), and area under the concentration time- curve from time 0 to infinite time ($AUC_{0-\infty}$) were selected as the primary endpoints to evaluate PK similarity in Study HLX11-001.

Study HLX11-BC301 was conducted to demonstrate that HLX11 and EU-Perjeta have similar clinical efficacy on HER2-positive and HR-negative early-stage or locally advanced breast cancer. Secondary objective was to compare the safety, PK, and immunogenicity of HLX11 vs. EU-Perjeta. Blood samples for determination of HLX11 serum concentrations were collected at the following time points: before HLX11 or EU-Perjeta infusion (within 2 h); immediately after end of infusion (within 10 min) in Cycle (C) 1, C2, C4, C9, C13, C17, and C21; and at the end/termination of treatment.

Pharmacokinetic analyses were performed based on the Pharmacokinetic Set (PKS). The PK analyses were performed by treatment periods and treatment groups:

• For neoadjuvant therapy and adjuvant chemotherapy periods: HLX11 group and EU-Perjeta group.

• For adjuvant HER2-targeted therapy period: HLX11-HLX11 group, EU-Perjeta -HLX11 group, the total of HLX11-HLX11 and EU-Perjeta -HLX11 group, and EU-Perjeta -EU-Perjeta group.

Serum concentrations of HLX11/EU-Perjeta were descriptively summarized by treatment groups and planned sampling time points, and the mean serum drug concentration-time profiles were plotted by planned sampling time points. Abnormal PK data (measured drug concentrations occurring before the first dose, below quantification limits after dosing at each treatment cycle, or the concentration after dosing was lower than pre-dose at the same cycle) were excluded for sensitivity analysis.

5.2.2.2. Bioequivalence

Figure 1: Mean (± SD) serum concentration-time profiles by treatment (linear and semi-logarithmic scale) in study HLX11-001 (PKS)

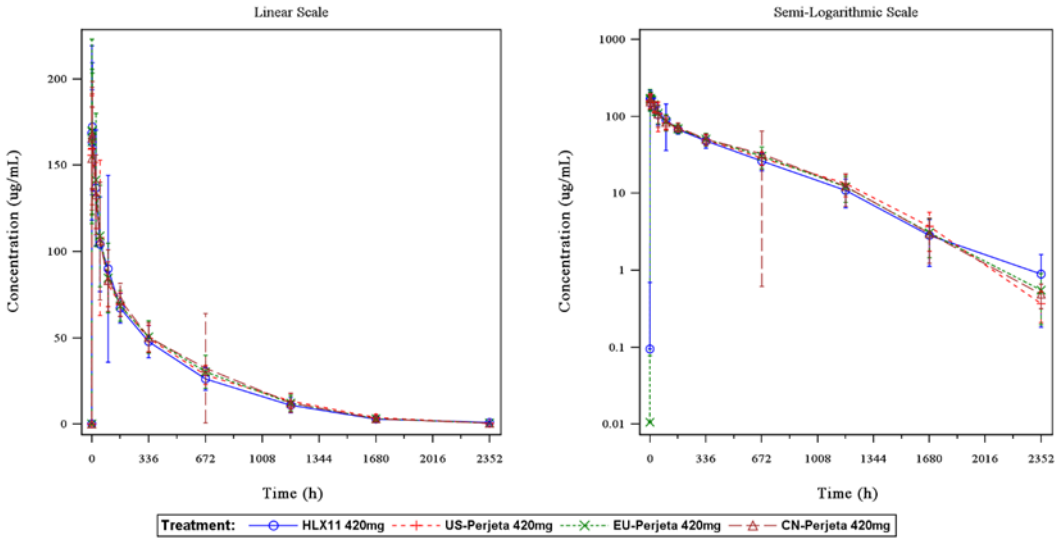


Table 4: Summary of PK parameters of study drugs in study HLX11-001 (PKS)

PK Parameter (unit)	Mean ± SD (CV%)			
	HLX11 (N=40)	US-Perjeta (N=40)	EU-Perjeta (N=40)	CN-Perjeta (N=40)
T_{max} (h)	4.150 (1.17, 25.15)	4.150 (1.17, 49.15)	4.150 (1.17, 25.15)	4.150 (1.17, 672.92) [a]
C_{max} (µg/mL)	189.39±53.5994 (28.30)	178.28±45.8143 (25.70)	189.63±55.5370 (29.29)	182.45±34.1514 (18.72)
AUC_{0-t} (h*µg/mL)	49925.9±9771.448 (19.57)	52876.8±7125.275 (13.48)	53220.2±10238.04 (19.24)	53824.1±14108.88 (26.21)
$AUC_{0-\infty}$ (h*µg/mL)	51259.2±9929.16 (19.37)	54308.4±7775.226 (14.32)	54390.0±10192.88 (18.74)	53299.9±9927.872 (18.63)
$\%AUC_{ex}$ (%)	2.6177±1.8257 (69.74)	2.4966±1.9055 (76.32)	2.2331±1.6591 (74.30)	2.7872±4.6360 (166.33) [b]
λ_z (1/h)	0.0023±0.0004 (17.39)	0.0022±0.0006 (27.27)	0.0023±0.0005 (21.74)	0.0024±0.0006 (25.00)
$t_{1/2}$ (h)	316.089±52.2015 (16.51)	330.392±69.3940 (21.00)	310.725±56.6082 (18.22)	307.217±68.4140 (22.27)
CL (L/h)	0.0085±0.0017 (20.00)	0.0079±0.0012 (15.19)	0.0080±0.0015 (18.75)	0.0081±0.0015 (18.52)
V_z (L)	3.8198±0.7071 (18.51)	3.7026±0.6628 (17.90)	3.5940±0.9730 (27.07)	3.5359±0.7009 (19.82)
MRT (h)	459.365±66.0719 (14.38)	501.507±69.8857 (13.94)	476.889±57.5458 (12.07)	471.921±68.5419 (14.52)

$\%AUC_{ex}$=percentage of $AUC_{0-\infty}$obtained by extrapolation; CV=coefficient of variation; D=Day; PK=pharmacokinetics; PKS=Pharmacokinetics Parameter Set

Note: T_{max} was expressed as median (min, max).
[a] One subject in the CN-Perjeta group exhibited an abnormal observed T_{max}. At 672 h after dosing (D29), the serum concentration was 224.7 μg/mL, whereas the concentrations at the previous (336 h after dosing, D15) and the latter (1176 h after dosing, D50) scheduled sampling points were 48.38 μg/mL and 19.51 μg/mL, respectively. This resulted in an unusual T_{max} of 672 h for this subject. As the terminal elimination phase could not be accurately fitted, λ_z and its related parameters (including $AUC_{0-\infty}$, $\%AUC_{ex}$, $t_{1/2}$, V_z, CL, and MRT) could not be accurately calculated. Therefore, these parameters of this subject were not included in the analysis. However, the T_{max} of this subject was included in this analysis. The results of the sensitivity analysis excluding this subject's T_{max} value showed that the median (min, max) of T_{max} in the CN-Perjeta group was 4.150 (1.17, 49.15) h, comparable to the other groups (HLX11, US-Perjeta , and EU-Perjeta groups). This indicated that the median T_{max} of CN-Perjeta group was not affected by this abnormal subject given that the proportion of abnormal subjects was very small (2.5%, 1/40), and there were no differences in the median T_{max} across all groups.
[b] One subject in the CN-Perjeta group missed the sampling points of 1176 h (D50), 1680 h (D71), and 2352 h (D99) due to poor compliance and lost follow-up, and the $\%AUC_{ex}$ was 29% (higher than 20%), resulting in that the λ_z and its related parameters (including $AUC_{0-\infty}$, $t_{1/2}$, V_z, CL, and MRT) could not be accurately calculated, so the relevant parameters of this subject were not included in this analysis. The $\%AUC_{ex}$ of this subject was included in this analysis.

For the primary PK endpoints (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$), analysis of variance was performed after logarithmic transformation. The difference in least squares means (LSM) and associated 90% CIs were calculated for HLX11 vs. US-Perjeta , HLX11 vs. EU-Perjeta , HLX11 vs. CN-Perjeta , US-Perjeta vs. EU-Perjeta , CN-Perjeta vs. EU-Perjeta , CN-Perjeta vs. US-Perjeta. The GeoMeans ratio and its 90% CI were obtained by back-transforming the difference in least squares means. The PK profiles of study drugs were considered similar if the 90% CIs of the GeoMeans ratio for Cmax, AUC_{0-t}, and $AUC_{0-\infty}$ fell within 80.00% to 125.00% which was achieved for all primary PK endpoints. The results for the primary PK endpoints (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) in the pairwise comparisons between HLX11 and US-, EU-, and CN-Perjeta are presented in Table 4.

Table 5: Analyses for PK similarity of each pairwise comparison-primary PK endpoints (AUC0-∞, AUC0-t, and Cmax) in study HLX11-001 (PKS)

		GeoLSM					
PK Parameter (unit)	**T vs. R**	**n**	**T**	**n**	**R**	**T/R Ratio (%)**	**90% CI of T/R Ratio (%)**
$AUC_{0-\infty}$ (h*μg/mL)	HLX11 vs. US-Perjeta	40	50297.1	40	53745.1	93.58	(87.66, 99.90)
	HLX11 vs. EU-Perjeta	40	50297.1	40	53478.1	94.05	(87.54, 101.05)
	HLX11 vs. CN-Perjeta	40	50297.1	38	52415.2	95.96	(89.23, 103.20)
AUC_{0-t} (h*μg/mL)	HLX11 vs. US-Perjeta	40	48972.0	40	52393.5	93.47	(87.65, 99.68)
	HLX11 vs. EU-Perjeta	40	48972.0	40	52276.4	93.68	(87.07, 100.79)
	HLX11 vs. CN-Perjeta	40	48972.0	39	52432.5	93.40	(86.29, 101.09)
C_{max} (μg/mL)	HLX11 vs. US-Perjeta	40	183.64	40	173.81	105.66	(97.03, 115.06)
	HLX11 vs. EU-Perjeta	40	183.64	40	183.33	100.17	(91.39, 109.80)
	HLX11 vs. CN-Perjeta	40	183.64	40	179.56	102.27	(94.53, 110.65)

$\%AUC_{ex}$=percentage of $AUC_{0-\infty}$ obtained by extrapolation; GeoLSM=Geostatistical Least Squares Mean; PK=pharmacokinetics; PKS=Pharmacokinetics Parameter Set; R=reference drug; T=test drug
Note: The serum concentration of one subject in the CN-Perjeta group at 672 h after dosing (D29) was 224.7 μg/mL, which was abnormally higher compared with other subjects. The serum concentration was 48.38 μg/mL at the previous scheduled sampling point (336 h after dosing, D15) and 19.51 μg/mL at the latter scheduled sampling point (1176 h after dosing, D50), resulting in that the terminal elimination phase could not be accurately fitted and the $AUC_{0-\infty}$ could not be accurately calculated. Therefore, the $AUC_{0-\infty}$ of this subject was not included in the analysis.
One subject of CN-Perjeta group missed the sampling points of 1176 h (D50), 1680 h (D71), and 2352 h (D99) due to poor compliance and lost follow-up, and the $\%AUC_{ex}$ was 29% (higher than 20%). Therefore, the AUC_{0-t} and $AUC_{0-\infty}$ of this subject were not included in the primary analysis.

For the secondary PK endpoint (T_{max}), a non-parametric statistical method was applied for analyses with pairwise comparisons using the Wilcoxon rank sum test.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

HLX11 (pertuzumab) is a humanized IgG1 kappa monoclonal antibody that targets the extracellular dimerization domain (subdomain II) of HER2. HLX11 may mediate antibody-dependent cell-mediated cytotoxicity (ADCC) through its Fc region which might be considered part of the MoA as well.

Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2, thereby blocking ligand-dependent heterodimerization of HER2 with other HER family members, including the epidermal growth factor receptor, HER3, and HER4. The currently approved indications include use in combination with trastuzumab and chemotherapy in the neoadjuvant treatment and adjuvant treatment of HER2-positive early breast cancer and use in combination with trastuzumab and docetaxel for treatment of HER2-positive metastatic breast cancer.

5.2.3.2. Immunological events

In study HLX11-001 the overall positive rate of ADA after infusion of HLX11, US-Perjeta, EU-Perjeta and CN Perjeta were 62.50% (25/40), 37.50% (15/40), 37.50% (15/40) and 37.50% (15/40), respectively.

With regards to neutralizing antibodies the incidence of NAb of HLX11 and EU-Perjeta were low and similar and no Nab were observed after a single transition of treatment from EU-Perjeta to HLX11.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

N/A

5.2.5. Dose selection and therapeutic window

The dose selected for study PK study HLX11-001 in healthy subjects is the current clinical dose of the reference product pertuzumab, and has been reported in the literature to have a manageable safety profile in healthy subjects with no serious or unintended toxicities observed

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Poherdy has been developed by Shanghai Henlius Biotech, Inc. as a proposed biosimilar of Perjeta. and contains the active substance pertuzumab.

The Phase I study HLX11-001 was a randomized, double-blind, parallel, 4-arm, single dose study comparing the PK, safety, and immunogenicity of HLX11 vs. the reference product Perjeta (US-Perjeta, EU-Perjeta, and CN-Perjeta) in healthy Chinese male subjects. No pharmacodynamic (PD) endpoints or measures were included in the protocol of this study or in the in the Phase III study HLX11-BC301 conducted in breast cancer patients.

The binding capacity of HLX11 vs. pertuzumab to HER2 antigen was investigated in preclinical *in vitro* and *in vivo* studies. Full data from *in vitro* PD studies were included and discussed under the Quality dossier and are evaluated under the Quality/Biosimilarity assessment.

The absence of PD measures in the clinical studies is acceptable, since no approved and validated surrogate clinical markers relevant for the pharmacological action of the active substance are available.

The pharmacokinetics of HLX11 was investigated in two clinical studies (i.e., a PK similarity study in healthy Chinese male subjects [a phase I clinical study, HLX11-001], and a comparative clinical study in patients with HER2-positive and HER2-negative early-stage or locally advanced breast cancer [a phase III clinical study, HLX11-BC301). In study HLX11-001, pertuzumab was administered as a single IV infusion of 420 mg for 60 minutes (± 10 minutes). In study HLX11-BC301, the dose of pertuzumab was 840 mg initially, followed by 420 mg, once every 3 weeks. Other study drugs used in this study included trastuzumab, docetaxel, doxorubicin, and cyclophosphamide.

Bioanalytical methods

The bioanalytical methods developed and validated for the clinical study of HLX11 and its similarity to the originator EU-Perjeta were the following:

- Quantification of pertuzumab human serum concentration
- Immunogenicity assessment including determination of antidrug antibodies (ADA) and neutralizing antibodies (NAb) against pertuzumab in human serum
- Immunohistochemistry staining of HER2, ER (estrogen receptor), PR (progesterone receptor) and FISH (fluorescence *in situ* hybridization) of HER2 on tissue samples

These developed and validated methods were used in the clinical studies HLX11-001 and HLX11-BC301.

In the investigation of patient population eligibility, breast cancer and healthy tissue samples were analysed using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). IHC staining of HER2, ER and PR were performed using fully validated Ventana Benchmark Ultra automated staining platform. Fluorescence *in situ* hybridization of HER2 was performed using well established existing methodology based on the ThermoBrite hybridization instrument. The verification of these methodologies to be used for these clinical studies was performed acceptably.

Immunogenicity testing (both ADA and NAb) of a biosimilar is advised to be preferably conducted in a comparability assay with the originator using the same assay format and sampling schedule. However, the single assay approach with only the biosimilar molecule used as antigen can also be accepted, if a proper cross validation with both antigens has been executed. Here, the assay validation for immunogenicity detection in Phase I clinical study (HLX11-001) is done using the single assay approach as mentioned above, but no cross validation has been executed. Since the single assay approach is able to detect all antibodies to the biosimilar product but not necessarily all antibodies to the reference product, the finding of biosimilar being more immunogenic than the reference product should trigger an investigation of the root cause of the difference, including methodological issues (EMA Guideline on Immunogenicity assessment of therapeutic proteins). In Phase I study, Poherdy is indeed reported to trigger far more frequent ADA levels than any of the investigated Perjeta products. This likely indicates a reason in the single assay approach without any cross validation performed. The ADA assay could detect LPC 10 ng/mL of ADA at up to 14 µg/mL of HLX11. At D15 concentrations of HLX11 were too high to detect ADA at this low amount; detection was possible only above 50 ng/mL. But at D50 mean drug concentrations were in the range of 10-13 µg/mL which means that the drug tolerance was sufficient to detect relevant ADAs at D50 if they were present.

The serum concentration-time profiles of the study drugs and the serum concentrations were similar over time independently from ADA status and thus, immunogenicity had no obvious effect on serum concentration. This is agreed. The number of subjects who developed ADAs after infusion of the three reference products US-Perjeta, EU-Perjeta and CN Perjeta is exactly the same.

PK similarity study in healthy Chinese male subjects (study HLX11-001)

The study design and selected dose are considered adequate, and the demographic and baseline characteristics were comparable across the treatment groups.

Only subjects without previous exposure to pertuzumab were to be included in the study, but two non-zero pre-dose concentrations (one subject 3.768 µg/ml in HLX11 group and one subject 0.4214 µg/ml in EU-Perjeta group) were found, which was not discussed by the applicant. However, as these two pre-dose concentrations were small (< 5% of C_{max}), no impact on the study outcomes is expected.

The AUC_{ex} was < 20% for all subjects, except for one subject in CN-Perjeta group, whose AUC_{ex} was 29% due to missed sampling time points.

After administration of a single IV infusion of 420 mg HLX11, US-Perjeta, EU-Perjeta, or CN-Perjeta in healthy Chinese male subjects, the geometric mean ratios and their 90% CIs of the primary PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) in the pairwise comparisons of study drugs were all within the prespecified range of 80.00% to 125.00%, demonstrating PK similarity between HLX11 and US-, EU-, and CN-sourced Perjeta.

Also, the means of the secondary PK parameters (i.e., $t_{1/2}$, λ_z, CL, V_z and MRT) and median T_{max} were comparable between the study treatments.

The Applicant performed a sensitivity analysis excluding the PK parameters of one subject in the CN-Perjeta group having abnormally high serum concentration at day 29 and including the PK parameters of one subject in the CN-Perjeta group lacking sampling time points on day 50, day 71 and day 99. The geometric mean ratios and 90% CIs of the primary PK parameters between studied treatments were all within the range of 80.00% and 125.00%. The results of sensitivity analysis were consistent with those in the primary analysis.

The PK similarity between Poherdy and EU-Perjeta, US-Perjeta and CN-Perjeta has been demonstrated in healthy subjects.

In study HLX11-001 the overall positive rate of ADA after infusion of Poherdy, US-Perjeta, EU-Perjeta and CN Perjeta were 62.50% (25/40), 37.50% (15/40), 37.50% (15/40) and 37.50% (15/40), respectively. The ADA assay was able to detect all antibodies to HLX11 but not necessarily all antibodies to Perjeta. This could explain the finding of the biosimilar being more immunogenic than the reference product (62,5 vs 37,5% ADA positive). It is reassuring that incidences of NAbs were similar across all study groups in this study and immunogenicity had no obvious effect on PK.

Clinical study in adult patients with early-stage or locally advanced HER2-positive and HR-negative breast cancer with a primary tumor > 2 cm (study HLX11-BC301)

The concentration-time plot of HLX11/EU Perjeta showed that serum concentrations at each time point were comparable between studied treatments throughout the entire study.

There was no accumulation of HLX11/EU-Perjeta groups observed throughout the entire study, indicating that the PK characteristics of HLX11 and EU-Perjeta were similar.

The serum concentrations and accumulation ratios (Rac) of HLX11/EU-Perjeta were comparable at each time point between the HLX11 and EU-Perjeta groups in the neoadjuvant therapy and adjuvant chemotherapy periods, and between the HLX11 group (total of HLX11-HLX11 and EU-Perjeta -HLX11)

and EU-Perjeta group (EU-Perjeta -EU-Perjeta) in the adjuvant HER2-targeted therapy period, and there was no accumulation of HLX11/EU-Perjeta observed in any treatment group throughout the entire study, indicating that the PK characteristics of HLX11 and EU-Perjeta were similar. The sensitivity analyses results confirmed the primary analysis results supporting the PK similarity between the HLX11 and EU-Perjeta in the target population.

In the exploratory analysis of serum concentration by age group, the serum concentrations in the HLX11 and EU-Perjeta groups were comparable between the adult (< 65 years, n=824) and geriatric (≥ 65 years, n=83) subjects throughout the entire study. The age seems to have no clinically meaningful impact on the PK exposure of HLX11/EU-Perjeta.

The PK and immunogenicity data from the study HLX11-BC301 supports the biosimilarity of HLX11 and EU-Perjeta in target patient population.

5.2.6.2. Conclusions

Overall, the PD/PK/Immunogenicity data support biosimilarity between HLX-11 and EU-Perjeta.

5.3. Clinical efficacy

5.3.1. Dose response studies

Not applicable.

5.3.2. Main study

5.3.2.1. HLX11-BC301

5.3.2.1.1. Study title

A Multicenter, Randomized, Double-Blind, Parallel-Controlled Phase III Clinical Study to Evaluate the Efficacy and Safety of Pertuzumab Biosimilar HLX11 vs. EU-Perjeta in the Neoadjuvant Therapy of HER2-Positive and HR-Negative Early-Stage or Locally Advanced Breast Cancer.

5.3.2.1.2. Study design

The pivotal Phase III study was a double-blind, randomized, parallel-controlled, multicenter, equivalence study with 2 treatment arms to compare the similarity of efficacy and safety between a pertuzumab biosimilar candidate HLX11 and EU-Perjeta in early-stage or locally advanced, HER2-positive and HR-negative breast cancer with a primary tumor diameter > 2 cm. This study consisted of a screening period, a treatment period, and an end/discontinuation of study treatment follow-up.

Screening period: Subjects meeting all the inclusion criteria and none of the exclusion criteria were randomly assigned to the test group (HLX11) or the control group (EU-Perjeta) at a 1:1 ratio and entered the treatment period.

Treatment Period:

Neoadjuvant Therapy Period (Cycles 1 to 4):

- four cycles of neoadjuvant therapy (dosing once every 3 weeks, in 3-week cycles)
- test group: HLX11 in combination with docetaxel and trastuzumab
- control group: EU-Perjeta in combination with docetaxel and trastuzumab

Surgery Period:

- subjects completed surgery within 3 to 6 weeks after Cycle 4 administration in the neoadjuvant therapy period
- tumor samples were assessed by the study site and the IRC to determine whether tpCR (ypT0/Tis, ypN0) was achieved.
- subjects who achieved tpCR assessed by study site continued the adjuvant therapy period

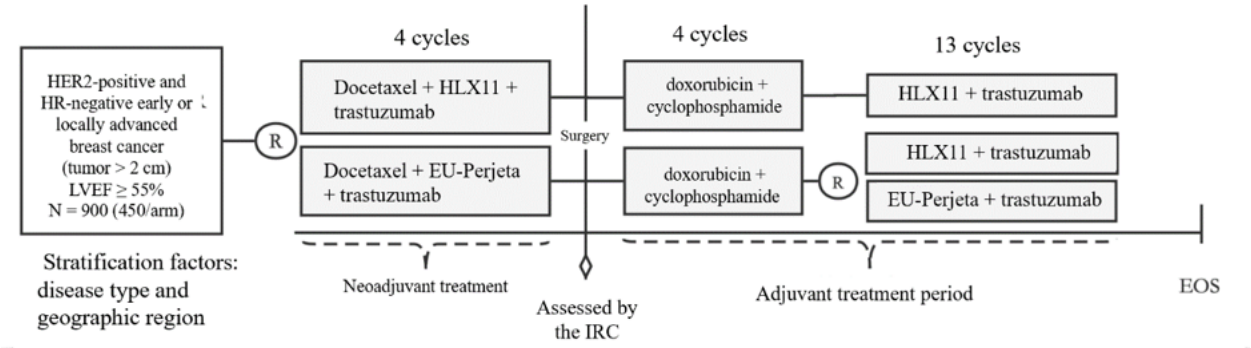
Adjuvant Therapy Period (Cycles 5 to 21):

- subjects who achieved tpCR assessed by study site started adjuvant therapy within 2 to 9 weeks after surgery
- regimen: 4 cycles (Cycles 5 to 8) of AC chemotherapy, followed by 13 cycles (Cycles 9 to 21) of HLX11 or EU-Perjeta in combination with trastuzumab
- after completing 4 cycles of AC chemotherapy: the subjects included in the EU-Perjeta group were rerandomized at a 1:1 ratio under blinded conditions to the HLX11 in combination with trastuzumab group or continued in the EU-Perjeta in combination with trastuzumab group

End/Discontinuation of Study Treatment

- within 30 ± 7 days after the last dose or within 7 days after discontinuation of study treatment (whichever occurred later), i.e., safety follow-up.

Figure 2: Study schema



Treatment

Trial intervention

Neoadjuvant period (4 cycles):

- Trastuzumab Q3W
  - Loading dose: 8 mg/kg IV C1
  - Maintenance dose: 6 mg/kg IV C2-4
- HLX11/ EU-Perjeta Q3W

    - Loading dose: 840 mg IV C1
    - Maintenance dose: 420 mg IV C2-4
- Docetaxel Q3W
    - 75 mg/m² IV C1-C4

Adjuvant period (17 cycles)

- Doxorubicin Q3W: 60 mg/m² IV C5-8
- Cyclophosphamide Q3W: 600 mg/m² IV C5-8
- Trastuzumab Q3W:
    - Loading dose: 8 mg/kg IV C9
    - Maintenance dose: 6 mg/kg IV C10-21
- HLX11/ EU-Perjeta Q3W:
    - Loading dose: 840 mg IV C9
    - Maintenance dose: 420 mg IV C10-21

HLX11 or EU Perjeta in combination with trastuzumab and docetaxel could be delayed due to toxicity, but dose reduction was not allowed.

The doses of doxorubicin and cyclophosphamide could be reduced or adjusted due to toxicity, according to local clinical guidelines.

Concomitant therapies

Permitted medications included antiviral drugs, prophylactic steroids, H1- or H2-receptor antagonists, adjuvant radiotherapy after chemotherapy, antiemetics, anticoagulant therapy, analgesics/anti-inflammatory drugs (e.g., acetaminophen, pethidine, etc.), antidiarrheals (e.g., loperamide), Granulocyte colony-stimulating factors (not allowed given as prophylactic medication prior to Cycle 1), bisphosphonates, antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics).

When needed, subjects could receive complete supportive care according to the standard of care, including blood transfusion and blood products, antibiotics, vitamins, and mineral supplements.

Permitted therapies included radiotherapy (except for adjuvant radiotherapy after chemotherapy), chemotherapy, anti-tumour Chinese patent medicines and Chinese medicine decoctions, anti-tumour biological products, immunotherapy, surgery, and other anti-tumour treatments; use of high-dose systemic corticosteroids (defined as more than 20 mg of dexamethasone [or equivalent] per day for 7 consecutive days) and any IPs in other clinical trials; any oral, injectable, or implanted hormonal contraceptive methods.

Randomisation

The subjects were randomly assigned to arm A/treatment group (HLX11) or arm B/control group (EU-Perjeta) at a 1:1 ratio. The stratification factors included disease category (early-stage vs. locally advanced) and geographic region (Asia vs. non-Asia). In the adjuvant therapy period, after completing 4 cycles of doxorubicin in combination with cyclophosphamide (AC) chemotherapy, the subjects in arm B/control group were randomly assigned again at a ratio of 1:1 to receive either HLX11 or EU-Perjeta.

The randomisation program used a central randomisation system, the Interactive Web Response System (IWRS), by disease category (early-stage vs. locally advanced) and geographic region (Asia vs. non-Asia), and randomisation codes were generated at a ratio of 1:1.

Blinding

In this study, a randomisation number table was generated by an unblinded statistician using relevant software. Preparation for the blinding of the investigational product was completed by personnel not involved in this trial. In this study, an unblinded team was set up and carried out restrictive unblinding when the primary efficacy endpoint was observed in all subjects. The final overall unblinding will be performed after the last subject completed the last study visit. This study used the IWRS system for online emergency unblinding without the need to prepare a paper version of the emergency letter.

Patient population

The study screened subjects from 75 study sites in China, 2 study sites in Spain, 1 study site in Hungary, and 1 study site in Poland; all enrolled subjects were from 74 study sites in China.

Main inclusion criteria

- Primary breast cancer that is:
  1) Histologically confirmed invasive breast carcinoma with a primary tumor size of > 2 cm by standard local assessment technique;
  2) Breast cancer staging (in accordance with the AJCC staging system (8th edition)): early-stage (T2–3, N0–1, M0) or locally advanced (T2–3, N2 or N3, M0; T4, any N, M0);
  3) HER2 positive confirmed by central laboratory, defined as immunohistochemistry (IHC) 3 +, or IHC2 + and ISH positive;
  4) Hormone receptor (HR, including oestrogen receptor [ER] and progesterone receptor [PR]) negative by central laboratory.
- Patients agree to undergo surgery while meeting the criteria for surgery after neoadjuvant therapy.
- (Within 28 days prior to the first dose) Left ventricular ejection fraction (LVEF) at baseline ≥ 55% measured by echocardiography (ECHO) or multiple gated acquisition (MUGA) scan.
- Adequate major organ functions
- An Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 within 7 days prior to the first dose.

Main exclusion criteria

- Inflammatory breast cancer.
- Stage IV (metastatic) breast cancer, bilateral breast cancer, or multicentric (multiple tumors involving more than 1 quadrant with more than 5 cm interval) breast cancer.
- No prior or current systemic anti-tumor therapy for this invasive breast cancer (including systemic chemotherapy, molecular targeted therapy, biological therapy, and other investigational therapies, etc.).
- With serious heart disease or medical history, including but not limited to the following conditions:
  1) History of documented heart failure or systolic dysfunction with any NYHA classification;
  2) High-risk uncontrolled arrhythmia, such as atrial tachycardia with a heart rate> 100 bpm at rest, significant ventricular arrhythmia (e.g.,ventricular tachycardia), or higher-grade atrioventricular (AV) block (i.e.,Mobitz II second-degree AV block or third degree AV block);
  3) Unstable angina pectrois, or angina pectoris requiring anti-angina medication;
  4) Evidence of transmural myocardial infarction on ECG;
  5) Clinically-significant valvular heart disease;
  6) Poorly controlled hypertension (systolic blood pressure> 160 mmHg and/or diastolic blood pressure> 100 mmHg).

- History of doxorubicin exposure > 360 mg/m^2 (or equivalent)

5.3.2.1.3. Objectives and estimands

Primary objective

The primary objective was to demonstrate that Poherdy and EU-Perjeta have similar clinical efficacy on HER2-positive and HR-negative early-stage or locally advanced breast cancer.

The primary endpoint was tpCR rate, as assessed by the IRC. tpCR was defined as the histological absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis, ypN0 in accordance with the AJCC staging system, 8th edition).

tpCR rate was defined as the proportion of subjects who achieved tpCR after surgery. Subjects who did not undergo surgery were considered failure to achieve tpCR. In the ITT Set, subjects whose tpCR assessment was missing or invalid were imputed as not achieving tpCR.

The clinical equivalence margin of the tpCR risk difference in this study was [−13% to 13%]. This was based on preserving 35% of the lower limit of 70% CI of the reference treatment effect (26.22%; 70%CI: 20.36% - 32.09%). The clinical equivalence margin of the tpCR risk ratio was [0.79 to 1.26] to preserve 50% of the lower limit of the 85% CI.

Table 6: Estimand for the primary objective

Population	**Patients with early-stage or locally advanced, HER2-positive and HR-negative breast cancer and a primary tumour size of > 2 cm who met all the inclusion criteria and none of the exclusion criteria**
Treatment conditions	▪ Neoadjuvant treatment period: HLX11 or EU-Perjeta in combination with trastuzumab and docetaxel, every 3 weeks as a treatment cycle, and 4 cycles of neoadjuvant therapy was given ▪ Surgery period: subjects who were eligible for surgery completed surgery within 3 to 6 weeks after Cycle 4 administration in the neoadjuvant therapy period
Endpoint (variable)	Response of tpCR as assessed by the IRC
Population-level summary	Risk ratio and risk difference
Intercurrent events and strategy to handle them	
Treatment discontinuation for reasons other than PD in the neoadjuvant therapy period	Treatment policy strategy: Considering that treatment discontinuation for reasons other than PD during neoadjuvant therapy has little impact on the primary efficacy endpoint and conformed to clinical practice, the therapeutic strategy was adopted to continue to collect the postoperative tpCR results.
Dose changes due to intolerance in the neoadjuvant therapy period	Treatment policy strategy: Considering that treatment discontinuation for reasons other than dose change due to intolerance during neoadjuvant therapy has little impact on the primary efficacy endpoint and conformed to clinical practice, the therapeutic strategy was adopted to continue to collect the postoperative tpCR results.

Population	Patients with early-stage or locally advanced, HER2-positive and HR-negative breast cancer and a primary tumour size of > 2 cm who met all the inclusion criteria and none of the exclusion criteria
PD in the neoadjuvant therapy period	Composite variable strategies: PD in the neoadjuvant therapy period, inability to undergo surgery for various reasons, or start of another anti-tumor therapy due to failure to achieve the purpose of neoadjuvant therapy or loss of clinical benefit in the neoadjuvant therapy period was considered as unable to achieve postoperative tpCR.
The subjects were unable to undergo surgery for various reasons	Composite variable strategies
Start of another anti-tumor therapy in the neoadjuvant therapy period	Composite variable strategies

The clinical question of interest was to determine whether neoadjuvant treatment of Poherdy in combination with trastuzumab and docetaxel followed by surgery is equivalent to neoadjuvant treatment of EU-Perjeta in combination with trastuzumab and docetaxel followed by surgery are equivalent, measured by the difference in tpCR rate regardless of treatment discontinuations for reasons other than PD or dose changes due to intolerance in the neoadjuvant therapy (i.e. using treatment policy strategy). PD in the neoadjuvant therapy period, inability to undergo surgery for various reasons, or start of another anti-tumour therapy due to failure to achieve the purpose of neoadjuvant therapy or loss of clinical benefit in the neoadjuvant therapy period was considered as unable to achieve postoperative tpCR (i.e. using composite strategy).

Statistical methods for estimation and sensitivity analysis on primary estimand

Analysis sets

Intent-to-treat (ITT) Set was defined as all subjects randomized into the study, and was the primary analysis set for the efficacy analysis in this study. The analysis of the ITT Set was based on the groups to which the subjects were randomly assigned.

Per-protocol set (PPS) was a subset of ITT Set, consisting of all randomized subjects without any major protocol deviation and other events that significantly affected the primary efficacy evaluation. The PPS was confirmed prior to database lock. The analysis based on the PPS served as a support and supplement of the ITT Set analysis. The analysis was based on the groups to which the subjects were randomly assigned.

Primary efficacy analysis

In this study, the risk ratio and risk difference of tpCR as assessed by the IRC were used as the indicators to evaluate the similarity of clinical efficacy. The primary analysis was based on the ITT Set.

The stratified CMH test was used to calculate the risk ratio of tpCR and its 90% CI, the risk difference of tpCR and its 95% Newcombe CI between the HLX11 and EU-Perjeta .

The stratification factor was the same as the randomization stratification factor. 95% CI in individual treatment groups was calculated using the Clopper-Pearson method.

For the risk ratio of tpCR between the two treatment groups, the equivalence margin was defined as [0.79 to 1.26], and for the risk difference of tpCR the equivalence margin was defined as [−13% to 13%].

The following sensitivity analyses were defined:

- tpCR as assessed by investigator
- tpCR as assessed by IRC analysis using actual stratification instead of randomisation strata
- tpCR as assessed by investigator using actual stratification instead of randomisation strata

A supplementary analysis was defined: tpCR as assessed by IRC using the PPS.

Missing data

Missing baseline, efficacy, safety, pharmacokinetics, and immunogenicity results were not imputed unless otherwise specified.

In the ITT Set, subjects whose tpCR assessment was missing or invalid were imputed as not achieving tpCR.

Multiplicity

No interim efficacy analysis was planned for this study. No multiplicity adjustment mentioned.

Secondary objectives

The secondary objective was to compare the safety, PK, and immunogenicity of Poherdy vs. EU-Perjeta.

The secondary endpoints were:

- tpCR rate, as assessed by the investigator
- bpCR rate, as assessed by the IRC

  bpCR was defined as the histological evidence of no malignancy in the primary lesion of breast cancer, or only carcinoma in situ (i.e., ypT0/Tis in accordance with the AJCC staging system, 8th edition).
- bpCR rate, as assessed by the investigator
- ORR, as assessed by the investigator

  ORR was defined as the percentage of subjects whose best overall responses were evaluated as CR or PR by the investigator according to RECIST v1.1 criteria during the neoadjuvant therapy period.
- EFS

EFS was defined as the time from randomization to the first documentation of one of the following events:

- (Before surgery) PD as determined by the investigator (according to RECIST v1.1), any evidence of in situ contralateral disease was not identified as PD, and any evidence of invasive contralateral disease was considered as PD
- (After surgery) disease recurrence or metastasis (local, regional, distant, or contralateral)
- Death from any cause

- DFS

  DFS was defined as the time from no lesion after surgery to the first documentation of one of the following events:

  - (After surgery) disease recurrence or metastasis (local, regional, distant, or contralateral)
  - Death from any cause

Estimands for the secondary objectives

The estimand, intercurrent events and strategy for

- tpCR rate, as assessed by the investigator
- bpCR rate, as assessed by the IRC
- bpCR rate, as assessed by the investigator

are the same as defined for the primary objective tpCR rate as assessed by IRC.

Estimands were also defined for ORR, EFS and DFS in the SAP.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

bpCR: The same analysis method was defined as for tpCR. RR and RD of the incidence of bpCR was not to be used to determine clinical equivalence.

ORR: The same analysis method was defined as for tpCR. The ORR analysis results were not to be used to determine clinical equivalence.

EFS: The hazard ratio (HR) and its 95% confidence interval (Efron method) was estimated using the stratified Cox proportional hazards model between the two treatment groups (HLX11(not rerandomized) vs EU-Perjeta (not re-randomized), HLX11-HLX11 vs EU-Perjeta - EU-Perjeta , EUPerjeta -HLX11 vs EU-Perjeta - EU-Perjeta). The stratification factor were the same as the randomization stratification factor. The median EFS and its 95% CI were estimated using the Kaplan-Meier method (Brookmeyer-Crowley method based on log-log transformation), and the Kaplan-Meier curve were plotted.

DFS: The hazard ratio (HR) and its 95% confidence interval (Efron method) were estimated using the stratified Cox proportional hazards model between the two treatment groups (HLX11 vs EU-Perjeta, EU-Perjeta -HLX11 vs EU-Perjeta). The stratification factor were the same as the randomization stratification factor. The median DFS and 95% confidence interval (based on the log-log transformation

Brookmeyer-Crowley method) were estimated using the Kaplan Meier method, and the Kaplan-Meier curve will be plotted.

For the secondary efficacy endpoints, supplementary analyses were defined, analysing these endpoints using the PPS.

5.3.2.1.4. Results

Participant flow and numbers analysed

Participant flow

Study Initiation Date: 25 Apr 2022 (first subject signed informed consent form)
Last subject enrolment date: 30 Jan 2024
Data Cut-off Date: 15 May 2024 (last subject completed pathologic response evaluation)
Database Lock Date: 04 Jul 2024

Figure 3: Participant flow

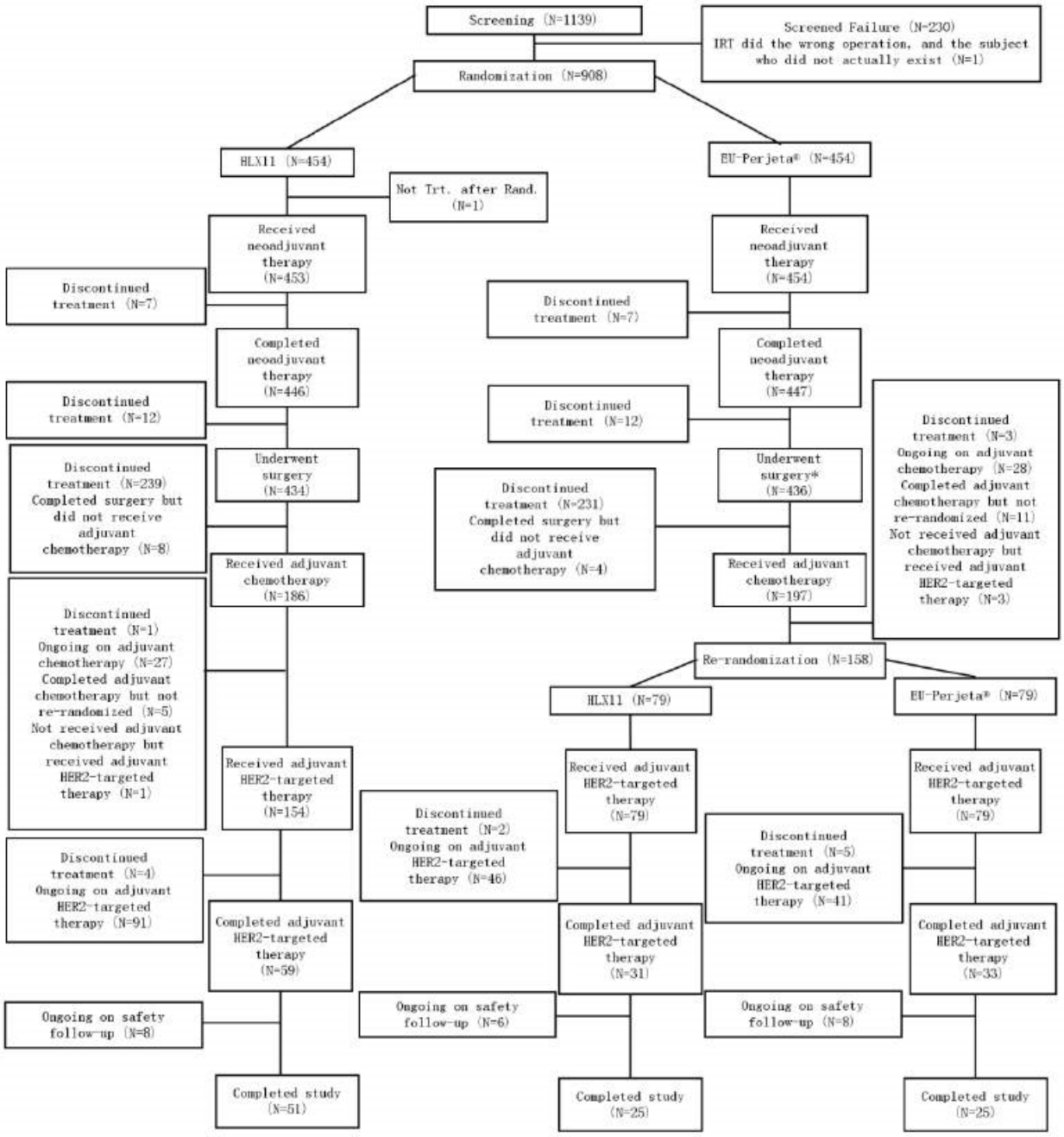


Table 7: Subject Disposition (All Screened Subjects)

	HLX11	EU-Perjeta®	Total
Screened, n			1139
Screened failure			230
IRT did the wrong operation, and the subject who did not actually exist			1
Randomized, n	454	454	908
Randomized but not treated, n	1	0	1
Received neoadjuvant therapy, n (%) [1]	453 (99.8)	454 (100)	907 (99.9)
Completed neoadjuvant therapy period, n (%)	446 (98.2)	447 (98.5)	893 (98.3)
Treatment discontinued during neoadjuvant therapy period, n (%)	7 (1.5)	7 (1.5)	14 (1.5)
Adverse event	0	1 (0.2)	1 (0.1)
Progressive disease	3 (0.7)	3 (0.7)	6 (0.7)
Subject decision	4 (0.9)	3 (0.7)	7 (0.8)
Treatment discontinued between neoadjuvant therapy period and surgery, n (%)	12 (2.6)	12 (2.6)	24 (2.6)
Progressive disease	2 (0.4)	1 (0.2)	3 (0.3)
Lost to follow-up	0	1 (0.2)	1 (0.1)
Physician decision	4 (0.9)	6 (1.3)	10 (1.1)
Subject decision	6 (1.3)	4 (0.9)	10 (1.1)
Underwent surgery[a], n (%)	434 (95.6)	436 (96.0)	870 (95.8)
Treatment discontinued between surgery and adjuvant chemotherapy period, n (%)	239 (52.6)	231 (50.9)	470 (51.8)
Adverse event	0	1 (0.2)	1 (0.1)
Physician decision	1 (0.2)	0	1 (0.1)
Poor compliance	0	1 (0.2)	1 (0.1)
Subject decision	2 (0.4)	1 (0.2)	3 (0.3)
Failure to achieve tpCR after surgery	235 (51.8)	227 (50.0)	462 (50.9)
Other	1 (0.2)	1 (0.2)	2 (0.2)
Treatment discontinued after surgery but not the study, n (%)	0	4 (0.9)	4 (0.4)
Completed surgery but did not receive adjuvant chemotherapy, n (%)	8 (1.8)	4 (0.9)	12 (1.3)
Received adjuvant chemotherapy, n (%) [2]	186 (41.0)	197 (43.4)	383 (42.2)
Ongoing on adjuvant chemotherapy period, n (%)	27 (5.9)	28 (6.2)	55 (6.1)
Completed adjuvant chemotherapy period, n (%)	158 (34.8)	166 (36.6)	324 (35.7)
Treatment discontinued during adjuvant chemotherapy period, n (%)	1 (0.2)	3 (0.7)	4 (0.4)
Physician decision	0	1 (0.2)	1 (0.1)
Poor compliance	0	1 (0.2)	1 (0.1)
Subject decision	1 (0.2)	1 (0.2)	2 (0.2)
Not received adjuvant chemotherapy but received adjuvant HER2-targeted therapy, n (%)	1 (0.2)	3 (0.7)	4 (0.4)
Treatment discontinued between adjuvant chemotherapy period and adjuvant HER2-targeted therapy period, n (%)	0	0	0
Completed adjuvant chemotherapy but not re-randomized, n (%)	5 (1.1)	11 (2.4)	16 (1.8)

After re-randomization	HLX11-HLX11	EU-Perjeta®			Total
		EU-Perjeta®-HLX11[3]	EU-Perjeta®-EU-Perjeta®[3]	Total	
Re-randomized after adjuvant chemotherapy, n (%) [4]	154 (33.9)	79 (17.4)	79 (17.4)	158 (34.8)	312 (34.4)
Received adjuvant HER2-targeted therapy, n (%) [5]	154 (100)	79 (100)	79 (100)	158 (100)	312 (100)
Ongoing on adjuvant HER2-targeted therapy period, n (%)	91 (59.1)	46 (58.2)	41 (51.9)	87 (55.1)	178 (57.1)
Completed adjuvant HER2-targeted therapy period, n (%)	59 (38.3)	31 (39.2)	33 (41.8)	64 (40.5)	123 (39.4)
Treatment discontinued during adjuvant HER2-targeted therapy period, n (%)	4 (2.6)	2 (2.5)	5 (6.3)	7 (4.4)	11 (3.5)
Adverse event	2 (1.3)	0	2 (2.5)	2 (1.3)	4 (1.3)
Subject decision	2 (1.3)	2 (2.5)	2 (2.5)	4 (2.5)	6 (1.9)
Failure to achieve tpCR after surgery[b]	0	0	1 (1.3)	1 (0.6)	1 (0.3)
Ongoing on the safety follow-up period, n (%)	8 (5.2)	6 (7.6)	8 (10.1)	14 (8.9)	22 (7.1)
Discontinued the study during safety follow-up period, n (%)	0	0	0	0	0
Completed the study, n (%)	51 (33.1)	25 (31.6)	25 (31.6)	50 (31.6)	101 (32.4)

	HLX11	EU-Perjeta®	Total
Discontinued the study[c], n (%)	264 (58.1)	256 (56.4)	520 (57.3)
Adverse event	2 (0.4)	4 (0.9)	6 (0.7)
Physician decision	5 (1.1)	7 (1.5)	12 (1.3)
Poor compliance and fails to attend follow-up in time	0	3 (0.7)	3 (0.3)
Serious protocol violation	1 (0.2)	1 (0.2)	2 (0.2)
Subject decision	16 (3.5)	13 (2.9)	29 (3.2)
Failure to achieve tpCR after surgery	235 (51.8)	224 (49.3)	459 (50.6)
Other	5 (1.1)	4 (0.9)	9 (1.0)

HER2=human epidermal growth factor receptor 2; IRT=Interactive Response System; tpCR=total pathologically complete response

Note: The percentages before [5] (exclusive) were based on the number of subjects randomized (Initial). The percentages after [5] (inclusive) were based on the number of subjects who re-randomized.

[1] The neoadjuvant therapy regimen is HLX11 in combination with docetaxel and trastuzumab or EUPerjeta in combination with docetaxel and trastuzumab.

[2] Adjuvant chemotherapy regimen is doxorubicin in combination with cyclophosphamide chemotherapy.

[3] Subjects who achieved tpCR in the EU-Perjeta group were re-randomized after adjuvant chemotherapy.

[4] Subjects in the control group (EU-Perjeta) were randomly assigned again at a ratio of 1:1 to receive HLX11 or EU-Perjeta .

[5] HER2-targeted therapy regimen is HLX11 or EU-Perjeta in combination with trastuzumab. One subject discontinued neoadjuvant treatment prior to undergoing surgery.

b One subject was misjudged by investigator as having achieved tpCR and entered the adjuvant HER2-targeted therapy period.

c The percentages were based on the number of subjects randomized (Initial).

Numbers analysed

The Intent-to-Treat Set (ITT) was the primary analysis set for efficacy which comprised all subjects randomized into the study.

The Per-Protocol-Set (PPS) was a subset of the ITT set consisting of all randomized subjects without any major protocol deviation and other events that significantly affected the primary efficacy evaluation.

Deviations from study plan

Protocol amendments

Three protocol amendments were implemented to the first protocol version (v1.0 dated 10 November 2021).

The first amendment (v2.0 dated 02 March 2022) was implemented prior to study initiation and included the addition of DFS as secondary endpoint, changes in stratification factors, re-randomization of patients in the Perjeta arm after adjuvant chemotherapy, addition of clear definitions for HER2-positive and HR-negative and a clarification concerning the methods and timing of tumour assessments and imaging examinations, among others.

The second protocol amendment was implemented shortly after study initiation (v3.0 dated 30 May 2022) and included a change in the definition of end of study, refined exclusion criteria with regard to multicentric breast cancer, changes in the requirements of tumour assessments and imaging examinations and pathological assessment and changes in the timing of ORR assessments, among others.

The third protocol amendment was implemented appr. 1 year after study initiation (v4.0 dated 31 March 2023) and included the addition of the time of end/ discontinuation visit for patients who did not reach tpCR after surgery, a clarification of the primary endpoint criterion, wording changes for secondary efficacy endpoints EFS and DFS and changes in infusion time according to the Perjeta label among others.

Protocol deviations

Similar number of patients had protocol deviations in the different treatment periods.

Prior to the neoadjuvant therapy, 38/908 (4.2%) subjects had major protocol deviations, with similar proportions between the HLX11 and EU-Perjeta groups (each 19 (4.2%) subjects). During the neoadjuvant therapy period, 166/907 (18.3%) subjects had major protocol deviations, with similar proportions between the HLX11 and EU-Perjeta groups (each 83 [18.3%] subjects). In the adjuvant chemotherapy period, 46/383 (12.0%) subjects had major protocol deviations, with similar proportions between the HLX11 and EU-Perjeta groups (23 [12.4%] vs. 23 [11.7%]).

For 312 subjects who entered the adjuvant HER2-targeted therapy period, 87 (27.9%) subjects had major protocol deviations in the adjuvant HER2-targeted therapy period (39 [25.3%] in HLX11-HLX11 group, 30 [38.0%] in EU-Perjeta -EU-Perjeta group, and 18 [22.8%] in EU-Perjeta -HLX11 group), and 136 (43.6%) subjects had major protocol deviations in the overall period (66 [42.9%] in HLX11-HLX11 group, 36 [45.6%] in EU-Perjeta -EU-Perjeta group, and 34 [43.0%] in EU-Perjeta -HLX11 group), with similar proportions across the three groups after re-randomization.

Baseline data

Table 8: Demographic Characteristics by Initial Treatment Group (Intent-to-Treat Set)

	HLX11 (N=454)	EU-Perjeta® (N=454)	Total (N=908)
Age at screening (years)			
n	454	454	908
Mean (SD)	52.4 (9.62)	52.6 (9.12)	52.5 (9.37)
Median (Q1, Q3)	54.0 (47.0, 59.0)	53.0 (47.0, 59.0)	54.0 (47.0, 59.0)
Min, Max	26, 80	22, 83	22, 83
< 40 years	57 (12.6)	42 (9.3)	99 (10.9)
40 ~ 49 years	85 (18.7)	101 (22.2)	186 (20.5)
50 ~ 64 years	267 (58.8)	273 (60.1)	540 (59.5)
≥ 65 years	45 (9.9)	38 (8.4)	83 (9.1)
Sex, n (%)			
Female	454 (100)	454 (100)	908 (100)
Race, n (%)			
Asian	454 (100)	454 (100)	908 (100)
Height (cm)			
n	454	454	908
Mean (SD)	157.5 (5.94)	157.6 (5.44)	157.6 (5.69)
Median (Q1, Q3)	158.0 (154.0, 161.0)	158.0 (154.5, 161.0)	158.0 (154.0, 161.0)
Min, Max	136, 175	140, 174	136, 175
Weight (kg)			
n	454	454	908
Mean (SD)	60.7 (9.53)	61.5 (9.89)	61.1 (9.71)
Median (Q1, Q3)	60.0 (54.0, 67.0)	60.0 (54.0, 67.0)	60.0 (54.0, 67.0)
Min, Max	40, 103	41, 98	40, 103
BSA (m^2)			
n	454	454	908
Mean (SD)	1.61 (0.127)	1.62 (0.131)	1.61 (0.129)
Median (Q1, Q3)	1.60 (1.51, 1.68)	1.61 (1.52, 1.70)	1.60 (1.52, 1.69)
Min, Max	1.3, 2.2	1.3, 2.1	1.3, 2.2

BSA=body surface area; Max=maximum; Min=minimum; Q1=first quartile; Q3=third quartile; SD=standard deviation

Note: Percentages were based on the number of subjects in Intent-to-Treat set.

Note: BSA=0.007184 × Weight0.425 × Height0.725, keep one decimal place.

Table 9: Other Baseline Characteristics by Initial Treatment Group (Intent-to-Treat Set)

	HLX11 (N=454)	EU-Perjeta® (N=454)	Total (N=908)
Smoking history, n (%)			
Never	452 (99.6)	448 (98.7)	900 (99.1)
Former	1 (0.2)	1 (0.2)	2 (0.2)
Current	1 (0.2)	5 (1.1)	6 (0.7)
Drinking history, n (%)			
Never	452 (99.6)	448 (98.7)	900 (99.1)
Former	2 (0.4)	5 (1.1)	7 (0.8)
Current	0	1 (0.2)	1 (0.1)
Drug abuse status, n (%)			
Never	454 (100)	454 (100)	908 (100)
History of drug allergies, n (%)			
Yes	30 (6.6)	32 (7.0)	62 (6.8)
No	424 (93.4)	422 (93.0)	846 (93.2)
ECOG, n (%)			
0	390 (85.9)	397 (87.4)	787 (86.7)
1	64 (14.1)	57 (12.6)	121 (13.3)
LVEF, n (%)			
≥ 55%	454 (100)	454 (100)	908 (100)
NYHA			
NA [1]	454 (100)	454 (100)	908 (100)
HER2 IHC (central lab), n (%)			
Positive	454 (100)	453 (99.8)	907 (99.9)
2+*	20 (4.4)	21 (4.6)	41 (4.5)
3+	434 (95.6)	432 (95.2)	866 (95.4)
NA [2]	0	1 (0.2)	1 (0.1)
Estrogen receptor (central lab), n (%)			
Negative	454 (100)	453 (99.8)	907 (99.9)
NA [2]	0	1 (0.2)	1 (0.1)
Progesterone receptor (central lab), n (%)			
Negative	454 (100)	453 (99.8)	907 (99.9)
NA [2]	0	1 (0.2)	1 (0.1)
Baseline lymph node status, n (%) [3]			
Positive	314 (69.2)	322 (70.9)	636 (70.0)
Negative	140 (30.8)	132 (29.1)	272 (30.0)

ECOG=Eastern Cooperative Oncology Group; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ISH=in situ hybridization; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association

Note: Percentages were based on the number of subjects in Intent-to-Treat set.

*: HER2 ICH 2+ subjects were also ISH positive.

[1] All subjects had no related symptoms and did not require the investigator to evaluate the NYHA rating.

[2] Two subjects were handled to "NA".

[3] Lymph node status was negative when regional lymph node was cN0, and the others were positive except for cN0 and cNx.

Baseline disease characteristics

Table 10: Baseline Disease Characteristics by Initial Treatment Group (Intent-to-Treat Set)

	HLX11 (N=454)	EU-Perjeta® (N=454)	Total (N=908)
Time since first diagnosed (month) [1]			
n	454	454	908
Mean (SD)	0.22 (0.29)	0.26 (0.60)	0.24 (0.47)
Median (Q1, Q3)	0.16 (0.10, 0.26)	0.20 (0.10, 0.26)	0.16 (0.10, 0.26)
Min, Max	−0.03, 3.65	−0.26, 11.83	−0.26, 11.83
Classification of initial diagnosis, n (%)			
Invasive breast cancer	454 (100)	454 (100)	908 (100)
Tumor bed location, n (%)			
Left breast	242 (53.3)	247 (54.4)	489 (53.9)
Right breast	211 (46.5)	207 (45.6)	418 (46.0)
Missing	1 (0.2)	0	1 (0.1)
Number of lesion, n (%)			
Single lesion	370 (81.5)	360 (79.3)	730 (80.4)
Multiple lesions [2]	84 (18.5)	92 (20.3)	176 (19.4)
Missing	0	2 (0.4)	2 (0.2)
TNM classification and clinical stage at enrollment			
Primary tumor (T), n (%)			
T2	330 (72.7)	326 (71.8)	656 (72.2)
T3	99 (21.8)	91 (20.0)	190 (20.9)
T4	23 (5.1)	35 (7.7)	58 (6.4)
T4b	2 (0.4)	2 (0.4)	4 (0.4)
Regional lymph node (N), n (%)			
cNX	0	0	0
cN0	140 (30.8)	132 (29.1)	272 (30.0)
cN1	208 (45.8)	237 (52.2)	445 (49.0)
cN2	67 (14.8)	50 (11.0)	117 (12.9)
cN2a	2 (0.4)	0	2 (0.2)
cN3	36 (7.9)	34 (7.5)	70 (7.7)
cN3b	1 (0.2)	0	1 (0.1)
cN3c	0	1 (0.2)	1 (0.1)
Distant metastasis (M), n (%)			
M0	454 (100)	454 (100)	908 (100)
Stage at screening, n (%)			
Stage IIA	121 (26.7)	106 (23.3)	227 (25.0)
Stage IIB	170 (37.4)	190 (41.9)	360 (39.6)
Stage IIIA	108 (23.8)	94 (20.7)	202 (22.2)
Stage IIIB	18 (4.0)	29 (6.4)	47 (5.2)
Stage IIIC	37 (8.1)	35 (7.7)	72 (7.9)
Disease category at screening, n (%)			
Early stage	337 (74.2)	343 (75.6)	680 (74.9)
Locally advanced	117 (25.8)	111 (24.4)	228 (25.1)

Max=maximum; Min=minimum; Q1=first quartile; Q3=third quartile; SD=standard deviation; TNM=tumor node-metastasis

Note: Percentages were based on the number of subjects in Intent-to-Treat set.

[1] (Date of informed consent - Date of first diagnosed + 1) × 12 / 365.25.

[2] Multiple tumors involving more than 1 quadrant with less than 5 cm interval.

Outcomes and estimation

Primary Endpoint

tpCR Rate Assessed by the IRC

Table 11: Analysis of tpCR Assessed by the IRC (ITT Set)

Characteristic	HLX11 (N=454)	EU-Perjeta (N=454)
Tis/T0 N0, n (%)	210 (46.3)	208 (45.8)
tpCR achieved		
n (%)	210 (46.3)	208 (45.8)
95% CI [1]	(41.60, 50.96)	(41.16, 50.52)
Stratified risk ratio and 90% CI [2]	1.01 (0.898, 1.136)	
Stratified risk difference (%) and 95% CI [3]	0.47 (−5.992, 6.924)	
CMH test P-value [4]	0.8867	

CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CSR=clinical study report; IRC=Independent Review Committee; ITT=Intent-to-Treat; tpCR=total pathologic complete response

[1] Clopper-Pearson method.

[2] The stratified risk ratio and 95% CI were estimated by the CMH method with disease category (early stage, locally advanced) as the stratification factor in the randomization system.

[3] Estimates were computed using the CMH method and CIs were computed using the stratified Newcombe method, adjusting for the stratification factor: disease category (early stage, locally advanced).

[4] CMH test stratified by disease category (early stage, locally advanced).

Ancilliary Analysis

Sensitivity analyses

Table 12: Analysis of tpCR Assessed by IRC Based on Actual Stratum (ITT Set)

Characteristic	HLX11 (N=454)	EU-Perjeta® (N=454)
Tis/T0 N0, n (%)	210 (46.3)	208 (45.8)
tpCR achieved		
n (%)	210 (46.3)	208 (45.8)
95% CI [1]	(41.60, 50.96)	(41.16, 50.52)
Stratified risk ratio and 90% CI [2]	1.01 (0.901, 1.140)	
Stratified risk difference (%) and 95% CI [3]	0.60 (−5.859, 7.058)	
CMH test P-value [4]	0.8547	

CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IRC=Independent Review Committee; tpCR=total pathologic complete response

[1] Clopper-Pearson method.

[2] The stratified risk ratio and 90% CI were estimated by CMH method with disease category (early stage, locally advanced) as stratification factors in case report form.

[3] Estimates were computed using the CMH method and CIs were computed using the stratified Newcombe method, adjusting for the stratification factors: disease category (early stage, locally advanced).

[4] CMH test stratified by disease category (early stage, locally advanced).

Table 13: Analysis of tpCR based on Actual Stratum by Investigator (ITT Set)

Characteristic	HLX11 (N=454)	EU-Perjeta® (N=454)
Tis/T0 N0, n(%)	197 (43.4)	206 (45.4)
tpCR achieved		
n (%)	197 (43.4)	206 (45.4)
95% CI [1]	(38.78, 48.09)	(40.73, 50.08)
Stratified Risk Ratio and 90% CI [2]	0.96 (0.849, 1.083)	
Stratified Risk Difference (%) and 95% CI [3]	-1.86 (-8.284, 4.590)	
CMH Test P-value [4]	0.5724	

[1] Clopper-Pearson method.

[2] The Stratified Risk Ratio and 90% CI were estimated by Cochran-Mantel-Haenszel method with disease category (early-stage, locally advanced) as stratification factors in CRF.

[3] Estimates were computed using the Cochran-Mantel-Haenszel method and confidence intervals were computed using the stratified Newcombe method, adjusting for the stratification factors: disease category (early-stage, locally advanced).

[4] Cochran-Mantel-Haenszel (CMH) test stratified by disease category (early-stage, locally advanced).

Table 14: Analysis of tpCR by Investigator - PPS

Characteristic	HLX11 (N=442)	EU-Perjeta® (N=444)
Tis/T0 N0, n(%)	197 (44.6)	205 (46.2)
tpCR achieved		
n (%)	197 (44.6)	205 (46.2)
95% CI [1]	(39.87, 49.34)	(41.46, 50.93)
Stratified Risk Ratio and 90% CI [2]	0.97 (0.856, 1.090)	
Stratified Risk Difference (%) and 95% CI [3]	-1.57 (-8.087, 4.970)	
CMH Test P-value [4]	0.6385	

[1] Clopper-Pearson method.

[2] The Stratified Risk Ratio and 90% CI were estimated by Cochran-Mantel-Haenszel method with disease category (early-stage, locally advanced) as stratification factors in randomization system.

[3] Estimates were computed using the Cochran-Mantel-Haenszel method and confidence intervals were computed using the stratified Newcombe method, adjusting for the stratification factors: disease category (early-stage, locally advanced).

[4] Cochran-Mantel-Haenszel (CMH) test stratified by disease category (early-stage, locally advanced).

Table 15: Analysis of tpCR Assessed by the Investigator (ITT Set)

Characteristic	**HLX11 (N=454)**	**EU-Perjeta (N=454)**
Tis/T0 N0, n (%)	197 (43.4)	206 (45.4)
tpCR achieved		
n (%)	197 (43.4)	206 (45.4)
95% CI [1]	(38.78, 48.09)	(40.73, 50.08)
Stratified risk ratio and 90% CI [2]	0.96 (0.847, 1.081)	
Stratified risk difference (%) and 95% CI [3]	−1.96 (−8.384, 4.488)	
CMH test P-value [4]	0.5511	

CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CSR=clinical study report; ITT=Intent-to-Treat; tpCR=total pathologic complete response

[1] Clopper-Pearson method.

[2] The stratified risk ratio and 95% CI were estimated by the CMH method with disease category (early stage, locally advanced) as the stratification factor in the randomization system.

[3] Estimates were computed using the CMH method and CIs were computed using the stratified Newcombe method, adjusting for the stratification factor: disease category (early stage, locally advanced).

[4] CMH test stratified by disease category (early stage, locally advanced).

Table 16: Analysis of bpCR Assessed by the IRC (ITT Set)

Characteristic	HLX11 (N=454)	EU-Perjeta (N=454)
Tis/T0, n (%)	241 (53.1)	245 (54.0)
bpCR achieved		
n (%)	241 (53.1)	245 (54.0)
95% CI [1]	(48.38, 57.75)	(49.26, 58.62)
Stratified risk ratio and 90% CI [2]	0.98 (0.889, 1.089)	
Stratified risk difference (%) and 95% CI [3]	−0.86 (−7.318, 5.604)	
CMH test P-value [4]	0.7941	

bpCR=breast pathologic complete response; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CSR=clinical study report; IRC=Independent Review Committee; ITT=Intent-to-Treat

[1] Clopper-Pearson method.

[2] The stratified risk ratio and 95% CI were estimated by the CMH method with disease category (early stage, locally advanced) as the stratification factor in the randomization system.

[3] Estimates were computed using the CMH method and CIs were computed using the stratified Newcombe method, adjusting for the stratification factor: disease category (early stage, locally advanced).

[4] CMH test stratified by disease category (early stage, locally advanced).

bpCR Rate Assessed by the Investigator

Table 17: Analysis of bpCR Assessed by the Investigator (ITT Set)

Characteristic	HLX11 (N=454)	EU-Perjeta (N=454)
Tis/T0, n (%)	227 (50.0)	240 (52.9)
bpCR achieved		
n (%)	227 (50.0)	240 (52.9)
95% CI [1]	(45.30, 54.70)	(48.16, 57.53)
Stratified risk ratio and 90% CI [2]	0.95 (0.851, 1.052)	
Stratified risk difference (%) and 95% CI [3]	−2.85 (−9.306, 3.638)	
CMH test P-value [4]	0.3900	

bpCR=breast pathologic complete response; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CSR=clinical study report; ITT=Intent-to-Treat

[1] Clopper-Pearson method.

[2] The stratified risk ratio and 95% CI were estimated by the CMH method with disease category (early stage, locally advanced) as the stratification factor in the randomization system.

[3] Estimates were computed using the CMH method and CIs were computed using the stratified Newcombe method, adjusting for the stratification factor: disease category (early stage, locally advanced).

[4] CMH test stratified by disease category (early stage, locally advanced).

Table 18: Best Overall Response by the Investigator (RECIST v1.1) (ITT Set)

Characteristics	HLX11 (N=454)	EU-Perjeta (N=454)
Best overall response, n (%)		
CR	48 (10.6)	41 (9.0)
PR	320 (70.5)	316 (69.6)
SD	64 (14.1)	83 (18.3)
PD	10 (2.2)	4 (0.9)
NE or NA	12 (2.6)	10 (2.2)
Objective response rate (CR+PR), n (%)	368 (81.1)	357 (78.6)
95% CI (%) [1]	(77.14, 84.56)	(74.57, 82.32)
Stratified odds ratio and 95% CI [2]	1.16 (0.841, 1.613)	
Stratified risk ratio and 95% CI [3]	1.03 (0.966, 1.100)	
Stratified risk difference (%) and 95% CI [4]	2.44 (−2.787, 7.649)	
CMH test P-value [5]	0.3591	

CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CR=complete response; CSR=clinical study report; ITT=Intent-to-Treat; NA=not applicable; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease

[1] Clopper-Pearson method.

[2] The stratified odds ratio and 95% CI were estimated by the CMH method with disease category (early stage, locally advanced) as the stratification factor in the randomization system.

[3] The stratified risk ratio and 95% CI were estimated by the CMH method with disease category (early stage, locally advanced) as the stratification factor in the randomization system.

[4] Estimates were computed using the CMH method and CIs were computed using the stratified Newcombe method, adjusting for the stratification factor: disease category (early stage, locally advanced).

[5] CMH test stratified by disease category (early stage, locally advanced).

EFS

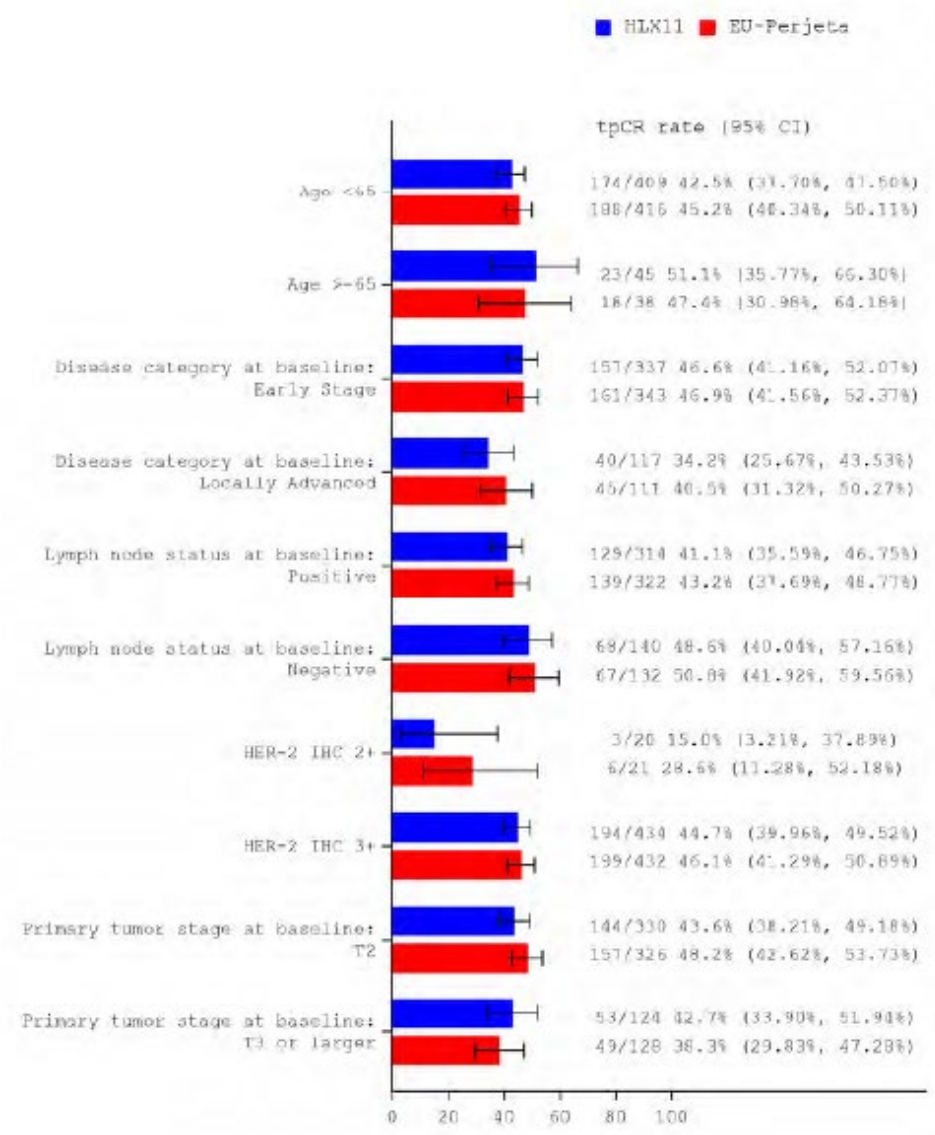
As of the data cut-off date, events for EFS (PD/metastases/recurrence/death) occurred in 17 (1.9%) subjects in the ITT Set, including 10 (3.3%) PDs in the HLX11 (not re-randomized) group, 6 (2.0%) PDs in the EU-Perjeta (not re-randomized) group, and 1 (0.6%) death in the HLX11-HLX11 group. No EFS events occurred in the EU-Perjeta - HLX11 group or EU-Perjeta -EU-Perjeta group.

DFS

As of the data cut-off date, among the 403 subjects who achieved tpCR after surgery and had no lesion in the ITT Set, DFS events (metastases/recurrence/death) occurred only in 1 subject (death) in the HLX11 group.

Pre-defined and post-hoc subgroup analyses

Figure 4: Summary of tpCR Rate by Investigator across Subgroups - ITT



(Source: CSR Figure 4)

5.3.3. Clinical studies in special populations

Not applicable.

5.3.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

5.3.5. Supportive studies

Not applicable.

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

Not applicable.

5.3.7. Patient experience data (PED)

Not applicable.

5.3.8. Healthcare professional engagement

Not applicable.

5.3.9. Overall discussion and conclusions on clinical efficacy

5.3.9.1. Discussion

The clinical development programme is based on a Phase I PK similarity study (HLX11-001) and a pivotal Phase III study (HLX11-BC301). The Phase III study was a double-blind, randomized, parallel controlled, multicentre equivalence study comparing the efficacy and safety of HLX11 and EU-Perjeta in women with early-stage or locally-advanced, HER2-positive and HR-negative breast cancer with a primary tumour diameter > 2 cm in the neoadjuvant setting. The study was ongoing during the assessment period of the primary and some of the key secondary endpoints were completed and were provided with the submission.

The clinical development programme is considered acceptable and sufficient to support the biosimilarity to EU-Perjeta.

Scientific Advice

The applicant received scientific advice (SA) from the CHMP on 11 Nov 2021. The CHMP had some comments on the study design for the phase 3 study. The clinical comments by the CHMP were mostly taken in account by the applicant. The CHMP commented on the protocol draft of the Phase 3 study allowing dose reductions for docetaxel (neoadjuvant) and doxorubicin in combination with cyclophosphamide (adjuvant chemotherapy, AC), which may lead to increased variability and heterogeneity that may ultimately (negatively) impact evaluation of biosimilarity. However, in the final study protocol, no docetaxel dose reductions were allowed and the final exposure and compliance to these medications, i.e., docetaxel in the neoadjuvant therapy period, and doxorubicin and cyclophosphamide during the AC period were closely similar between the study groups. Nevertheless, as of the DCO, treatment with adjuvant chemotherapy was still ongoing for several patients and a final assessment of exposure will be possible with submission of the final CSR. The CHMP recommended that trastuzumab used in the phase 3 study during the neoadjuvant and adjuvant therapy periods should be restricted to one brand only. Even though the protocol does not define the brand, according to the Clinical Overview, trastuzumab used in the study was a China-licensed trastuzumab biosimilar, which is now also approved in the EU and the US.

The equivalence margin (EM) of the primary endpoint was also deemed too wide by the CHMP. However, the EM was not changed, since a narrower EM would have required a marked increase in the study size, which was already large (see below for further discussions on the EM).

HLX11-BC301 study design

The study setting is not entirely in line with the current European Society for Medical Oncology (ESMO) Clinical Practice Guideline, which recommends ≥6 cycles of neoadjuvant therapy prior to surgery for patient with HER2-positive and HR-negative breast cancer; after surgery, treatment is decided based on histology (https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/her2-positive-breast-cancer/her2-positive-breast-cancer/first-and-second-lines). However, the study scheme was endorsed by the CHMP during SA in 2021 and approved by the Independent Ethics Committees and Institutional Review Boards in China. The study setting is considered appropriate for comparison of efficacy and safety of HLX11 vs. EU-Perjeta.

Study population

The chosen study population of HER2-positive and HR-negative patients is considered sensitive to detect differences between HLX11 and EU-Perjeta. The subjects represent a more homogenous and consequently less variable population than a population including also patients with metastatic breast cancer in terms of concomitant treatment, coexisting pathologies, health status, and tumour histology (e.g., HER2 positivity between metastases and their primary tumours). However, only limited data is available as regards to the clinical add-on effect of pertuzumab in the chosen target population (pooled from subpopulations from the PEONY and NeoSphere trials) so that a bias in the estimated pertuzumab effect cannot be excluded.

Trial intervention

The backbone chemotherapy regimens are considered acceptable and in line with CHMP recommendations.

The reference medicinal product Perjeta is authorised in the EU which is endorsed.

Study assessments

Pathological completes responses (tpCR and bpCR) were assessed on resected specimens of tumour tissue obtained during surgery (tumour tissue and lymph nodes) by study site and IRC.

Imaging and overall objective response assessments were performed according to RECIST v1.1. Assessment results obtained at study sites were used for ORR assessment. Patients underwent clinical breast exam during cycles 1-4 and 14 days prior to surgery, clinical breast exam (CBE) examination, breast MRI and chest and upper-abdomen CT. Same techniques should be used for each subject throughout the treatment period to ensure consistency of results. The distribution of used imaging techniques was well comparable between treatment groups.

Randomisation and Blinding

An IWRS was used for randomisation. A randomisation number table was generated by an unblinded statistician using relevant software. For the Neoadjuvant Therapy Period*, r*andomisation codes were generated at a ratio of 1:1. The assignment was stratified by disease category and geographic region.

For Adjuvant Therapy Period, after AC adjuvant chemotherapy, the subjects included in arm B/control group (EU-Perjeta) who achieved tpCR after surgery were to be re-randomised at 1:1 under blinded conditions to the HLX11 in combination with trastuzumab group or continued to stay in the EU-Perjeta in combination with trastuzumab group to receive the adjuvant therapy, and the subjects included in arm A/treatment group (HLX11) who achieved tpCR were to continue to stay in the HLX11 in combination with trastuzumab group to receive the adjuvant therapy.

Overall, this is acceptable.

Blinding and Unblinding

The study was designed as double-blind study. An unblinded team was set up and carried out restrictive unblinding when the primary efficacy endpoint was observed in all subjects. The final overall unblinding will be performed after the last subject completed the last study visit. The execution plan and guide manual for maintaining the blind during data unblinding of the equivalence analysis was provided by the Applicant.

Objectives and endpoints

The primary endpoint was defined as tpCR rate assessed by IRC and is considered acceptable for the demonstration of the comparability between HLX11 and EU-Perjeta. The risk ratio of tpCR was presented with 90% CI and the risk difference of tpCR with 95% CI. The primary efficacy analysis was based on the ITT set.

The secondary endpoints were defined as tpCR rate assessed by investigator, bpCR rate assessed by IRC and investigator, ORR assessed by investigator as well as EFS and DFS and are considered acceptable.

tpCR is considered adequate as primary efficacy endpoint considering the correlation with survival / lower risk of disease recurrence, especially in HER2-positive and HR-negative patients.

The equivalence margin for tpCR RD of [-13%, 13%] was derived from an analysis of pooled data of the NeoSphere and PEONY trial using results from subgroup analysis (HR-negative patients) which resulted in an add-on effect of pertuzumab of appr. 25.1%. The margin was set to preserve 35% of the lower limit of the 70% CI of the reference treatment effect.

Results from NeoSphere and PEONY trials present very small patient numbers in the subgroups of HR-negative patients leading to uncertainties regarding the effect size estimates.

The calculation of the equivalence margin using the 95% CI and preserving at least 50% of the add-on effect would have led to an equivalence margin of [-7.6%, 7.6%] and a sample size of over 2200. The chosen equivalence margin of [−13%, 13%] is considered very wide taking in account the estimated treatment effect of appr. 25%. However, the final study results on efficacy of HLX11 and EU-Perjeta were very similar. From a practical point of view, a narrower EM would have required an extensive number of subjects likely difficult to attain. Of note, the study already included over 900 patients. Furthermore, for a biosimilar, structural, analytical, and functional similarity and similar PK are primary for demonstration of biosimilarity and the issue of the wide EM was not further pursued.

The equivalence margin for tpCR RR [0.76, 1.26] was set to preserve 50% of the lower limit of the 85% CI.

Analysis method

The stratified CMH test was used to calculate the risk ratio of tpCR and its 90% CI, the risk difference of tpCR and its 95% Newcombe CI between the HLX11 and EU-Perjeta.

Results

The protocol was amended three times. The first amendment was implemented prior to study initiation and the second amendment shortly after the first patient signed IC. The third study amendment was implemented appr. 1 year after study initiation. Endpoint definitions were refined and infusion times were adapted to be in accordance with Perjeta label, which are agreeable.

Participant flow and numbers analysed

Overall, 1139 patients were screened of whom 908 subjects were randomized to the two treatment

arms (454 patients in each group). 11 patients were re-screened. Comparable number of patients discontinued treatment during the neoadjuvant treatment period with most common reasons including "subject decision", "progressive disease" and "adverse event". Comparable numbers of patients completed neoadjuvant therapy (HLX11 vs. Perjeta: 446/454 vs. 447/454) and 434/454 patients (95.6%) in the HLX-11 group vs. 436/454 (96.0%) in the Perjeta group underwent surgery. Comparable numbers of patients received adjuvant chemotherapy (HLX11 vs. Perjeta: 186/454 vs. 197/454 patients).

Treatment discontinuation numbers are comparable for all treatment periods. Most patients discontinued treatment between surgery and adjuvant chemotherapy (HLX11 vs. Perjeta: 239/454 [52.6%] vs. 231/454 [50.9%]) with "failure to achieve tpCR after surgery" being the most common reason (HLX11 vs. Perjeta: 235/454 [51.8%] vs. 227/454 [50.0%].

As of the data lock point, 101 patients of the 312 re-randomized patients (32.4%) completed the study (51 [33.1%] vs. 25 [31.6%] vs. 25 [31.6%] (HLX11-HLX-11 vs. Perjeta-HLX11 vs. Perjeta-Perjeta)), 83 subjects had not yet started adjuvant HER2-targeted therapy: 12 subjects completed surgery but did not receive adjuvant chemotherapy, 55 were receiving adjuvant chemotherapy, and 16 completed adjuvant chemotherapy but were not re-randomized. Therefore, the submitted data is final for the primary endpoint that was assessed after surgery. It should be noted that only subjects achieving tpCR as assessed by the study site continued according to protocol in the adjuvant therapy trial, while those ineligible for surgery or failing to achieve tpCR post-surgery discontinued the study and received subsequent treatment according to local clinical guidelines.

Overall, this is acceptable.

Data sets analysed

The Intent-to-Treat Set (ITT) was the primary analysis set for efficacy which comprised all subjects randomized into the study. The Per-Protocol-Set (PPS) was a subset of the ITT set consisting of all randomized subjects without any major protocol deviation and other events that significantly affected the primary efficacy evaluation.

Of the 908 randomized subjects, all subjects were included in the Intent-to-Treat (ITT) Set, and 886 (97.6%) were included in the Per-Protocol Set (PPS, 442 subjects [97.4%] of the HLX11 and 444 [97.8%] of the EU-Perjeta group), and 907 (99.9%) subjects were included in both the Safety Set (SS) and the Pharmacokinetic Set (PKS). Reasons for not including a subject in the PP set were overall similar between the HLX11 and EU-Perjeta groups. The one subject that was not included in the SS and PKS was randomized but not treated.

Protocol deviations

Major protocol deviations were comparable between treatment groups prior to neoadjuvant therapy period (HLX11 vs. Perjeta: 19/454 [4.2%] vs. 19/454 [4.2%]), during neoadjuvant therapy period (HLX11 vs. Perjeta: 83/454 [18.3%] vs. 83/454 [18.3%]) and in the adjuvant chemotherapy period (HLX11 vs. Perjeta: 23/454 [12.4%] vs. 23/454 [11.7%]). There was a concern regarding the use of "expired and overheated drugs", but the applicant clarified that no expired drugs were used in the study and that in the seven reported cases, storage temperatures deviated only very slightly from storage conditions. No related adverse event occurred and efficacy in these patients was consistent with the ITT population.

Baseline data

Demographic characteristics were balanced between the treatment groups. Mean age was 52.4 vs. 52.6 years (HLX11 vs. Perjeta) and numbers of geriatric patients were 45/454 (9.9%) vs. 38/454 (8.4%) (HLX11 vs. Perjeta). ECOG PS 1 applied for 64/454 (14.1%) vs. 57/454 (12.6) (HLX11 vs.

Perjeta) and baseline lymph node status was positive for 314/454 (69.2%) vs. 322/454 (70.9%) (HLX11 vs. Perjeta). At screening, 74.9% of subjects were in early stage (74.2% in the HLX11 and 75.6% in the EU-Perjeta group) and 25.1 % in locally advanced stage (25.8% in the HLX11 and 24.4% in the EU-Perjeta group).

Baseline disease characteristics were balanced as well. Mean (SD) time since first diagnosis was 0.22 (0.29) months vs. 0.26 (0.60) months (HLX11 vs. Perjeta). Most patients had a single lesion (HLX11 vs. Perjeta: 370 [81.5%] vs. 360 [79.3%]) and T2 (HLX11 vs. Perjeta: 330 [72.7%] vs. 326 [71.8%]) to T3 (HLX11 vs. Perjeta: 99 [21.8%] vs. 91 [20.0%]) status as well as cN0 to cN2. The majority of patients had stage IIA (121 [26.7%] vs. 106 [23.3%]), IIB (170 [37.4%] vs. 190 [41.9%]) and IIIA (108 [23.8%] vs. 94 [20.7%]) stage disease.

Underlying diseases like "breast mass", "mastectomy", "breast tumour excision", "breast conserving surgery" were discussed by the applicant considering the exclusion criteria of the study. All cases were presented in detail and all related lesions were classified as "benign" by the investigators prior to study start. Furthermore, the applicant discussed, whether pre-existing cardiac disorders in the medical history fell under the exclusion criteria. All cases were presented and evaluated as not clinically significant heart diseases prior to study inclusion.

Prior and concomitant medication

Slightly more patients in the HLX11 group had received at least 1 prior medication (HLX11 vs. Perjeta: 241/454 [53.1%] vs. 219/454 [48.2%]). The most frequently (≥5% of total patients) reported prior medications were anaesthetics (HLX11 vs. Perjeta: 146/454 [32.2%] vs. 134/454 [29.5%], corticosteroids for systemic use (87/454 [19.2%] vs. 88/454 [19.4%]), cardiac therapy (HLX11 vs. Perjeta: 37/454 [8.1%] vs. 48/454 [10.6%]) and antihemorrhagics (HLX11 vs. Perjeta: 21/454 [4.6%] vs. 25/454 [5.5%]).

A similar proportion of patients in the HLX11 and Perjeta group received at least one concomitant medication (453 and 454 patients in the HLX11 and Perjeta groups, respectively).

There was high treatment compliance of HLX11 and EU-Perjeta in all study groups throughout the study. Exposure and compliance to other study treatments was also comparable across study groups.

Primary Efficacy Endpoint

The applicant assessed therapeutic equivalence if 90% CI for the risk ratio in tpCR falls within the predefined equivalence margin of [0.79, 1.26], and the 95% CI for the risk difference in tpCR falls within the margin of [-13%, 13%].

Similar proportions of subjects in the HLX11 (210 [46.3%]) and EU-Perjeta (208 [45.8%]) groups achieved tpCR after surgery in the ITT Set. The risk ratio was 1.01 with a 90% CI of [0.898, 1.136] falling within the pre-defined limits. The risk difference was 0.47 with a 95% CI of [-5.992, 6.924]. The CI was within the predefined equivalence margin of [-13%, 13%].

For tpCR, subjects who did not undergo surgery, missing values were imputed as non-responder for both arms. The frequency and pattern of missing values among both arms was not initially provided but is needed to evaluate the impact of the missing value imputation. Furthermore, intercurrent events such as treatment discontinuation or start of new anti-tumor therapy and corresponding strategies were defined by the applicant but the frequency and pattern of these intercurrent events could be informative about the risk difference between the treatment arms. The applicant provided further details on the number and reason for missing values and intercurrent events and the number of missing values and number of intercurrent events were mostly equally distributed among both arms. The most common reasons for missing values were "subject decision", "progressive disease" and "physician decision" with low frequencies.

Clinical equivalence of efficacy between HLX11 and EU-Perjeta were demonstrated.

The sensitivity and supplementary analyses support the primary analysis. Subgroup analyses were conducted by age group (<65 vs. ≥65 years), disease category at baseline (early stage vs. locally advanced), lymph node status at baseline (negative vs. positive), HER2 IHC status (2+ vs. 3+), and primary tumour stage at baseline (T2 vs. T3 or larger) for the tpCR rate assessed by the IRC. The results in each subgroup were comparable, except for the small HER2 IHC 2+ subgroup. In the HER2 IHC 2+ subgroup, 3/20 subjects in the HLX11 group vs. 6/21 in the EU-Perjeta group achieved tpCR. Taking in account the small number of HER2 IHC 2+ subjects and the findings in other subgroups, the numerical difference in this subgroup is likely due to chance. In the HER-2 IHC 3+ group, the results were comparable: 207 (47.7%) in the HLX11 group and 201 (46.5%) in the EU-Perjeta group achieved tpCR.

Secondary Efficacy Endpoints

The applicant assessed the tpCR rate by investigator in the ITT set as secondary efficacy endpoint. The risk ratio of tpCR (90% CI) between the two treatment groups was 0.96 [0.847, 1.081]. The risk difference of tpCR (95% CI) between the two treatment groups was −1.96% [−8.384%, 4.488%].

Furthermore, the applicant assessed the bpCR rate by IRC and by investigator in the ITT set. Similar proportions of subjects in the HLX11 (241 [53.1%]) and EU-Perjeta (245 [54.0%]) groups achieved bpCR after surgery in the ITT set. The risk ratio of bpCR (90% CI) between the two treatment groups was 0.98 [0.889, 1.089]. The risk difference of bpCR (95% CI) between the two treatment groups was −0.86% [−7.318%, 5.604%]. Similar proportions of subjects in the HLX11 (227 [50.0%]) and EU-Perjeta (240 [52.9%]) groups achieved bpCR after surgery in the ITT set. The risk ratio of bpCR (90% CI) between the two treatment groups was 0.95 [0.851, 1.052]. The risk difference of bpCR (95% CI) between the two treatment groups was −2.85% [−9.306%, 3.638%].

Objective Response Rates (ORR) were assessed by investigator in the ITT set and similar proportions of subjects in the HLX11 and EU-Perjeta groups achieved CR (48 [10.6%] for HLX11 group vs. 41 [9.0%] for EU-Perjeta group) and PR (320 [70.5%] vs. 316 [69.6%]) during the neoadjuvant therapy period in the ITT Set, resulting in similar ORRs between the two treatment groups (368 [81.1%] vs. 357 [78.6%]). The odds ratio (95% CI) of the ORR between the treatment groups was 1.16 [0.841, 1.613].

As of the data cut-off date, events for EFS (progressive disease [PD]/metastases/recurrence/death) occurred in 17 (1.9%) subjects in the ITT Set, including 10 (3.3%) PDs in the HLX11 (not re-randomized) group, 6 (2.0%) PDs in the EU-Perjeta (not re-randomized) group, and 1 (0.6%) death in the HLX11-HLX11 group. No EFS events occurred in the EU-Perjeta-HLX11 group or EU-Perjeta-EU-Perjeta group. The 15-month EFS rate was 99.3%, 100%, and 100% for the HLX11-HLX11, EU-Perjeta-HLX11, and EU-Perjeta-EU-Perjeta groups, respectively.

As of the data cut-off date, among the 403 subjects who achieved tpCR after surgery and had no lesion in the ITT Set, DFS events (metastases/recurrence/death) occurred only in 1 subject (death) in the HLX11 group; therefore, the 12-month DFS rate was 99.2%, 100%, and 100% for the HLX11, EU-Perjeta, and EU-Perjeta-HLX11 groups, respectively.

Supplementary analyses in the PPS were consistent with the results in the ITT group.

Similar clinical efficacy between HLX11 and EU-Perjeta is further demonstrated by the secondary efficacy endpoints.

5.3.9.2. Conclusions on the clinical efficacy

The applicant provided data from study HLX11-BC301 investigating the primary efficacy endpoint of

tpCR rate after neoadjuvant therapy with docetaxel + trastuzumab + HLX11/ EU-Perjeta. The risk difference was 0.47 with a 95% CI of [-5.992, 6.924] falling within the predefined equivalence margin of [-13%, 13%].

Results from secondary efficacy endpoints are in line with results of the primary analysis.

Overall, the provided efficacy data support the biosimilarity between HLX11 and EU-Perjeta given the observed difference in the tpCR rate and its clinical relevance.

5.4. Clinical safety

The safety of HLX11 versus EU-Perjeta has been assessed in two clinical studies: a single-dose Phase 1 study in healthy subjects (HLX11-001), and a multiple-dose Phase 3 study in patients with early-stage or locally advanced, HER2 positive and HR negative breast cancer (HLX11-BC301).

The safety set, defined as all subjects who received at least one dose of the study drug, comprised 907 female patients in study HLX11-BC301 and 160 healthy male volunteers in study HLX-001.

Study HLX11-001 has been completed. The Phase III Study HLX11-BC301 is ongoing as of 15 May 2024 (data cut-off date). For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The safety evaluations for both studies included AEs, death, other serious adverse events (SAEs), interruptions/discontinuations due to AEs, AESIs, clinical laboratory measurements (haematology, blood/serum chemistry, coagulation [in Study HLX11-BC301 only], urinalysis, and myocardial enzyme [in Study HLX11-001 only]), vital signs, physical examination, 12- lead electrocardiogram (ECG), and Left ventricular ejection fraction (LVEF).

In study HLX11-001 AEs were coded using ICH Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. All AE reported terms in study HLX11-BC301 were coded MedDRA version 27.0. AEs are summarized by system organ class (SOC) and preferred term (PT). Clinical laboratory measurements and other safety indicators were also descriptively summarized.

Safety data collection occurred through study visits at reasonable and regular timepoints during both studies from signing the ICF to 30 days (study HLX11-001) and 30 ± 7days (Study HLX11-BC301) after the last administration.

Owing to the differences of the two studies in terms of population, dosing regimen and study duration, pooling of data did not occur, which is acceptable.

5.4.2. Patient exposure

HLX11-001

160 healthy male subjects were enrolled and treated in the study, and 159 (99.38%) subjects completed the study. Only 1 subject discontinued from the study due to poor compliance and failure to attend follow-up in time.

Two (5.0%) subjects in the HLX11 group, 2 (5.0%) subjects in the US-Perjeta group, 1 (2.5%) subject in the EU-Perjeta group, and 1 (2.5%) subject in the CN-Perjeta group experienced interruptions during the infusion. No subjects experienced infusion discontinuation. Infusion rate was not changed in any subjects

The study was completed on 08 February 2021.

HLX11-BC301

The study comprised of two parts:

- *Neoadjuvant treatment (12 weeks, Cycles 1 to 4)*

Eligible patients were assigned in a 1:1 ratio to receive either HLX11 or EU-Perjeta. Patients received 4 cycles (initial loading dose of 840mg followed by 420mg every 3 weeks (Q3W)) of pertuzumab in combination with docetaxel and trastuzumab

907 out of 908 randomised subjects received HLX11 (453) or EU-Perjeta (454).

This study part is completed.

- *Adjuvant treatment (51 weeks, Cycles 5 to 21)*

Patients who achieved tpCR started adjuvant therapy within 2 to 9 weeks after surgery and received 4 cycles (Cycles 5 to 8) of chemotherapy (docetaxel and cyclophosphamide), followed by 13 cycles (Cycles 9 to 21) of HLX11 or EU-Perjeta (420mg Q3W) in combination with trastuzumab.

Table 19: Summary of Exposure to HLX11/EU-Perjeta in Neoadjuvant Therapy Period (Safety Set) – Study HLX11-BC301

	HLX11 (N=453)	EU-Perjeta® (N=454)
Study drug administrated at the neoadjuvant therapy period, n (%)	453 (100)	454 (100)
Number of cycles completed		
n	453	454
Mean (SD)	4.0 (0.20)	4.0 (0.28)
Median (Q1, Q3)	4.0 (4.0, 4.0)	4.0 (4.0, 4.0)
Min, Max	2, 4	1, 4
1	0	2 (0.4)
2	4 (0.9)	4 (0.9)
3	3 (0.7)	1 (0.2)
4	446 (98.5)	447 (98.5)
Subjects who have infusion interrupted	11 (2.4)	4 (0.9)
Planned cumulative total dose (mg) [1]		
n	453	454
Mean (SD)	2089.8 (85.50)	2086.1 (115.91)
Median (Q1, Q3)	2100.0 (2100.0, 2100.0)	2100.0 (2100.0, 2100.0)
Min, Max	1260, 2100	840, 2100
Actual cumulative total dose (mg) [2]		
n	453	454
Mean (SD)	2089.70 (85.518)	2085.82 (116.061)
Median (Q1, Q3)	2100.00 (2100.00, 2100.00)	2100.00 (2100.00, 2100.00)
Min, Max	1260.0, 2100.0	840.0, 2100.0
Planned duration of exposure (weeks) [3]		
n	453	454
Mean (SD)	9.07 (0.611)	9.04 (0.828)
Median (Q1, Q3)	9.14 (9.14, 9.14)	9.14 (9.14, 9.14)
Min, Max	3.1, 9.1	0.1, 9.1
Actual duration of exposure (weeks) [4]		
n	453	454
Mean (SD)	9.40 (1.052)	9.39 (1.241)
Median (Q1, Q3)	9.14 (9.14, 9.57)	9.14 (9.14, 9.43)
Min, Max	3.1, 16.9	0.1, 17.4
Relative dose intensity (%) [5]		
n	453	454
Mean (SD)	97.05 (6.753)	96.95 (6.983)
Median (Q1, Q3)	100.00 (95.52, 100.00)	100.00 (96.97, 100.00)
Min, Max	54.2, 108.5	52.5, 106.7

Max=maximum; Min=minimum; Q1=first quartile; Q3=third quartile; SD=standard deviation

[1] Planned cumulative total dose received = summation of all planned dose from the first dosing date to the planned dosing date.

[2] Actual cumulative total dose received = summation of all actual dose administrated from the first dosing date to the last dosing date.

[3] Planned duration of exposure (weeks) = ((number of dosing cycles − 1) × 21+days) / 7.

[4] Actual duration of exposure (weeks) = (date of last dose − date of first dose + 1) / 7.

[5] Relative dose intensity = 100 × (actual dose intensity) / (planned dose intensity).

Adjuvant HER2-targeted therapy period

Table 20: Summary of Exposure to HLX11/EU-Perjeta in Adjuvant HER2-Targeted Therapy Period (Safety Set) – Study HLX11-BC301

	HLX11-HLX11 (N=154)	EU-Perjeta®-EU-Perjeta® (N=79)	EU-Perjeta®-HLX11 (N=79)
Study drug administrated at the adjuvant HER2-targeted therapy period, n (%)	154 (100)	79 (100)	78 (98.7)
Number of cycles completed			
n	154	79	78
Mean (SD)	8.9 (4.25)	8.9 (4.47)	9.3 (4.19)
Median (Q1, Q3)	10.0 (4.0, 13.0)	11.0 (5.0, 13.0)	11.0 (6.0, 13.0)
Min, Max	1, 13	1, 13	1, 13
1	6 (3.9)	6 (7.6)	3 (3.8)
2	9 (5.8)	4 (5.1)	4 (5.1)
3	12 (7.8)	7 (8.9)	7 (8.9)
4	12 (7.8)	2 (2.5)	3 (3.8)
5	4 (2.6)	3 (3.8)	2 (2.5)
6	6 (3.9)	3 (3.8)	3 (3.8)
7	3 (1.9)	5 (6.3)	2 (2.5)
8	12 (7.8)	2 (2.5)	3 (3.8)
9	8 (5.2)	4 (5.1)	4 (5.1)
10	8 (5.2)	3 (3.8)	4 (5.1)
11	3 (1.9)	3 (3.8)	6 (7.6)
12	13 (8.4)	4 (5.1)	6 (7.6)
13	58 (37.7)	33 (41.8)	31 (39.2)
Subjects who have infusion interrupted	1 (0.6)	2 (2.5)	1 (1.3)
Planned cumulative total dose (mg) [1]			
n	154	79	78
Mean (SD)	4175.5 (1782.71)	4157.5 (1876.60)	4340.0 (1758.18)
Median (Q1, Q3)	4620.0 (2100.0, 5880.0)	5040.0 (2520.0, 5880.0)	5040.0 (2940.0, 5880.0)
Min, Max	840, 5880	840, 5880	840, 5880
Actual cumulative total dose (mg) [2]			
n	154	79	78
Mean (SD)	4175.5 (1782.71)	4157.5 (1876.60)	4338.1 (1756.55)
Median (Q1, Q3)	4620.0 (2100.0, 5880.0)	5040.0 (2520.0, 5880.0)	5040.0 (2940.0, 5880.0)
Min, Max	840, 5880	840, 5880	840, 5880
Planned duration of exposure (weeks) [3]			
n	154	79	78
Mean (SD)	23.95 (12.750)	23.84 (13.404)	25.10 (12.585)
Median (Q1, Q3)	27.14 (9.14, 36.14)	30.14 (12.14, 36.14)	30.14 (15.14, 36.14)
Min, Max	0.1, 36.1	0.1, 36.1	0.1, 36.1
Actual duration of exposure (weeks) [4]			
n	154	79	78
Mean (SD)	24.47 (13.056)	24.31 (13.744)	25.76 (12.842)
Median (Q1, Q3)	28.00 (9.86, 36.29)	30.00 (12.14, 36.43)	31.21 (15.43, 36.29)
Min, Max	0.1, 42.3	0.1, 40.1	0.1, 42.9
Relative dose intensity (%) [5]			
n	154	79	78
Mean (SD)	98.06 (4.534)	98.71 (3.464)	97.74 (5.490)
Median (Q1, Q3)	99.22 (96.93, 100.00)	99.22 (96.93, 100.40)	98.45 (96.10, 100.00)
Min, Max	61.1, 107.5	89.6, 110.0	72.6, 110.0

5.4.3. Adverse events

HLX11-001

Table 21: Summary of Adverse Events for Study HLX11-001 (Safety Set)

	HLX11 (N=40)	US-Perjeta (N=40)	EU-Perjeta (N=40)	CN-Perjeta (N=40)	Total (N=160)
During the whole study, n (%)					
Any AEs	39 (97.5)	39 (97.5)	39 (97.5)	36 (90.0)	153 (95.6)
Any drug-related TEAEs	35 (87.5)	37 (92.5)	37 (92.5)	36 (90.0)	145 (90.6)
Any AEs with CTCAE Grade ⩾ 3	1 (2.5)	1 (2.5)	1 (2.5)	1 (2.5)	4 (2.5)
Any AESI	0	0	0	0	0
Any serious AEs	0	1(2.5)	0	0	1 (0.6)
Any drug-related serious AEs	0	1(2.5)	0	0	1 (0.6)
Any AEs resulting in death	0	0	0	0	0
During treatment period, n (%)					
Any TEAEs	39 (97.5)	39 (97.5)	39 (97.5)	36 (90.0)	153 (95.6)
Maximum CTCAE grade for any TEAEs					
Grade 1	30 (75.0)	34 (85.0)	29 (72.5)	25 (62.5)	118 (73.8)
Grade 2	8 (20.0)	4 (10.0)	9 (22.5)	10 (25.0)	31 (19.4)
Grade 3	1 (2.5)	1 (2.5)	1 (2.5)	1 (2.5)	4 (2.5)
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Any drug-related TEAEs, n (%)	35 (87.5)	37 (92.5)	37 (92.5)	36 (90.0)	145 (90.6)
Any TEAEs with CTCAE Grade ⩾ 3, n (%)	1 (2.5)	1 (2.5)	1 (2.5)	1 (2.5)	4 (2.5)
Any drug-related TEAEs with CTCAE Grade ⩾ 3, n (%)	0	1 (2.5)	0	1 (2.5)	2 (1.3)
Any AESI, n (%)	0	0	0	0	0
Any serious TEAEs	0	1 (2.5)	0	0	1 (0.6)
Any drug-related serious TEAEs	0	1 (2.5)	0	0	1 (0.6)
Any TEAEs resulting in death	0	0	0	0	0
Any drug-related TEAEs resulting in death	0	0	0	0	0
Any TEAEs leading to withdrawn	0	0	0	0	0
Any drug-related TEAEs leading to withdrawn	0	0	0	0	0
Any TEAEs leading to infusion interrupted	0	0	0	0	0
Any drug-related TEAEs leading to infusion interrupted	0	0	0	0	0

AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; PT=Preferred Term; SOC=System Organ Class; TEAE=treatment-emergent adverse event
Note: n=number of subjects, 1 subject with more than 1 history in the same SOC/PT was counted once for that SOC/PT.

Common TEAE by SOC and PT

Table 22: Summary of Treatment-Emergent Adverse Events by SOC and PT for Study HLX11-001 (Safety Set) - Excerpt

	HLX11 (N=40)	US-Perjeta (N=40)	EU-Perjeta (N=40)	CN-Perjeta (N=40)	Total (N=160)
Subjects with at least 1 TEAE, n (%) [1]	39 (97.5)	39 (97.5)	39 (97.5)	36 (90.0)	153 (95.6)
Investigations, n (%)	28 (70.0)	23 (57.5)	27 (67.5)	18 (45.0)	96 (60.0)
Neutrophil count increased	6 (15.0)	3 (7.5)	5 (12.5)	7 (17.5)	21 (13.1)
Blood cholesterol increased	5 (12.5)	5 (12.5)	5 (12.5)	3 (7.5)	18 (11.3)
White blood cells urine positive	3 (7.5)	5 (12.5)	5 (12.5)	5 (12.5)	18 (11.3)
Blood pressure decreased	7 (17.5)	1 (2.5)	2 (5.0)	2 (5.0)	12 (7.5)
Red blood cells urine positive	3 (7.5)	4 (10.0)	2 (5.0)	2 (5.0)	11 (6.9)
Alanine aminotransferase increased	4 (10.0)	1 (2.5)	3 (7.5)	2 (5.0)	10 (6.3)
Blood glucose increased	1 (2.5)	3 (7.5)	3 (7.5)	3 (7.5)	10 (6.3)

	HLX11 (N=40)	US-Perjeta (N=40)	EU-Perjeta (N=40)	CN-Perjeta (N=40)	Total (N=160)
Blood and lymphatic system disorders, n (%)	21 (52.5)	21 (52.5)	26 (65.0)	20 (50.0)	88 (55.0)
Leukocytosis	21 (52.5)	21 (52.5)	25 (62.5)	20 (50.0)	87 (54.4)
Metabolism and nutrition disorders, n (%)	17 (42.5)	20 (50.0)	10 (25.0)	18 (45.0)	65 (40.6)
Hypertriglyceridaemia	14 (35.0)	18 (45.0)	7 (17.5)	10 (25.0)	49 (30.6)
Hyperuricaemia	5 (12.5)	6 (15.0)	5 (12.5)	9 (22.5)	25 (15.6)
Gastrointestinal disorders, n (%)	11 (27.5)	17 (42.5)	13 (32.5)	21 (52.5)	62 (38.8)
Diarrhoea	7 (17.5)	13 (32.5)	8 (20.0)	14 (35.0)	42 (26.3)
Mouth ulceration	7 (17.5)	8 (20.0)	5 (12.5)	10 (25.0)	30 (18.8)
Infections and infestations, n (%)	13 (32.5)	15 (37.5)	17 (42.5)	14 (35.0)	59 (36.9)
Urinary tract infection	10 (25.0)	10 (25.0)	13 (32.5)	12 (30.0)	45 (28.1)
Upper respiratory tract infection	2 (5.0)	4 (10.0)	5 (12.5)	2 (5.0)	13 (8.1)
Renal and urinary disorders, n (%)	15 (37.5)	10 (25.0)	16 (40.0)	18 (45.0)	59 (36.9)
Proteinuria	15 (37.5)	10 (25.0)	16 (40.0)	18 (45.0)	59 (36.9)
Cardiac disorders, n (%)	3 (7.5)	7 (17.5)	8 (20.0)	1 (2.5)	19 (11.9)
Sinus bradycardia	2 (5.0)	5 (12.5)	5 (12.5)	0	12 (7.5)
Ventricular extrasystoles	0	1 (2.5)	4 (10.0)	1 (2.5)	6 (3.8)
Skin and subcutaneous tissue disorders, n (%)	3 (7.5)	5 (12.5)	6 (15.0)	5 (12.5)	19 (11.9)
Rash	3 (7.5)	5 (12.5)	6 (15.0)	4 (10.0)	18 (11.3)
Respiratory, thoracic and mediastinal disorders, n (%)	2 (5.0)	6 (15.0)	4 (10.0)	5 (12.5)	17 (10.6)
Epistaxis	1 (2.5)	6 (15.0)	4 (10.0)	4 (10.0)	15 (9.4)

Note 2: Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

TEAEs by severity

Table 23: Summary of TEAEs with CTCAE Grade ≥ 3 by SOC and PT (Safety Set) – Study HLX11-001

	HLX11 (N=40)	US-Perjeta® (N=40)	EU-Perjeta® (N=40)	CN-Perjeta® (N=40)	Total (N=160)
Subjects with at least one Grade ≥ 3 TEAE, n (%) [1]	1 (2.5)	1 (2.5)	1 (2.5)	1 (2.5)	4 (2.5)
Metabolism and nutrition disorders, n (%)	1 (2.5)	0	1 (2.5)	0	2 (1.3)
Hypertriglyceridaemia	1 (2.5)	0	1 (2.5)	0	2 (1.3)
Gastrointestinal disorders, n (%)	0	1 (2.5)	0	0	1 (0.6)
Duodenal ulcer	0	1 (2.5)	0	0	1 (0.6)
Renal and urinary disorders, n (%)	0	0	0	1 (2.5)	1 (0.6)
Proteinuria	0	0	0	1 (2.5)	1 (0.6)

HLX11-BC301

- *Neoadjuvant treatment period*

Table 24: Overall Summary of Adverse Events – Neoadjuvant Therapy Period in Study HLX11-BC301 (Safety Set)

	HLX11 (N=453)	EU-Perjeta (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Neoadjuvant therapy period	453	454	907
Any TEAEs	440 (97.1) 3921	439 (96.7) 4043	879 (96.9) 7964
TEAEs ≥ Grade 3	155 (34.2) 341	157 (34.6) 362	312 (34.4) 703
TEAEs related to HLX11/EU-Perjeta	247 (54.5) 1693	266 (58.6) 1704	513 (56.6) 3397
TEAEs related to HLX11/EU-Perjeta ≥ Grade 3	79 (17.4) 181	84 (18.5) 185	163 (18.0) 366
Serious TEAEs	41 (9.1) 73	60 (13.2) 89	101 (11.1) 162
Serious TEAEs ≥ Grade 3	28 (6.2) 44	49 (10.8) 73	77 (8.5) 117
TEAEs leading to death	0	0	0
TEAEs leading to death and related to HLX11/EU-Perjeta	0	0	0
TEAEs leading to any study drug discontinuation	0	4 (0.9) 5	4 (0.4) 5
TEAEs leading to HLX11/EU-Perjeta discontinuation	0	2 (0.4) 3	2 (0.2) 3
AESIs	18 (4.0) 65	19 (4.2) 46	37 (4.1) 111

AE=adverse event; AESI=TEAE of special interest; E=number of events; IRR=infusion-related reaction; LVEF=left ventricular ejection fraction; TEAE=treatment-emergent adverse event

Common TEAE by SOC and PT

Table 25: Most Common TEAEs (Incidence ≥ 10%) by SOC and PT – Neoadjuvant Therapy Period (Safety Set) – Study HLX11-BC301

System Organ Class Preferred Term	HLX11 (N=453)	EU-Perjeta (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Neoadjuvant therapy period	453	454	907
Any most common (incidence ⩾ 10%) TEAEs	405 (89.4) 2128	415 (91.4) 2234	820 (90.4) 4362
Investigations	239 (52.8) 891	267 (58.8) 1010	506 (55.8) 1901
Neutrophil count decreased	157 (34.7) 310	169 (37.2) 316	326 (35.9) 626
White blood cell count decreased	155 (34.2) 302	169 (37.2) 322	324 (35.7) 624
Alanine aminotransferase increased	105 (23.2) 136	120 (26.4) 152	225 (24.8) 288
Aspartate aminotransferase increased	74 (16.3) 97	105 (23.1) 153	179 (19.7) 250
Gamma-glutamyltransferase increased	42 (9.3) 46	55 (12.1) 67	97 (10.7) 113
Gastrointestinal disorders	201 (44.4) 520	205 (45.2) 536	406 (44.8) 1056
Diarrhoea	149 (32.9) 260	140 (30.8) 216	289 (31.9) 476
Nausea	90 (19.9) 165	86 (18.9) 184	176 (19.4) 349
Vomiting	52 (11.5) 95	65 (14.3) 136	117 (12.9) 231
Skin and subcutaneous tissue disorders	178 (39.3) 179	179 (39.4) 181	357 (39.4) 360
Alopecia	178 (39.3) 179	179 (39.4) 181	357 (39.4) 360
Blood and lymphatic system disorders	142 (31.3) 209	137 (30.2) 204	279 (30.8) 413
Anaemia	142 (31.3) 209	137 (30.2) 204	279 (30.8) 413
General disorders and administration site conditions	101 (22.3) 152	95 (20.9) 144	196 (21.6) 296

System Organ Class Preferred Term	HLX11 (N=453)	EU-Perjeta (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Pyrexia	62 (13.7) 71	65 (14.3) 80	127 (14.0) 151
Infections and infestations	96 (21.2) 123	83 (18.3) 97	179 (19.7) 220
Upper respiratory tract infection	54 (11.9) 72	40 (8.8) 48	94 (10.4) 120
Urinary tract infection	44 (9.7) 51	46 (10.1) 49	90 (9.9) 100
Respiratory, thoracic and mediastinal disorders	49 (10.8) 54	57 (12.6) 62	106 (11.7) 116
Cough	49 (10.8) 54	57 (12.6) 62	106 (11.7) 116

Note: Percentages were based on the number of subjects in each treatment group for each treatment period.
Note: Adverse events were coded using MedDRA Version 27.0.

TEAEs by severity

Table 26: Most Common Grade ≥ 3 TEAEs (Incidence ≥ 5%) by SOC and PT – Neoadjuvant Therapy Period (Safety Set) – Study HLX11-BC301

System Organ Class Preferred Term	HLX11 (N=453) n (%) E	EU-Perjeta® (N=454) n (%) E	Total (N=907) n (%) E
Neoadjuvant therapy period	453	454	907
Any most common (incidence ≥ 5%) TEAEs with CTCAE Grade ≥ 3	111 (24.5) 247	119 (26.2) 249	230 (25.4) 496
Investigations	111 (24.5) 247	119 (26.2) 249	230 (25.4) 496
Neutrophil count decreased	106 (23.4) 157	114 (25.1) 162	220 (24.3) 319
White blood cell count decreased	72 (15.9) 90	64 (14.1) 87	136 (15.0) 177

- *Adjuvant HER2-targeted therapy period*

Table 27: Overall Summary of Adverse Events – Adjuvant HER2-Targeted Therapy Period in Study HLX11-BC301 (Safety Set)

	HLX11- HLX11 (N=154)	EU-Perjeta - EU-Perjeta (N=79)	EU-Perjeta - HLX11 (N=79)	Total (N=312)
	n (%) E	n (%) E	n (%) E	n (%) E
Adjuvant HER2-targeted therapy period	154	79	79	312
Any TEAEs	137 (89.0) 1191	68 (86.1) 501	72 (91.1) 539	277 (88.8) 2231
TEAEs ≥ Grade 3	36 (23.4) 73	18 (22.8) 40	17 (21.5) 26	71 (22.8) 139
TEAEs related to HLX11/EU-Perjeta	94 (61.0) 559	42 (53.2) 201	42 (53.2) 243	178 (57.1) 1003
TEAEs related to HLX11/EU-Perjeta ≥ Grade 3	12 (7.8) 24	5 (6.3) 9	8 (10.1) 12	25 (8.0) 45
Serious TEAEs	9 (5.8) 13	6 (7.6) 9	2 (2.5) 2	17 (5.4) 24
Serious TEAEs ≥ Grade 3	7 (4.5) 9	5 (6.3) 7	1 (1.3) 1	13 (4.2) 17
TEAEs leading to death	1 (0.6) 1	0	0	1 (0.3) 1
TEAEs leading to death and related to HLX11/EU-Perjeta	0	0	0	0
TEAEs leading to any study drug discontinuation	1 (0.6) 2	2 (2.5) 3	0	3 (1.0) 5
TEAEs leading to HLX11/EU-Perjeta discontinuation	1 (0.6) 2	2 (2.5) 3	0	3 (1.0) 5

	HLX11- HLX11 (N=154)	EU-Perjeta - EU-Perjeta (N=79)	EU-Perjeta - HLX11 (N=79)	Total (N=312)
	n (%) E	n (%) E	n (%) E	n (%) E
AESIs	4 (2.6) 4	3 (3.8) 5	3 (3.8) 8	10 (3.2) 17

Common TEAE by SOC and PT

Table 28: Most Common TEAEs (Incidence ≥ 10%) by SOC and PT – Adjuvant HER2-Targeted Therapy Period (Safety Set) – Study HLX11-BC301

System Organ Class Preferred Term	HLX11-HLX11 (N=154)	EU-Perjeta - EU-Perjeta (N=79)	EU-Perjeta - HLX11 (N=79)	Total (N=312)
	n (%) E	n (%) E	n (%) E	n (%) E
Adjuvant HER2-targeted therapy period	154	79	79	312
Any most common (incidence ⩾ 10%) TEAEs	121 (78.6) 685	60 (75.9) 294	58 (73.4) 306	239 (76.6) 1285
Investigations	99 (64.3) 457	45 (57.0) 196	44 (55.7) 205	188 (60.3) 858
White blood cell count decreased	67 (43.5) 145	28 (35.4) 55	28 (35.4) 75	123 (39.4) 275
Neutrophil count decreased	51 (33.1) 110	21 (26.6) 51	17 (21.5) 39	89 (28.5) 200
Aspartate aminotransferase increased	37 (24.0) 58	17 (21.5) 25	16 (20.3) 34	70 (22.4) 117
Alanine aminotransferase increased	35 (22.7) 46	17 (21.5) 29	15 (19.0) 26	67 (21.5) 101
Lymphocyte count decreased	33 (21.4) 49	14 (17.7) 19	14 (17.7) 19	61 (19.6) 87
Platelet count decreased	16 (10.4) 26	5 (6.3) 9	6 (7.6) 8	27 (8.7) 43
Weight decreased	16 (10.4) 23	6 (7.6) 8	4 (5.1) 4	26 (8.3) 35
Infections and infestations	38 (24.7) 68	18 (22.8) 21	17 (21.5) 25	73 (23.4) 114
Upper respiratory tract infection	19 (12.3) 32	11 (13.9) 13	10 (12.7) 14	40 (12.8) 59
Urinary tract infection	20 (13.0) 36	8 (10.1) 8	9 (11.4) 11	37 (11.9) 55
Blood and lymphatic system disorders	34 (22.1) 54	13 (16.5) 21	15 (19.0) 24	62 (19.9) 99
Anaemia	34 (22.1) 54	13 (16.5) 21	15 (19.0) 24	62 (19.9) 99
Metabolism and nutrition disorders	15 (9.7) 34	13 (16.5) 24	10 (12.7) 14	38 (12.2) 72
Hypertriglyceridaemia	15 (9.7) 34	13 (16.5) 24	10 (12.7) 14	38 (12.2) 72
Injury, poisoning and procedural complications	18 (11.7) 18	12 (15.2) 12	6 (7.6) 6	36 (11.5) 36
Radiation skin injury	18 (11.7) 18	12 (15.2) 12	6 (7.6) 6	36 (11.5) 36
Gastrointestinal disorders	22 (14.3) 41	7 (8.9) 13	6 (7.6) 22	35 (11.2) 76
Diarrhoea	22 (14.3) 41	7 (8.9) 13	6 (7.6) 22	35 (11.2) 76
General disorders and administration site conditions	12 (7.8) 13	7 (8.9) 7	10 (12.7) 10	29 (9.3) 30
Pyrexia	12 (7.8) 13	7 (8.9) 7	10 (12.7) 10	29 (9.3) 30

Note: Percentages were based on the number of subjects in each treatment group for each treatment period.
Note: Adverse events were coded using MedDRA Version 27.0.
Source: Module 5.3.5.1 HLX11-BC301 CSR Table 42

TEAEs by severity

Table 29: Most Common Grade ≥ 3 TEAEs (Incidence ≥ 5%) by SOC and PT – Adjuvant HER2-Targeted Therapy Period (Safety Set) – Study HLX11-BC301

System Organ Class Preferred Term	HLX11- HLX11 (N=154) n (%) E	EU-Perjeta®- EU-Perjeta® (N=79) n (%) E	EU-Perjeta®- HLX11 (N=79) n (%) E	Total (N=312) n (%) E
Adjuvant HER2-targeted therapy period	154	79	79	312
Any most common (incidence ≥ 5%) TEAEs with CTCAE Grade ≥ 3	23 (14.9) 46	12 (15.2) 24	10 (12.7) 17	45 (14.4) 87
Investigations	23 (14.9) 46	12 (15.2) 24	10 (12.7) 17	45 (14.4) 87
Lymphocyte count decreased	18 (11.7) 22	9 (11.4) 11	5 (6.3) 5	32 (10.3) 38
Neutrophil count decreased	6 (3.9) 12	6 (7.6) 7	6 (7.6) 7	18 (5.8) 26
White blood cell count decreased	6 (3.9) 12	3 (3.8) 6	5 (6.3) 5	14 (4.5) 23

Note: Percentages were based on the number of subjects in each treatment group for each treatment period.
Note: Adverse events were coded using MedDRA Version 27.0.

5.4.3.1. Adverse drug reactions

HLX11-001

Common treatment-related TEAE by SOC and PT

Table 30: Summary of Treatment-Emergent Adverse Events Related to the Study Drugs by SOC and PT for Study HLX11-001 (Safety Set) Excerpt

	HLX11 (N=40)	US-Perjeta (N=40)	EU-Perjeta (N=40)	CN-Perjeta (N=40)	Total (N=160)
Subjects with at least 1 drug-related TEAE, n (%)	35 (87.5)	37 (92.5)	37 (92.5)	36 (90.0)	145 (90.6)
Blood and lymphatic system disorders, n (%)	21 (52.5)	21 (52.5)	26 (65.0)	20 (50.0)	88 (55.0)
Leukocytosis	21 (52.5)	21 (52.5)	25 (62.5)	20 (50.0)	87 (54.4)
Anaemia	0	0	1 (2.5)	0	1 (0.6)
Gastrointestinal disorders, n (%)	11 (27.5)	17 (42.5)	12 (30.0)	21 (52.5)	61 (38.1)
Diarrhoea	7 (17.5)	13 (32.5)	8 (20.0)	14 (35.0)	42 (26.3)
Mouth ulceration	7 (17.5)	8 (20.0)	5 (12.5)	10 (25.0)	30 (18.8)
Infections and infestations, n (%)	13 (32.5)	15 (37.5)	17 (42.5)	14 (35.0)	59 (36.9)
Urinary tract infection	10 (25.0)	10 (25.0)	13 (32.5)	12 (30.0)	45 (28.1)
Upper respiratory tract infection	2 (5.0)	4 (10.0)	5 (12.5)	2 (5.0)	13 (8.1)
Renal and urinary disorders, n (%)	15 (37.5)	10 (25.0)	16 (40.0)	18 (45.0)	59 (36.9)
Proteinuria	15 (37.5)	10 (25.0)	16 (40.0)	18 (45.0)	59 (36.9)
Investigations, n (%)	14 (35.0)	11 (27.5)	12 (30.0)	11 (27.5)	48 (30.0)
Neutrophil count increased	6 (15.0)	3 (7.5)	5 (12.5)	7 (17.5)	21 (13.1)
Red blood cells urine positive	3 (7.5)	4 (10.0)	2 (5.0)	2 (5.0)	11 (6.9)
Alanine aminotransferase increased	4 (10.0)	1 (2.5)	3 (7.5)	2 (5.0)	10 (6.3)

	HLX11 (N=40)	US-Perjeta (N=40)	EU-Perjeta (N=40)	CN-Perjeta (N=40)	Total (N=160)
Skin and subcutaneous tissue disorders, n (%)	3 (7.5)	5 (12.5)	6 (15.0)	5 (12.5)	19 (11.9)
Rash	3 (7.5)	5 (12.5)	6 (15.0)	4 (10.0)	18 (11.3)
Respiratory, thoracic and mediastinal disorders, n (%)	2 (5.0)	6 (15.0)	4 (10.0)	5 (12.5)	17 (10.6)
Epistaxis	1 (2.5)	6 (15.0)	4 (10.0)	4 (10.0)	15 (9.4)
Cardiac disorders, n (%)	1 (2.5)	2 (5.0)	4 (10.0)	1 (2.5)	8 (5.0)
Ventricular extrasystoles	0	1 (2.5)	4 (10.0)	1 (2.5)	6 (3.8)
Sinus tachycardia	1 (2.5)	1 (2.5)	0	0	2 (1.3)

Note 1: n=number of subjects, one patient with more than one history in the same SOC/PT is counted once for that SOC/PT.
Note 2: Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

HLX11-BC301

- *Neoadjuvant treatment period*

Table 31: Summary of drug-related Adverse Events – Neoadjuvant Therapy Period – Study HLX11-BC301 (Excerpt from CSR Table 14.3.2.1)

	HLX11 (N=453)	EU-Perjeta (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Neoadjuvant therapy period	453	454	907
Any TEAEs	440 (97.1) 3921	439 (96.7) 4043	879 (96.9) 7964
TEAEs related to HLX11/EU-Perjeta	247 (54.5) 1693	266 (58.6) 1704	513 (56.6) 3397
TEAEs related to HLX11/EU-Perjeta ≥ Grade 3	79 (17.4) 181	84 (18.5) 185	163 (18.0) 366

HLX11/EU-Perjeta-related TEAE by SOC and PT

Table 32: Most Common TEAEs (Incidence ≥ 5%) Related to HLX11/EU-Perjeta by SOC and PT – Neoadjuvant Therapy Period (Safety Set) – Study HLX11-BC301

System Organ Class Preferred Term	HLX11 (N=453)	EU-Perjeta (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Neoadjuvant therapy period	453	454	907
Any most common (incidence ⩾ 5%) TEAEs related to HLX11/EU-Perjeta	202 (44.6) 1078	212 (46.7) 1098	414 (45.6) 2176
Investigations	128 (28.3) 525	138 (30.4) 578	266 (29.3) 1103
Neutrophil count decreased	88 (19.4) 182	91 (20.0) 185	179 (19.7) 367
White blood cell count decreased	85 (18.8) 179	92 (20.3) 187	177 (19.5) 366
Alanine aminotransferase increased	46 (10.2) 59	52 (11.5) 61	98 (10.8) 120
Aspartate aminotransferase increased	32 (7.1) 39	49 (10.8) 65	81 (8.9) 104
Lymphocyte count decreased	28 (6.2) 45	23 (5.1) 47	51 (5.6) 92
Gastrointestinal disorders	108 (23.8) 278	112 (24.7) 250	220 (24.3) 528
Diarrhoea	84 (18.5) 155	90 (19.8) 137	174 (19.2) 292
Nausea	43 (9.5) 78	35 (7.7) 65	78 (8.6) 143
Vomiting	24 (5.3) 45	26 (5.7) 48	50 (5.5) 93
Blood and lymphatic system disorders	67 (14.8) 103	68 (15.0) 104	135 (14.9) 207
Anaemia	67 (14.8) 103	68 (15.0) 104	135 (14.9) 207

System Organ Class Preferred Term	HLX11 (N=453)	EU-Perjeta (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Skin and subcutaneous tissue disorders	66 (14.6) 66	69 (15.2) 69	135 (14.9) 135
Alopecia	66 (14.6) 66	69 (15.2) 69	135 (14.9) 135
General disorders and administration site conditions	36 (7.9) 56	26 (5.7) 47	62 (6.8) 103
Malaise	36 (7.9) 56	26 (5.7) 47	62 (6.8) 103
Metabolism and nutrition disorders	26 (5.7) 50	27 (5.9) 50	53 (5.8) 100
Decreased appetite	26 (5.7) 50	27 (5.9) 50	53 (5.8) 100

Note: Percentages were based on the number of subjects in each treatment group for each treatment period.
Note: Adverse events were coded using MedDRA Version 27.0.

Table 33: Summary of drug-related Adverse Events – Adjuvant HER2-targeted therapy period – Study HLX11-BC301 (Excerpt)

	HLX11- HLX11 (N=154)	EU-Perjeta - EU-Perjeta (N=79)	EU-Perjeta - HLX11 (N=79)	Total (N=312)
	n (%) E	n (%) E	n (%) E	n (%) E
Adjuvant HER2-targeted therapy period	154	79	79	312
Any TEAEs	137 (89.0) 1191	68 (86.1) 501	72 (91.1) 539	277 (88.8) 2231
TEAEs related to HLX11/EU-Perjeta	94 (61.0) 559	42 (53.2) 201	42 (53.2) 243	178 (57.1) 1003
TEAEs related to HLX11/EU-Perjeta ≥ Grade 3	12 (7.8) 24	5 (6.3) 9	8 (10.1) 12	25 (8.0) 45

Table 34: Most Common TEAEs (Incidence ≥ 5%) Related to HLX11/EU-Perjeta by SOC and PT – Adjuvant HER2-Targeted Therapy Period (Safety Set) – Study HLX11-BC301

System Organ Class Preferred Term	HLX11- HLX11 (N=154)	EU-Perjeta - EU-Perjeta (N=79)	EU-Perjeta - HLX11 (N=79)	Total (N=312)
	n (%) E	n (%) E	n (%) E	n (%) E
Adjuvant HER2-targeted therapy period	154	79	79	312
Any most common (incidence ⩾ 5%) TEAEs related to HLX11/EU-Perjeta	78 (50.6) 373	34 (43.0) 125	31 (39.2) 162	143 (45.8) 660
Investigations	58 (37.7) 265	26 (32.9) 95	23 (29.1) 123	107 (34.3) 483
White blood cell count decreased	33 (21.4) 76	12 (15.2) 25	14 (17.7) 44	59 (18.9) 145
Neutrophil count decreased	26 (16.9) 59	8 (10.1) 22	9 (11.4) 28	43 (13.8) 109
Aspartate aminotransferase increased	22 (14.3) 39	11 (13.9) 15	7 (8.9) 12	40 (12.8) 66
Alanine aminotransferase increased	21 (13.6) 30	10 (12.7) 15	8 (10.1) 16	39 (12.5) 61
Lymphocyte count decreased	18 (11.7) 25	7 (8.9) 10	6 (7.6) 11	31 (9.9) 46
Weight decreased	9 (5.8) 14	2 (2.5) 4	2 (2.5) 2	13 (4.2) 20
Platelet count decreased	8 (5.2) 15	1 (1.3) 1	3 (3.8) 5	12 (3.8) 21
Gastrointestinal disorders	24 (15.6) 57	8 (10.1) 16	8 (10.1) 27	40 (12.8) 100
Diarrhoea	20 (13.0) 37	4 (5.1) 10	3 (3.8) 17	27 (8.7) 64
Nausea	10 (6.5) 14	4 (5.1) 4	2 (2.5) 3	16 (5.1) 21
Vomiting	5 (3.2) 6	2 (2.5) 2	6 (7.6) 7	13 (4.2) 15
Blood and lymphatic system disorders	20 (13.0) 35	5 (6.3) 10	5 (6.3) 6	30 (9.6) 51
Anaemia	20 (13.0) 35	5 (6.3) 10	5 (6.3) 6	30 (9.6) 51

System Organ Class Preferred Term	HLX11-HLX11 (N=154)	EU-Perjeta - EU-Perjeta (N=79)	EU-Perjeta - HLX11 (N=79)	Total (N=312)
	n (%) E	n (%) E	n (%) E	n (%) E
Infections and infestations	8 (5.2) 16	4 (5.1) 4	5 (6.3) 6	17 (5.4) 26
Urinary tract infection	8 (5.2) 16	4 (5.1) 4	5 (6.3) 6	17 (5.4) 26

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Adverse events of special interest (AESI)

Cardiotoxicity and infusion-related reactions (IRRs) were classified as adverse events of special interest.

HLX11-001

No subject experienced AESIs in this study.

HLX11-BC301

Table 35: AESI – Neoadjuvant Therapy Period in Study HLX11-BC301 (Safety Set)

	HLX11 (N=453)	EU-Perjeta (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Neoadjuvant therapy period	453	454	907
Any TEAEs	440 (97.1) 3921	439 (96.7) 4043	879 (96.9) 7964
AESIs	18 (4.0) 65	19 (4.2) 46	37 (4.1) 111
AESIs ≥ Grade 3	0	1 (0.2) 1	1 (0.1) 1
Serious AESIs	0	1 (0.2) 1	1 (0.1) 1
Serious AESIs ≥ Grade 3	0	1 (0.2) 1	1 (0.1) 1
Cardiotoxicity	0	1 (0.2) 1	1 (0.1) 1
Symptomatic left ventricular systolic dysfunction (heart failure)	0	1 (0.2) 1	1 (0.1) 1
Cardiotoxicity ≥ Grade 3	0	1 (0.2) 1	1 (0.1) 1
Serious cardiotoxicity	0	1 (0.2) 1	1 (0.1) 1
Serious cardiotoxicity ≥ Grade 3	0	1 (0.2) 1	1 (0.1) 1
IRRs	35 (7.7) 94	36 (7.9) 82	71 (7.8) 176
IRRs ≥ Grade 3	0	0	0
Serious IRRs	0	0	0
IRRs related to HLX11/EU-Perjeta	18 (4.0) 65	18 (4.0) 45	36 (4.0) 110
IRRs related to HLX11/EU-Perjeta ≥ Grade 3	0	0	0
Serious IRRs related to HLX11/EU-Perjeta	0	0	0

AE=adverse event; AESI=TEAE of special interest; E=number of events; IRR=infusion-related reaction; LVEF=left ventricular ejection fraction; TEAE=treatment-emergent adverse event
Note: Subjects may have one or more than one AESI applied. Only the IRRs related to HLX11/EU-Perjeta were included in the AESI summaries in the study.

Table 36: AESI - Adjuvant HER2-Targeted Therapy Period in Study HLX11-BC301 (Safety Set)

	HLX11- HLX11 (N=154)	EU-Perjeta - EU-Perjeta (N=79)	EU-Perjeta - HLX11 (N=79)	Total (N=312)
	n (%) E	n (%) E	n (%) E	n (%) E
Adjuvant HER2-targeted therapy period	154	79	79	312
Any TEAEs	137 (89.0) 1191	68 (86.1) 501	72 (91.1) 539	277 (88.8) 2231
AESIs	4 (2.6) 4	3 (3.8) 5	3 (3.8) 8	10 (3.2) 17
AESIs ≥ Grade 3	1 (0.6) 1	0	0	1 (0.3) 1
Serious AESIs	1 (0.6) 1	0	0	1 (0.3) 1
Serious AESIs ≥ Grade 3	1 (0.6) 1	0	0	1 (0.3) 1
Cardiotoxicity	1 (0.6) 1	0	0	1 (0.3) 1
Symptomatic left ventricular systolic dysfunction (heart failure)	1 (0.6) 1	0	0	1 (0.3) 1
Cardiotoxicity ≥ Grade 3	1 (0.6) 1	0	0	1 (0.3) 1
Serious cardiotoxicity	1 (0.6) 1	0	0	1 (0.3) 1
Serious cardiotoxicity ≥ Grade 3	1 (0.6) 1	0	0	1 (0.3) 1
IRRs	4 (2.6) 4	3 (3.8) 5	4 (5.1) 11	11 (3.5) 20
IRRs ≥ Grade 3	0	0	0	0
Serious IRRs	0	0	0	0
IRRs related to HLX11/EU-Perjeta	3 (1.9) 3	3 (3.8) 5	3 (3.8) 8	9 (2.9) 16
IRRs related to HLX11/EU-Perjeta ≥ Grade 3	0	0	0	0
Serious IRRs related to HLX11/EU-Perjeta	0	0	0	0

Cardiotoxicity

As of the data cut-off date, cardiotoxicity was reported in 1 (0.2%) subject in the EU-Perjeta group in the *neoadjuvant therapy period* and 1 (0.6%) subject in the HLX11-HLX11 group in the *adjuvant HER2-targeted therapy period.* Both cardiotoxicities were symptomatic left ventricular systolic dysfunction (heart failure [PTs: acute left ventricular failure; cardiac failure]). Both events were Grade 4 and serious and were considered by the investigator as related to HLX11/EU-Perjeta and trastuzumab.

Infusion-Related Reactions (IRRs)

Table 37: HLX11/EU-Perjeta -Related IRRs by SOC and PT – Neoadjuvant Therapy Period (Safety Set) – Study HLX11-BC301

Category System Organ Class Preferred Term	HLX11 (N=453) n (%) E	EU-Perjeta® (N=454) n (%) E	Total (N=907) n (%) E
Neoadjuvant therapy period	453	454	907
IRRs related to HLX11/EU-Perjeta®	18 (4.0) 65	18 (4.0) 45	36 (4.0) 110
General disorders and administration site conditions	10 (2.2) 14	9 (2.0) 12	19 (2.1) 26
Chills	9 (2.0) 9	6 (1.3) 6	15 (1.7) 15
Pyrexia	5 (1.1) 5	6 (1.3) 6	11 (1.2) 11
Gastrointestinal disorders	9 (2.0) 50	8 (1.8) 30	17 (1.9) 80
Vomiting	9 (2.0) 26	5 (1.1) 15	14 (1.5) 41
Nausea	7 (1.5) 24	3 (0.7) 12	10 (1.1) 36
Diarrhoea	0	3 (0.7) 3	3 (0.3) 3
Cardiac disorders	0	2 (0.4) 2	2 (0.2) 2
Palpitations	0	1 (0.2) 1	1 (0.1) 1
Sinus tachycardia	0	1 (0.2) 1	1 (0.1) 1
Skin and subcutaneous tissue disorders	1 (0.2) 1	0	1 (0.1) 1
Erythema	1 (0.2) 1	0	1 (0.1) 1
Musculoskeletal and connective tissue disorders	0	1 (0.2) 1	1 (0.1) 1
Arthralgia	0	1 (0.2) 1	1 (0.1) 1

Table 38: HLX11/EU-Perjeta -Related IRRs by SOC and PT – Adjuvant HER2-Targeted Therapy Period (Safety Set) – Study HLX11-BC301

Category System Organ Class Preferred Term	HLX11-HLX11 (N=154) n (%) E	EU-Perjeta®-EU-Perjeta® (N=79) n (%) E	EU-Perjeta®-HLX11 (N=79) n (%) E	Total (N=312) n (%) E
Adjuvant HER2-targeted therapy period	154	79	79	312
IRRs related to HLX11/EU-Perjeta®	3 (1.9) 3	3 (3.8) 5	3 (3.8) 8	9 (2.9) 16
General disorders and administration site conditions	2 (1.3) 2	2 (2.5) 3	3 (3.8) 5	7 (2.2) 10
Chills	1 (0.6) 1	2 (2.5) 2	3 (3.8) 3	6 (1.9) 6
Pyrexia	1 (0.6) 1	1 (1.3) 1	2 (2.5) 2	4 (1.3) 4
Gastrointestinal disorders	0	1 (1.3) 2	3 (3.8) 3	4 (1.3) 5
Vomiting	0	1 (1.3) 1	3 (3.8) 3	4 (1.3) 4
Nausea	0	1 (1.3) 1	0	1 (0.3) 1
Skin and subcutaneous tissue disorders	1 (0.6) 1	0	0	1 (0.3) 1
Pruritus	1 (0.6) 1	0	0	1 (0.3) 1

Serious adverse events (SAE)

HLX11-001

One (0.6%) subject (from the US-Perjeta group) experienced a serious TEAE (Grade 3), which was drug-related. The reported serious TEAE was gastrointestinal disorders by SOC and duodenal ulcer by PT.

HLX11-BC301

Table 39: Serious TEAEs - Neoadjuvant Therapy Period in Study HLX11-BC301 (Safety Set)

	HLX11 (N=453)	EU-Perjeta (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Neoadjuvant therapy period	453	454	907
Serious TEAEs	41 (9.1) 73	60 (13.2) 89	101 (11.1) 162
Serious TEAEs ≥ Grade 3	28 (6.2) 44	49 (10.8) 73	77 (8.5) 117
Serious TEAEs related to HLX11/EU-Perjeta	17 (3.8) 24	28 (6.2) 46	45 (5.0) 70
Serious TEAEs related to HLX11/EU-Perjeta ≥ Grade 3	15 (3.3) 20	25 (5.5) 40	40 (4.4) 60

Table 40: Serious TEAEs by SOC and PT – Neoadjuvant Therapy Period (Safety Set) - Study HLX11-BC301 (Excerpt)

System Organ Class Preferred Term	HLX11 (N=453) n (%) E	EU-Perjeta® (N=454) n (%) E	Total (N=907) n (%) E
Neoadjuvant therapy period	453	454	907
Any serious TEAEs	41 (9.1) 73	60 (13.2) 89	101 (11.1) 162
Investigations	27 (6.0) 51	26 (5.7) 41	53 (5.8) 92
Neutrophil count decreased	19 (4.2) 20	18 (4.0) 18	37 (4.1) 38
White blood cell count decreased	8 (1.8) 8	9 (2.0) 9	17 (1.9) 17
Alanine aminotransferase increased	7 (1.5) 7	6 (1.3) 7	13 (1.4) 14
Aspartate aminotransferase increased	7 (1.5) 8	2 (0.4) 2	9 (1.0) 10
Infections and infestations	11 (2.4) 11	13 (2.9) 14	24 (2.6) 25
Pneumonia	4 (0.9) 4	4 (0.9) 4	8 (0.9) 8
Upper respiratory tract infection	3 (0.7) 3	0	3 (0.3) 3
Gastrointestinal disorders	4 (0.9) 4	7 (1.5) 9	11 (1.2) 13
Diarrhoea	0	4 (0.9) 5	4 (0.4) 5
Vomiting	2 (0.4) 2	0	2 (0.2) 2
Blood and lymphatic system disorders	1 (0.2) 1	8 (1.8) 8	9 (1.0) 9
Febrile neutropenia	1 (0.2) 1	4 (0.9) 4	5 (0.6) 5
Respiratory, thoracic and mediastinal disorders	1 (0.2) 1	3 (0.7) 3	4 (0.4) 4
Pneumonitis	1 (0.2) 1	0	1 (0.1) 1

Table 41: Serious TEAEs by SOC and PT – Adjuvant HER2-Targeted Therapy Period (Safety Set) – Study HLX11-BC301 (Excerpt)

System Organ Class Preferred Term	HLX11-HLX11 (N=154) n (%) E	EU-Perjeta®-EU-Perjeta® (N=79) n (%) E	EU-Perjeta®-HLX11 (N=79) n (%) E	Total (N=312) n (%) E
Adjuvant HER2-targeted therapy period	154	79	79	312
Any serious TEAE	9 (5.8) 13	6 (7.6) 9	2 (2.5) 2	17 (5.4) 24
Investigations	3 (1.9) 5	3 (3.8) 5	1 (1.3) 1	7 (2.2) 11
Alanine aminotransferase increased	1 (0.6) 1	2 (2.5) 2	1 (1.3) 1	4 (1.3) 4
Aspartate aminotransferase increased	1 (0.6) 1	2 (2.5) 2	0	3 (1.0) 3
Infections and infestations	3 (1.9) 4	2 (2.5) 3	0	5 (1.6) 7
Pneumonia	3 (1.9) 3	1 (1.3) 1	0	4 (1.3) 4
Cardiac disorders	1 (0.6) 1	0	0	1 (0.3) 1
Cardiac failure	1 (0.6) 1	0	0	1 (0.3) 1

HLX11/EU-Perjeta-related serious TEAEs

All treatment-related events in the EU-Perjeta group had the outcome resolved/recovered. Four patients in the HLX11 group had events that were not recovered/resolved: cardiac failure and pleural effusion Grade 4, paraneoplastic neurological syndrome Grade 3, interstitial lung disease Grade 2, AST/ALT (both Grade 2)/GGT (Grade 3) increased). For the initial three events (in 2 patients) treatment was discontinued while for the latter treatment was either already completed or continued.

Deaths

HLX11-001

No subjects died in this study.

HLX11-BC301

As of the data cut-off date, only one death was reported during the study. The death was in the HLX11-HLX11 group and occurred in the adjuvant HER2-targeted therapy period. The death was due to a TEAE with PT of craniocerebral injury, and this event was caused by a car accident and considered by the investigator as not related to any study drug.

5.4.5. Discontinuation due to adverse events

HLX11-001

No subjects experienced any TEAEs that led to interruption or discontinuation of study drug in this study.

HLX11-BC301

Table 42: Overview of TEAEs leading to study drug interruption or discontinuation – Neoadjuvant Therapy Period (Safety Set) - Study HLX11-BC301

	HLX11 (N=453)	EU-Perjeta (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Neoadjuvant therapy period	453	454	907

	HLX11 (N=453)	EU-Perjeta (N=454)	Total (N=907)
	n (%) E	n (%) E	n (%) E
Any TEAEs	440 (97.1) 3921	439 (96.7) 4043	879 (96.9) 7964
TEAEs leading to any study drug interruption	52 (11.5) 83	50 (11.0) 80	102 (11.2) 163
TEAEs leading to HLX11/EU-Perjeta interruption	41 (9.1) 62	34 (7.5) 42	75 (8.3) 104
TEAEs leading to HLX11/EU-Perjeta interruption ≥ Grade 3	7 (1.5) 8	9 (2.0) 9	16 (1.8) 17
TEAEs related to HLX11/EU-Perjeta leading to any study drug interruption	8 (1.8) 10	15 (3.3) 22	23 (2.5) 32
TEAEs related to HLX11/EU-Perjeta leading to HLX11/EU-Perjeta interruption	7 (1.5) 9	12 (2.6) 17	19 (2.1) 26
TEAEs leading to any study drug discontinuation	0	4 (0.9) 5	4 (0.4) 5
TEAEs leading to HLX11/EU-Perjeta discontinuation	0	2 (0.4) 3	2 (0.2) 3
TEAEs leading to HLX11/EU-Perjeta discontinuation ≥ Grade 3	0	1 (0.2) 2	1 (0.1) 2
TEAEs related to HLX11/EU-Perjeta leading to any study drug discontinuation	0	2 (0.4) 2	2 (0.2) 2
TEAEs related to HLX11/EU-Perjeta leading to HLX11/EU-Perjeta discontinuation	0	1 (0.2) 1	1 (0.1) 1

Table 43: Overview of TEAEs leading to study drug interruption or discontinuation - Adjuvant HER2-Targeted Therapy Period (Safety Set) – Study HLX11-BC301

	HLX11- HLX11 (N=154)	EU-Perjeta - EU-Perjeta (N=79)	EU-Perjeta - HLX11 (N=79)	Total (N=312)
	n (%) E	n (%) E	n (%) E	n (%) E
Adjuvant HER2-targeted therapy period	154	79	79	312
Any TEAEs	137 (89.0) 1191	68 (86.1) 501	72 (91.1) 539	277 (88.8) 2231
TEAEs leading to any study drug interruption	18 (11.7) 28	9 (11.4) 12	11 (13.9) 23	38 (12.2) 63
TEAEs leading to HLX11/EU-Perjeta interruption	18 (11.7) 28	9 (11.4) 12	10 (12.7) 20	37 (11.9) 60
TEAEs leading to HLX11/EU-Perjeta interruption ≥ Grade 3	5 (3.2) 6	1 (1.3) 1	3 (3.8) 4	9 (2.9) 11
TEAEs related to HLX11/EU-Perjeta leading to any study drug interruption	6 (3.9) 8	3 (3.8) 5	5 (6.3) 9	14 (4.5) 22
TEAEs related to HLX11/ EU-Perjeta leading to HLX11/EU-Perjeta interruption	6 (3.9) 8	3 (3.8) 5	5 (6.3) 9	14 (4.5) 22
TEAEs leading to any study drug discontinuation	1 (0.6) 2	2 (2.5) 3	0	3 (1.0) 5
TEAEs leading to HLX11/EU-Perjeta discontinuation	1 (0.6) 2	2 (2.5) 3	0	3 (1.0) 5
TEAEs leading to HLX11/ EU-Perjeta discontinuation ≥ Grade 3	1 (0.6) 2	2 (2.5) 3	0	3 (1.0) 5
TEAEs related to HLX11/EU-Perjeta leading to any study drug discontinuation	1 (0.6) 2	1 (1.3) 1	0	2 (0.6) 3
TEAEs related to HLX11/EU-Perjeta leading to HLX11/EU-Perjeta discontinuation	1 (0.6) 2	1 (1.3) 1	0	2 (0.6) 3

Table 44: Summary of study discontinuation due to TEAEs

	HLX11			EU-Perjeta				Total
	Not Re-randomized (N=299) N (%)	HLX11-HLX11 (N=154) N (%)	Total (N=453) N (%)	Not Re-randomized (N=296) N (%)	EU-Perjeta - EU-Perjeta (N=79) n (%)	EU-Perjeta - HLX11 (N=79) n (%)	Total (N=454) n (%)	Total (N=907) n (%)
Adjuvant HER2 Targeted Therapy Period		1 (0.6)	1 (0.6)		2 (2.5)	0	2 (1.3)	3 (1.0)

5.4.6. Safety in special populations

Not applicable

5.4.7. Immunological events

Table 45: Summary of Adverse Events by ADA Results in Study HLX11-001

	HLX11		Perjeta® Total	
	ADA Positive (N=25)	ADA Negative (N=15)	ADA Positive (N=45)	ADA Negative (N=75)
Number of subjects experiencing at least 1 AE	25 (100%)	14 (93.3%)	43 (95.6%)	71 (94.7%)
Number of subjects experiencing at least 1 AE with CTCAE Grade ≥ 3	1 (4.0%)	0	2 (4.4%)	1 (1.3%)
Number of subjects experiencing at least 1 SAE	0	0	1 (2.2%)	0
Number of subjects experiencing at least 1 drug-related adverse event with CTCAE Grade ≥ 3	0	0	2 (4.4%)	0
Number of subjects experiencing at least one AESI	0	0	0	0

ADA=anti-drug antibody; AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; SAE=serious adverse event
Note: Overall ADA positive is defined as at least 1 post-baseline ADA positive in entire study.

Table 46: Summary of Adverse Events by ADA Results in Study HLX11-BC301 - (Safety Set)

	HLX11* (N=453)		EU-Perjeta®** (N=375)		EU-Perjeta®-HLX11 (N=79)		Total (N=907)	
	ADA Positive (N=24)	ADA Negative (N=429)	ADA Positive (N=16)	ADA Negative (N=359)	ADA Positive (N=6)	ADA Negative (N=73)	ADA Positive (N=46)	ADA Negative (N=861)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
TEAEs	23 (95.8)	420 (97.9)	16 (100)	350 (97.5)	6 (100)	73 (100)	45 (97.8)	843 (97.9)
Grade ≥ 3 TEAEs	11 (45.8)	196 (45.7)	10 (62.5)	143 (39.8)	4 (66.7)	56 (76.7)	25 (54.3)	395 (45.9)
Serious TEAEs	2 (8.3)	65 (15.2)	5 (31.3)	58 (16.2)	1 (16.7)	17 (23.3)	8 (17.4)	140 (16.3)
HLX11/EU-Perjeta®-related TEAEs	17 (70.8)	251 (58.5)	12 (75.0)	213 (59.3)	3 (50.0)	57 (78.1)	32 (69.6)	521 (60.5)
Grade ≥ 3 HLX11/EU-Perjeta®-related TEAEs	6 (25.0)	81 (18.9)	4 (25.0)	66 (18.4)	1 (16.7)	20 (27.4)	11 (23.9)	167 (19.4)
HLX11/EU-Perjeta®-related serious TEAEs	0	24 (5.6)	2 (12.5)	23 (6.4)	0	5 (6.8)	2 (4.3)	52 (6.0)
AESIs	1 (4.2)	21 (4.9)	2 (12.5)	17 (4.7)	0	5 (6.8)	3 (6.5)	43 (5.0)

* The subjects who only received HLX11 during overall treatment period.
** The subjects who only received EU-Perjeta during overall treatment period.

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

Not applicable.

5.4.9. Vital signs and laboratory findings

HLX11-001

Laboratory values

Most of the subjects' hematology, serum chemistry, urinalysis, and myocardial enzyme clinical evaluations remained within normal or not clinically significant (NCS) during the study period. Only a few subjects were identified with normal or NCS values at baseline and clinically significant (CS) abnormal values post-baseline. The percentages of subjects experienced those shifts were comparable across groups.

Electrocardiograms (ECG)

A few subjects were identified with normal values at baseline and above or below normal range post-baseline. The percentages of subjects experienced above changes were comparable across groups. Most of the subjects' 12-lead ECG examination results remained normal or NCS during the study. Only a few subjects were identified with normal or NCS values at baseline and CS abnormal values post-baseline. Most of the subjects' ECG monitoring results remained normal or NCS during the study.

Echocardiography

Echocardiogram results of all subjects remained normal or NCS during the study.

HLX11-BC301

Laboratory values

There were no notable differences in the incidence of individual changes between the HLX11 and EU

Perjeta groups in the neoadjuvant therapy and adjuvant chemotherapy periods and across the HLX11-HLX11, EU Perjeta-EU Perjeta, and EU Perjeta-HLX11 groups throughout the entire study.

Electrocardiograms (ECG)

The proportions of subjects with ECG shifts from a normal or not clinically significant abnormal baseline value to a clinically significant abnormal post-baseline value were 9.9% for the HLX11 group and 9.5% for the EU-Perjeta group in the neoadjuvant therapy and adjuvant chemotherapy periods, and 18.2% for the HLX11-HLX11 group, 17.8% for the EU-Perjeta-EU-Perjeta group, and 19.0% for the EU-Perjeta-HLX11 group throughout the entire study.

Echocardiography

In the *neoadjuvant therapy period*, 48.1% of subjects in the HLX11 group and 48.2% of subjects in the EU-Perjeta group experienced at least once < 10% reduction from baseline in LVEF value, 18.8% of subjects in the HLX11 group and 15.2% of subjects in the EU-Perjeta group experienced at least once ≥ 10% reduction from baseline in LVEF value, but no subjects had any LVEF absolute value below 50%.

In the *adjuvant HER2-targeted therapy period*, the proportions of subjects with at least once < 10% reduction from baseline in LVEF value were 51.3% for the HLX11-HLX11 group, 62.0% for the EU-Perjeta-EU-Perjeta group, and 49.4% for the EU-Perjeta-HLX11 group; the proportions of subjects with at least once ≥ 10% reduction from baseline in LVEF value were 24.0%, 15.2%, and 22.8%, respectively, for the three groups after re-randomization; and only 1 (0.6%) subject in the HLX11-HLX11 group had LVEF absolute value below 50% and a reduction of ≥ 10% from baseline.

5.4.10. Post-marketing experience

Not applicable

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

Safety data collection

The safety of HLX11 versus EU-Perjeta has been assessed in two clinical studies: a single-dose Phase 1 study in healthy subjects (HLX11-001), and a multiple-dose Phase 3 study in patients with early-stage or locally advanced, HER2 positive and HR negative breast cancer (HLX11-BC301) which consisted of a neoadjuvant period (cycles 1-4), surgery, an adjuvant chemotherapy period (cycles 5 to 8) and a HER2-targeted therapy period (Cycles 9 to 21).

Safety data collection occurred at reasonable and regular timepoints during both studies. Coding of AEs by MedDRA version 27.0 (study HLX11-BC301) and MedDRA 23.0 (study HLX11-001) is adequate.

Owing to the differences of the two studies in terms of population, dosing regimen and study duration, pooling of data did not occur, which is acceptable.

The safety set, defined as all subjects who received at least one dose of the study drug, comprised 907 female patients in study HLX11-BC301 and 160 healthy male volunteers in study HLX-001 and is considered sufficiently large for evaluation of the safety profile HLX11 compared to EU-Perjeta.

Study HLX11-001 (Phase 1)

In study HLX11-001 a total of 160 subjects received pertuzumab after randomisation to the HLX11 group (40 subjects), US-Perjeta group (40 subjects), EU-Perjeta group (40 subjects) or CN-Perjeta group (40 subjects). All subjects received a single IV infusion of pertuzumab at 420 mg over a 60 minutes infusion time. All subjects were healthy males of Chinese origin. The study was completed on 08 February 2021.

The overall incidence of TEAEs was comparable between HLX11 and EU-Perjeta. The number of patients is limited with N=40 patients per arm. The most common treatment-related TEAEs by PT were leucocytosis, urinary tract infection, diarrhoea, proteinuria and neutropenia and reflect the known safety profile of pertuzumab. Four (2.5%) subjects experienced Grade ≥ 3 TEAEs. The reported PTs were hypertriglyceridaemia (2 subjects, from the HLX11 group and the EU-Perjeta group), duodenal ulcer (1subject, from the US-Perjeta group), and proteinuria (1 subject, from the CN-Perjeta group). The event of Grade 3 duodenal ulcer was the only TEAE classed as severe in the study.

No SAE or deaths were reported in the HLX11 and EU-Perjeta groups.

Cardiotoxicity and infusion-related reactions (IRRs) were classified as adverse events of special interest (AESI). No subject experienced an AESI.

No subjects experienced any TEAEs that led to interruption or discontinuation of study drug.

Overall, in the Phase 1 study HLX11-001 no relevant differences between treatment arms were seen in either nature, incidence or severity of adverse events.

Study HLX11-BC301 (Phase 3)

Exposure

In study HLX11-BC301 of the 908 randomised subjects N=446 and N=447 of patients in the HLX11 and EU-Perjeta group (98.5% in each treatment group), respectively, received all 4 cycles of *neoadjuvant treatment*. All enrolled subjects were from 74 study sites in China as the screening was unsuccessful in Europe.

The difference in planned and actual minimum between HLX11 and EU-Perjeta (1260mg vs 840mg) can be explained bv the fact, that 2 patients in the EU-Perjeta group only received the loading dose of 840 mg and no further doses, while patients in the HLX11 group received at least 2 doses (ie. 840 mg + 420mg) of treatment.

Although the number of patients with dose interruptions in the neoadjuvant period was higher in the HLX11 arm (18 events in 11 patients) compared to EU-Perjeta (6 events in 4 patients), this did not seem to impact exposure as only one patient in each treatment arm received a lower dose than planned. Chills and pyrexia were the most commonly reported PTs in both arms and except for one case of pyrexia, all events were Grade 1 and 2 in severity.

In the *adjuvant HER2-targeted therapy period* after surgery 232 subjects received HLX11 (154 in the HLX11-HLX11 group and 78 in the EU-Perjeta-HLX11 group) and 79 subjects received only EU-Perjeta (EU-Perjeta-EU-Perjeta group). As of data cut-off (15 May 2024) 37.7%, 41.8% and 39.2% of patients received all 13 treatment cycles of adjuvant HER2-targeted therapy in the HLX11-HLX11, EU-Perjeta-EU-Perjeta and EU-Perjeta-HLX11 groups, respectively.

This study part is still ongoing. At the time of data cut-off 15 May 2024 (last subject completed pathologic response evaluation) 91 patients (N=59.1%) in the HLX11-HLX11 group, 46 patients (58.2%) in the EU-Perjeta-HLX11 group and 41 patients (51.9%) in the EU-Perjeta-EU-Perjeta group were ongoing on adjuvant HER2-targeted therapy.

TEAE

In the *neoadjuvant period* the overall incidence of TEAE was similar between HLX11 and EU-Perjeta. Amongst others the most common PTs included neutropenia, diarrhoea, alopecia, anemia and upper respiratory tract infection, all of which are common or very common toxicities of pertuzumab. No apparent differences were noted between the treatment groups for Grade ≥ 3 TEAEs as well as HLX11/EU-Perjeta-related TEAEs (including Grade ≥3 TEAEs).

In the *adjuvant HER2-targeted therapy period* a comparable proportion of patients experienced any TEAEs. The most common TEAEs by SOC and PT were similar to those of the neoadjuvant period.

The nature and frequency of common TEAEs were generally in line with the Perjeta SmPC with the following exceptions:

1. No irregularities in hepatic enzymes are reported in the Perjeta SmPC. In this study shifts from normal baseline to clinically significant postbaseline AST and ALT values occurred very commonly (~25% in the neoadjuvant phase and 22% in the adjuvant phase) but with similar frequency across treatment arms. Hence, the finding raises no concerns regarding similarity. The design of this study does not allow conclusions regarding causality, and the concomitantly used docetaxel and trastuzumab are known to affect the liver. Therefore, this finding is not considered a relevant new safety signal for pertuzumab.
2. In the Perjeta SmPC it is stated that febrile neutropenia is a very common ADR and an increased incidence of febrile neutropenia was observed among Asian patients (25.8% in the Pertuzumab-treated group) compared with patients of other races and from other geographic regions. In Study HLX11-BC301, the incidence of febrile neutropenia was low despite all subjects being Asian. Only 14 (1.5%) subjects experienced this ADR over the whole reported period. As the cases were evenly distributed between study arms this finding does not raise concerns about similarity. The discrepancy with the originator SmPC might reflect a general improvement of treatment standards and management of neutropenia since the MA of the originator. Therefore, the issue does not require further scrutiny.

HLX11/EU-Perjeta-related TEAEs were reported with a higher incidence in the HLX11-HLX11 group compared to the EU-Perjeta-EU-Perjeta and EU-Perjeta-HLX11 groups, respectively (61.0% vs 53.2% vs 53.2%). For Grade ≥ 3 related TEAEs this difference was still evident - although less prominent – for the HLX11-HLX11 and EU-Perjeta-EU-Perjeta groups (7.8% vs 6.3%) but this did not seem to negatively impact treatment compliance as similar or even fewer number of patients interrupted or discontinued treatment with HLX11/EU-Perjeta due to a TEAE. The observed difference was mainly driven by the SOC investigations with the PTs decrease in lymphocyte, neutrophil and white blood cell count, which are listed as very common ADRs in the EU-Perjeta SmPC.

In the re-randomised group (EU-Perjeta-HLX11) the number of patients experiencing treatment-related Grade ≥3 TEAEs was higher compared to the other treatment groups (10.1%). In this group the proportion of patients interrupting treatment due to a treatment-related (HLX11/EU-Perjeta) TEAE was also the highest (6.3%) compared to HLX11-HLX11 (3.9%) and EU-Perjeta-HLX11 (3.8%). However, no patient discontinued treatment due to a TEAE (related or unrelated). Hence, the observed differences are not considered of major relevance in regards of similarity of HLX11 to EU-Perjeta.

Serious adverse events and deaths

It is noted that patients treated with HLX11 in the *neoadjuvant period* reported consistently fewer SAEs (9.1% vs 13.2%), treatment-related SAEs (3.8% vs 6.2%), Grade ≥3 SAE (6.2% vs 10.8%) and treatment-related Grade ≥3 SAE (3.3% vs 5.5%). Differences between the treatment groups for treatment-related SAEs were mainly observed for the SOC Investigations (HL11X 3.9%, EU-Perjeta

5.1%), Blood and lymphatic system disorders (0.6% vs 3.8%) and Gastrointestinal disorders (0.6% vs 2.5%). The most common SAEs by PT were neutrophil count decreased and white blood cell count decreased.

A similar finding of fewer reported SAEs was noted for the *adjuvant HER2-targeted therapy period (*HLX11-HLX11 5.8%, EU-Perjeta-EU-Perjeta 7.6%). However, no difference was observed in the frequency of HLX11/EU-Perjeta-related SAEs and related Grade ≥ 3 SAEs.

One death was reported in the adjuvant HER2-targeted therapy period in the HLX11-HLX11 group which was attributed to a car accident (PT of craniocerebral injury). There were no treatment-related deaths.

Adverse events of special interest

Similar to the Phase 1 study, cardiotoxicity and infusion-related reactions (IRRs) were classified as adverse events of special interest (AESI). Both AESIs were reported less frequently than in the pivotal studies of Perjeta.

Two events of cardiotoxicity were reported in 1 subject in the EU-Perjeta group in the neoadjuvant therapy period and 1 subject in the HLX11-HLX11 group in the adjuvant HER2-targeted therapy period. Both events were serious, related to study treatment and Grade 4 symptomatic left ventricular systolic dysfunctions. In addition, other TEAEs under the SOC "cardiac disorders" were reported: the most common TEAEs under the SOC "cardiac disorders" were sinus tachycardia, palpitations, arrhythmia, and ventricular extrasystoles. The incidences were similar between treatment arms in the neoadjuvant period. During the adjuvant chemotherapy period, the small differences in frequency are not deemed significant.

Infusion-related reactions occurred with a similar frequency in the *neoadjuvant period* of study HLX11-BC301 while fewer patients in the *adjuvant HER2-targeted therapy period* experienced IRRs and treatment-related IRRs in the HLX11-HLX11 group compared to the EU-Perjeta-EU-Perjeta and EU-Perjeta-HLX11 groups. All events were Grade 1 or 2 and not serious.

Study drug interruption due to adverse events

Dose interruptions occurred with a low frequency. In the *neoadjuvant period* slightly more patients in the HLX group interrupted treatment compared to the EU-Perjeta group (9.1% vs 7.5%). However, these differences are not attributed to a specific pattern but rather to minor imbalances in several PTs, the most prominent being upper respiratory tract infection and pyrexia. Moreover, it is reassuring that the frequency of Grade ≥3 TEAEs and treatment-related TEAEs leading to interruption was even lower in the HLX11 group compared to EU-Perjeta.

In the *adjuvant HER2-targeted period* dose interruptions due to a TEAE, treatment-related TEAE and SAE occurred with a comparable frequency for HLX11 and EU-Perjeta.

Study drug and study discontinuation due to adverse events

The number of patients discontinuing treatment due to a TEAE was low.

In the *neoadjuvant period* events were only observed in the EU-Perjeta group (SAE, acute left ventricular failure Grade 4). In the *adjuvant HER2-targeted therapy period* events occurred in 1 patient in the HLX11-HLX11 group and 2 patients in the EU-Perjeta-EU-Perjeta group, all of which were considered related to study treatment. These events were not serious.

The rate of patients discontinuing study due to TEAEs was overall low and comparable between the treatment arms in the overall study period.

Immunogenicity

Study HLX11-001

ADA development was much higher with HLX11 than with any of the Perjeta products. It is reassuring that the incidence of NAbs was similar across all study groups in this study, and no difference in the frequency of ADAs/Nabs was seen in the longer and larger phase 3 study.

There was no apparent difference in nature or frequency of adverse events between ADA positive and ADA negative subjects and no difference was seen between study arms in either ADA subgroup. The higher ADA frequencies compared to those seen in patients are not surprising since healthy subjects have an intact immune system and no additional suppression from dexamethasone as opposed to patients.

Study HLX11-BC301

In the *neoadjuvant period* of the study a marginally higher proportion of patients were ADA positive in the HLX11 arm compared to EU-Perjeta (4.9% vs 4.0%) with a comparable incidence of NAbs (2.2% vs 2.0%).

ADA positivity was reported in a similar number of patients in the *adjuvant HER2-targeted period* for the treatment groups HLX11-HLX11 and EU-Perjeta-HLX11 (each 1.3%) while patients receiving EU-Perjeta throughout the study (EU-Perjeta-EU-Perjeta) had a higher ADA incidence (3.8%). No patient developed NAbs.

ADA incidences are overall in accordance with those described in the SmPC (3.3% and 4.1%). There was no apparent effect of ADA status on efficacy or on the incidence, type, or severity of TEAEs. However, with very few ADA positive subjects per group, no meaningful comparison is feasible as slight fluctuations in the number of subjects achieving tpCR or reporting an ADR may have a great impact on the percentage.

SmPC

The SmPC is overall in accordance with the SmPC of the reference medicinal product. Owing to the fact that Poherdy includes sorbitol and polysorbate 20, which are excipients with known effect, the product information was amended to include a contraindication regarding patients with hereditary fructose intolerance (HFI).

5.4.11.1.2. Adverse drug reactions (ADRs) in the SmPC

Not applicable.

5.4.11.2. Conclusions on clinical safety

Based on the provided data of the two clinical studies, one in healthy Chinese male volunteers (Study HLX11-001) and one in female subjects with early stage or locally advanced, HER2-positive and HR negative breast cancer (Study HLX11-BC301), no relevant differences were seen between HLX11 and the originator in either type, incidence or severity of adverse events. No unexpected safety concerns were detected for HLX11. The observed safety findings correspond to the known safety profile of the reference product Perjeta and were largely balanced between treatment arms. The safety database is considered sufficient in terms of number of subjects and duration of treatment for adequate comparison between products.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

HLX11 has been developed as a biosimilar to EU-Perjeta, which has been marketed in the EU since 2013. The safety concerns of Poherdy are based on the originator's RMP (Perjeta: EPAR – Risk management plan, last updated on 05 April 2024).

The applicant proposed the following summary of safety concerns in the RMP (version 0.2, date of final sign-off 19 Sep 2025):

Table 47: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	• Infusion-related reactions, Hypersensitivity reactions / anaphylaxis • Congestive heart failure / Left ventricular dysfunction
Important potential risks	• Oligohydramnios* • Risk in fertility in humans • Risk in patients aged 75 years or older • Lack of efficacy due to immunogenicity • Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)
Missing information	• Risk in pregnant or lactating women

*Oligohydramnios has not been reported in patients treated with HLX11 or the reference product but occurred in cynomolgus monkeys administered pertuzumab and in pregnant women treated with trastuzumab. Due to age, prior adjuvant treatment, concurrent chemotherapy, the advanced stage of disease and poor prognosis in the patient population, the MAH assesses the likelihood of pregnancies to be low.

6.1.2. Discussion on proposed safety specification

The applicant proposes a summary of safety concerns as shown above.

The proposed summary of safety concerns is in line with the reference product's latest approved RMP version 14.1 (date of final sign-off: 30 Jan 2024).

However, Poherdy (in contrast to the reference product) is a sorbitol-containing product. Therefore, "serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance" has been as an important potential risk in the safety specification.

Poherdy also contains polysorbate 20. Polysorbates may cause allergic reactions. "Hypersensitivity to any of the excipients" has been added to Part II: Module SVII - Risk factors and risk groups for Infusion-related reactions, Hypersensitivity reactions/Anaphylaxis in the RMP V0.2.

Minor editorial changes in the product overview of the RMP (part I) were requested for the previous version of the RMP. These were implemented. No changes have been made in the safety specification (Part II) in RMP version 0.3 with final sign off date of 21 Jan 2026.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

- Guided Questionnaire Pregnancy-Related Adverse Events

Oligohydramnios has been classified as an important potential risk for pertuzumab. The guided questionnaire will be implemented as part of the Global Enhanced Pharmacovigilance Pregnancy Program to request additional information on the mother s medical and obstetric history, the current pregnancy, foetal and infant condition, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life (Annex 4).

- **Other forms of routine pharmacovigilance activities:**

Presentation of cumulative data in Periodic Safety Update Reports (PSURs) for the following risks:

- Infusion-related reactions, Hypersensitivity reactions/ anaphylaxis
- Congestive heart failure/ Left ventricular dysfunction
- Patients aged 75 years or older
- Lack of efficacy due to immunogenicity
- Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)

Global Enhanced Pharmacovigilance Pregnancy Program for safety concern:

- Oligohydramnios
- Risk in fertility in humans
- Risk in pregnant or lactating women

The standard pregnancy follow-up process was implemented for Poherdy to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, foetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

- Cumulative data will be presented in PSURs/PBRERs.

III.2 Additional pharmacovigilance activities

None.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

The proposed pharmacovigilance plan is in line with the originator medicinal product.

The applicant has included the proposed safety concern 'serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance' as part of the presentation of cumulative data in Periodic Safety Update Reports (PSURs).

Further, the applicant has included a statement concerning presentation of cumulative data in the PSURs/PBRERS in the end of Part III.1, in line with the originator medicinal product.

The proposed routine pharmacovigilance activities are acceptable.

6.2.2.2. Additional pharmacovigilance activities

The applicant did not propose any additional pharmacovigilance activities. This is agreed.

Routine pharmacovigilance activities are sufficient to identify and characterise the risks of Poherdy.

6.3. Plans for post-authorisation efficacy studies

None.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 48: Planned routine risk minimisation measures

Safety concern	Routine risk minimisation activities
Infusion-related reactions, Hypersensitivity reactions/anaphylaxis	Routine risk communication: • EU SmPC Section 4.8: Undesirable effects • Package Leaflet (PL) Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.4 of the EU SmPC, 'Infusion reactions' and 'Hypersensitivity reactions/anaphylaxis' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.

Congestive heart failure / Left ventricular dysfunction	Routine risk communication: • EU SmPC Section 4.8: Undesirable effect • PL Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.2 of the EU SmPC, 'Left ventricular dysfunction' part and Section 4.4 'Left ventricular dysfunction (including congestive heart failure)' provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Oligohydramnios	Routine risk communication: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Risk in fertility in humans	Routine risk communication: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Risk in patients aged ≥ 75 years	Routine risk communication: • EU SmPC Section 4.2: Elderly patients • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.4 of the EU SmPC: 'Diarrhoea' part provides

	recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Lack of efficacy due to immunogenicity	Routine risk communication: • EU SmPC Section 5.1: 'Immunogenicity' part Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (HFI)	Routine risk communication: • EU SmPC Section 2: Excipients with known effect and Section 4.3: Contraindications • Outer packaging Sections 3 and 7 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In Section 4.4 of the EU SmPC: 'Excipients with known effect - Sorbitol' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: Legal status: Poherdy is a medicinal product subject to restricted medical prescription.
Risk in pregnant or lactating women	Routine risk communication: • EU SmPC Section 4.6: Fertility, pregnancy and lactation • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • In section 4.6 of the EU SmPC: 'Fertility, pregnancy and lactation' part provides recommendations on risk management approach. Other routine risk minimisation measures beyond the Product Information: • Legal status: Poherdy is a medicinal product subject to restricted medical prescription.

Summary of additional risk minimisation measures

Not applicable. Risk minimisation measures in RMP version 0.3 are considered sufficient

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

Routine risk minimisation activities in accordance with the RMP for the originator are considered appropriate.

6.4.2.2. Additional risk minimisation measures

The agreed DHPC has been included as a safety communication tool and not as an additional risk minimisation measure. The RMP has been updated accordingly. The DHPC should be distributed in connection with launch in each Member state. The applicant will evaluate the need for redistribution of the DHPC in connection with submission of the PSUR.

6.5. RMP summary and RMP annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

☒The CHMP considers that the risk management plan version 0.3 (date of final sign-off: 21Jan2026) is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

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

7.2. Periodic safety update reports (PSURs) 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.

8. Product information

8.1. Summary of product characteristics (SmPC)

The Product information of HLX11 is in general concordant with that of EU-Perjeta. However, information on the excipients Sorbitol and Polysorbate 20 were included in SmPC section 2, section 4.4

and Annex IIIB section 2, to be in accordance with the update of the Annex to the guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (as per Amendment from 17 Apr 2024).

8.1.1. SmPC section 4.1 justification

The SmPC is aligned with the SmPC of Perjeta.

8.1.2. SmPC section 4.3 justification

A contraindication regarding patients with hereditary fructose intolerance (HFI) is included in SmPC Section 4.3, since parenteral administration of sorbitol in subjects with HFI is harmful and potentially life-threatening. Also, other parts of the SmPC were updated with information and warnings on sorbitol and polysorbate 20 content.

8.1.3. SmPC section 5.1 justification

Since the methodology on determination of ADA is different in the studies of the originator and the biosimilar, percentages of ADA response cannot be extrapolated from the originator to the biosimilar. The paragraph with the subtitle "Immunogenicity" was therefore simplified in line with other biosimilars to read:

"Immunogenicity

Anti-pertuzumab antibodies may develop during treatment with pertuzumab. No apparent correlation of antibody development with clinical response or adverse events has been observed".

8.2. Package leaflet (PL)

The PL was updated in line with the updated SmPC.

8.3. 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 Perjeta (EMEA/H/C/002547/0000). The bridging report submitted by the applicant has been found acceptable.

8.4. Additional monitoring

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

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

9. Biosimilarity assessment

9.1. Comparability exercise and indications claimed

HLX11 has been developed as a proposed biosimilar of Perjeta. HLX11 contains the active substance pertuzumab. One 14 ml vial of concentrate contains 420 mg of pertuzumab at a concentration of 30 mg/ml. This is the same amount and concentration of active substance as the reference medicinal product.

Proposed indications

The proposed indications for HLX11 are the same as those approved for Perjeta:

Early breast cancer

HLX11 is indicated for use in combination with trastuzumab and chemotherapy in:

- *the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence;*
- *the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.*

Metastatic breast cancer

HLX11 is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Comparability exercise

Quality aspects

The biosimilarity exercise for HLX11 followed the recommendations as laid down in EMA/CHMP/BWP/247713/2012.

The main analytical comparability (biosimilarity) study is described in sufficient detail. In total 17 EU-Perjeta, and 12 independent HLX11 have been included. A risk assessment identified a comprehensive QA list tested during the study using an approach developed by Roche/Genentech (Alt N 2016).

For quantitative analyses descriptive quality ranges were used to assess PQAs, which is determined as the mean ± X×SD of the reference medicinal product batches. The multiplier (X = 3) was used for both high and moderate risk QAs in this similarity study.

Visual comparisons, including raw data and graphical representations, were used for quality attributes with the lowest risk ranking, those that cannot be quantitatively measured (such as primary sequence), and attributes present in low abundance.

The approach is in general considered acceptable taking the high number of reference product batches into account. The Applicant considered biosimilarity as highly similar if 90% of HLX11 batches fall into the quality range. This is acceptable as the Applicant provided in general sufficient justifications.

Non-clinical

Not applicable, see conclusion on quality.

Clinical aspects

A comparability exercise for clinical data was carried out as part of the clinical development program for HLX11 (Poherdy), which included a phase 1 study in healthy Chinese male subjects (study HLX11-001) and a phase 3 efficacy and safety study in patients with early-stage or locally advanced, HER2positive, HR-negative breast cancer (study HLX11-BC301). The phase 1 study was a randomised, double-blind, intravenous single-dose, parallel, four-arm study that assessed PK, safety and immunogenicity of HLX11 and Perjeta (US, EU, and CN-sourced). The primary evaluation of biosimilarity in terms of clinical comparability was conducted in the phase 3 multicentre, randomised, double-blind, parallel-controlled study that evaluated the efficacy and safety of the pertuzumab biosimilar HLX11 vs. EU-Perjeta in the neoadjuvant therapy of HER2-positive and HR-negative early-stage or locally advanced breast cancer. This approach is in line with biosimilar development programs. The applicant has partly followed the recommendations made in the EMA Scientific Advice but the determination of the equivalence margin deviates from the EMA Scientific Advice.

9.2. Results supporting biosimilarity

Quality aspects

The analytical comparability supports the biosimilarity of HLX11 to its RMP EU-Perjeta. Only minor differences were reported, with the exception of significant differences in charged variants, glycosylation (mannose and afucosylation) and biological activity (ADCC).

The primary structure was determined using mass spectrometry methods. Peptide mapping results showed comparable results between HLX11 and EU-Perjeta. Mass spectrometry analysis of the peptide fragments confirmed that the amino acid sequences of HLX11 as comparable. Molecular weight was compared with the intact molecules or after reduction glycosylation or IdeS digestion. Comparable results were reported, with the following exceptions. EU-Perjeta showed additional peaks not present in HLX11 samples. The peaks correspond to a glycation in the LC and a N-terminal signal peptide residues Val-His-Ser (VHS) in the LC. This observation aligns with the PTM results which indicated that HLX11 exhibited lower glycation levels. The absence of the VHS does not raise a concern as it is not considered to have an effect on efficacy and would rather be considered a safety advantage for HLX11 in terms of less risk to immunogenicity. The disulphide bonds were confirmed and compared using LC-MS/MS. Both molecules showed comparable results. Furthermore, the glycosylation site was confirmed at HC-N299 for both molecules.

Post translational modification (PTM) as glycosylation, C-terminal lysine truncation, deamination, oxidation, isomerisation, N-terminal cyclisation and glycan processing were assessed using reduced tryptic peptide mapping with LC-MS/MS. The data showed high comparability between both products with the exception of glycation, which was shown to be slightly higher for the RMP. Furthermore, EU-Perjeta showed N-terminal extension due to the incomplete signal peptide (VHS) at levels between 5.6% to 7.6%. The VHS are associated with the CEX basic B2 peak. structure-function study of charge variants in CEX demonstrated that the VHS-related basic B2 peak exhibited comparable HER2 binding, anti-proliferation and ADCC activity to the main peak. Supporting the conclusion that the presents of VHS does not affect efficacy. Finally, EU-Perjeta had low levels of C-terminal lysines (1.5% to 3.9%.), whereas for HLX11 this modification was not reported. This does not raise concerns regarding biosimilarity. The levels of free thiol in HLX11 and RMP were measured using a Measure-iT free thiol assay kit. The amounts of free thiols levels in both products were found to be below the detection limit for this assay.

The higher order structure of HLX11 and its RMP were compared using several spectroscopic techniques (DSC, CD, FTIR and FLR). The presented spectra showed high comparability between both products.

Charged variants were compared using CEX-HPLC and iCIEF techniques. HLX11 showed increased main peaks and significantly lower acidic and basic peaks compared to the RMP. Even though the actual values differ both orthogonal methods show consistent results. In order to determine whether the differences in charged variants impact biological activity the variants were separated (by CEX fractionation) and tested using ELISA, cell-based assays including ADCC, FcRn- and FcgRIIIa-binding assays. In summary all variant peaks showed comparable activities, supporting that the differences do not impact efficacy of HLX11.

The glycosylation profile was investigated using HILIC. Differences were detected in high mannose and afucose structures. HLX11 showed higher values in comparison to EU-Perjeta. High mannose is known to have an impact on the PK of monoclonal antibodies. However, the average difference detected (1.4%) is according to literature not expected to affect serum clearance. This is further supported by the Phase I PK study where the HLX11 batch with the highest mannose content was used. To assess the impact of differences in high mannose levels, the ADCC activity of samples with similar total afucosylation (Afuc) levels but with different levels of total high mannose (average of 3.0% for HLX11 and 1.5% for RMP) was compared. The results showed that HLX11 had an average ADCC activity of 95%, while the RMP showed an average of 96%.

SEC-HPLC, CE-SDS (reduced and non-reduced), AUC-SV and SEC-MALS were used to compare size variants. Overall, the data show good comparability. SEC-monomer, CE-SDS-IgG and CE-SDS-LC+HC exceeded the values for HLX11 in comparison to its RMP. Taking the tight biosimilarity ranges and in general high purity rates into account this does not question overall biosimilarity but can be accepted in favour of better safety of the biosimilar in line with current guidance (EMA/CHMP/BWP/247713/2012).

The mode-of-action (MoA) of pertuzumab includes binding to HER2, antiproliferation of HER2-expressing cells and ADCC. Relevant assays including ELISA, SPR and cell-based antiproliferation assays were used to compare the biological efficacy of HLX11 and EU-Perjeta. Both molecules showed comparable activities in terms of HER2-binding and anti-proliferation. Concerning ADCC six of the commercial (Process P2.0 and P2.1) exceeded the upper biosimilarity range of the RMP. However, ADCC is not considered the main MoA of Pertuzumab and its impact on the overall efficacy is considered minor. Therefore, the differences seen in ADCC are not considered to impact efficacy or safety. This is also supported by the data from the Phase III study. Finally, the ADCC activity will be controlled at active substance release by testing the afucosylation an total mannose of HLX11, which is considered acceptable. CDC is not reported as a MoA of pertuzumab and absence of CDC was confirmed using an CDC assay using the human gastric cancer cell line NCI-N87 as the target cells.

IgG1 mAbs bind to Fcγ-Receptors, as well as C1q. The binding characteristics to Fcγ-RIIa-H, Fcγ-RIIa-R, Fcγ-RIIb/c, Fcγ-RIIIb, FcγRIIIa-V, FcγRIIIa-F, FcγRIa and FcRn of HLX11 and EU-Perjeta were compared using ELISA and SPR methods. The data show comparable results with the exception of Fcγ-RIIIa binding activities. HLX11 showed increased relative binding potencies, which corresponds to the increased afucosylation and higher ADCC activity reported. C1q binding was comparable between both molecules and given the absence of CDC as MoA the limited data (3 batches per molecule) provided are considered acceptable.

The degradation profiles of HLX11 and EU-Perjeta were compared using accelerated and forced temperature, as well as stress (photostability, low, pH, high pH and oxidation) studies.

Non-Clinical aspects

Not applicable, see conclusion on quality.

Clinical aspects

PK/PD

In Study HLX11-001 after a single IV infusion of HLX11, US-Perjeta, EU-Perjeta, or CN-Perjeta, the mean serum concentration-time profiles of the 4 study drugs are considered similar. For the primary PK endpoints (Cmax, AUC0-t and AUC0-∞), analysis of variance was performed after logarithmic transformation. The difference in least squares means (LSM) and associated 90% CIs were calculated for HLX11 vs. US-Perjeta, HLX11 vs. EU-Perjeta, HLX11 vs. CN-Perjeta, US-Perjeta vs. EU-Perjeta, CN-Perjeta vs. EU-Perjeta, CN-Perjeta vs. US-Perjeta. The GeoMeans ratio and its 90% CI were obtained by back-transforming the difference in least squares means. The PK profiles of study drugs were considered similar if the 90% CIs of the GeoMeans ratio for Cmax, AUC0-t, and AUC0-∞ fell within 80.00% to 125.00% which was achieved for all primary PK endpoints. The statistical analysis results of the secondary PK endpoint (Tmax) after administration of a single IV infusion in the pairwise comparisons between HLX11, US-, EU-, or CN-sourced Perjeta groups do not indicate a statistical difference of Tmax. Descriptive statistics of other PKS parameters of t1/2, λz, CL, Vz and MRT also indicate high similarity of HLX11 with the reference products. The mean serum concentration-time profiles of the study drugs and the serum concentrations were similar over time independently from ADA status and thus, immunogenicity had no obvious effect on serum concentration.

In Study HLX11-BC301, the serum concentrations and accumulation ratios (Rac) of HLX11/EU-Perjeta were comparable at each time point between the HLX11 and EU-Perjeta groups in the neoadjuvant therapy and adjuvant chemotherapy periods, and between the HLX11 group (total of HLX11-HLX11 and EU-Perjeta-HLX11) and EU-Perjeta group (EU-Perjeta - EU-Perjeta) in the adjuvant HER2-targeted therapy period, and there was no accumulation of HLX11/EU-Perjeta observed in any treatment group throughout the entire study, indicating that the PK characteristics of HLX11 and EU-Perjeta were similar. The sensitivity analyses results confirmed the primary analysis results supporting the PK similarity between the HLX11 and EU-Perjeta in the target population.

Efficacy

Data from study HLX11-BC301 conducted in patients with early-stage or locally advanced, HER2-positive and HR-negative breast cancer were provided to compare efficacy between HLX11 and Perjeta. The primary efficacy endpoint was defined as tpCR rate assessed by IRC after neoadjuvant therapy with docetaxel + trastuzumab + HLX11/ EU-Perjeta. The observed risk difference was 0.47% [95%CI: -5.992%, 6.924%] and risk ratio was 1.01 [90%CI: 0.898, 1.136]. The predefined equivalence margin for the risk difference was [-13%, 13%] and for the risk ratio was [0.79, 1.26]. Similar treatment responses were observed in tpCR by IRC which were supported by secondary efficacy endpoints.

Safety

HLX11-001

The overall incidence of TEAEs was comparable between HLX11 (97.5%) and EU-Perjeta (97.5%). The most common treatment-related TEAEs reflect the known safety profile of pertuzumab.

There were no SAEs, deaths, AESI and TEAEs leading to discontinuation reported for HLX11 or EU-Perjeta.

HLX11-BC301

Neoadjuvant:

The overall incidence of TEAE was similar between HLX11 (97.1%) and EU-Perjeta (96.7%). The most common PTs reflected common or very common toxicities of pertuzumab (as per SmPC).

No apparent differences were noted between the treatment groups for Grade ≥ 3 TEAEs, HLX11/EU-Perjeta-related TEAEs (including related Grade ≥3 TEAEs) and AESI.

For the following TEAEs lower frequencies were reported in the HLX11 group compared to the EU-Perjeta group: Serious TEAEs (including related, Grade ⩾ 3, treatment-related Grade ⩾ 3), TEAEs leading to dose interruption (Grade ≥3, treatment-related TEAEs).

Slightly more patients in the HLX group interrupted treatment compared to the EU-Perjeta group (9.1% vs 7.5%) but these differences cannot be attributed to a specific pattern.

No patient discontinued treatment due to a TEAE in the HLX11 group.

Adjuvant HER2-targeted therapy:

A comparable proportion of patients experienced any TEAEs (HLX11-HLX11 89.0%; EU-Perjeta-EU-Perjeta 86.1%). The most common TEAEs by SOC and PT were similar to those of the neoadjuvant period.

HLX11/EU-Perjeta-related TEAEs and Grade ≥ 3 related TEAEs were reported more frequently in the HLX11group compared to EU-Perjeta (61.0% vs 53.2% and 7.8% vs 6.3%, respectively). Treatment compliance was not impacted by this finding.

Lower frequencies were reported in the HLX11 group compared to the EU-Perjeta group for overall SAE, AESI and TEAE leading to study drug discontinuation

HLX11/EU-Perjeta-related SAEs, related Grade ≥ 3 SAEs and TEAEs leading to study drug interruption occurred in a similar proportion of patients.

Immunogenicity

ADA incidence rates were overall comparable between HLX11 and EU-Perjeta and in accordance with those described in the SmPC (3.3% and 4.1%). The incidence of TEAEs in ADA-positive patients was comparable between HLX11 and EU-Perjeta.

9.3. Uncertainties and limitations about biosimilarity

Quality

Three HLX11 lots (4.3%-4.5%) exceeded the upper limit of EU-Perjeta QR (1.3%- 3.9%) for afucosylation. The difference translated into a mean ADCC activity difference of 26% (93% for HLX11 vs 67% for EU-Perjeta). However, the results from the phase III clinical trial showed no difference in efficacy. Therefore, given that all HLX11 batches showed higher afucosylation and higher ADCC the difference could to be considered clinically irrelevant. Furthermore, the impact of afucosylation on ADCC activity has been thoroughly evaluated, and the active substance release specification limits have been established based on a correlation analysis, which is endorsed.

The Applicant has adequately demonstrated that slightly elevated level of high mannose does not has meaningful impact on ADCC activity. Additionally, based on literature, differences in high mannose levels of ~3% or less are unlikely to significantly impact on antibody clearance.

In conclusion, the observed difference in total afucosylation with high mannose is highly unlikely to have clinically meaningful impact, and therefore it does not preclude the similarity claim between HLX11 and EU-Perjeta. Furthermore, by controlling high mannose and afucosylated glycans separately in the active substance release specification with tight enough limits, it is ensured that sufficient similarity is maintained between the products in the future.

SEC-HPLC, CE-SDS (reduced and non-reduced), AUC-SV and SEC-MALS were used to compare size variants. Overall, the data show good comparability. SEC-monomer, CE-SDS-IgG and CE-SDS-LC+HC exceeded the values for HLX11 in comparison to its RMP. Taking the tight biosimilarity ranges and in general high purity rates into account this does not question overall biosimilarity but can be accepted in favour of better safety of the biosimilar in line with current guidance (EMA/CHMP/BWP/247713/2012).

PK

Pharmacokinetics

In relation to the clinical PK data there are no uncertainties and limitations that have an impact on the conclusion of biosimilarity.

The results for the primary PK endpoints (Cmax, AUC0-t, and AUC0-∞) in the pairwise comparisons between HLX11 and US-, EU-, and CN-Perjeta revealed a slightly lower HLX11 exposure compare to all three different reference products used in study HLX11-001.

Efficacy

None

Safety

None

Immunogenicity

In the Phase 1 study the ADA assay was able to detect all antibodies to HLX11 but not necessarily all antibodies to Perjeta. This could explain the finding of the biosimilar being more immunogenic than the reference product (62,5 vs 37,5% ADA positive). It is reassuring that incidences of NAbs were similar across all study groups in this study, and that no difference in the frequency of ADAs/Nabs was seen in the longer and larger phase 3 study, and immunogenicity had no obvious effect on PK, efficacy and safety in either study.

9.4. Discussion on biosimilarity

Quality

The Applicant has addressed the similarity between HLX11 and EU-Perjeta in a comprehensive comparability exercise.

Amino acid sequence, higher order structure, and post translational modifications in terms of deamidation, isomerisation, and oxidation, and pyroglutamate variants were demonstrated to be similar between products. Additionally, both products have the same glycosylation sites and similar structures could be observed in the glycosylation profiles. Similarity in terms of product variants could be agreed. In Fc-functions, similarity in binding to FcRn, FcγRIa, FcγRIIa-R, and FcγRIIa-H was demonstrated. For Fab-related functions similarity was shown for HER2 binding and in anti-proliferation activity. Similar degradation profile was demonstrated in stability, accelerated and

stressed studies. Some trends were slightly more pronounced in EU-Perjeta.

Differences in studied quality attributes were observed in post translation modifications (glycation, C-terminal Lysine, and N-terminal signal peptide residue VHS) which resulted also in a clear difference in molecular weight analysis, and in charge heterogeneity profiles. These differences were considered not to preclude similarity as no impact on biological activity and subsequently no clinical impact from these differences are expected.

Differences were also identified in afucosylated glycan levels including mannosylation levels. Clearly higher afucosylation and mannosylation levels were observed for HLX11 than for EU-Perjeta. The Applicant has provided comparative data separately for total afucosylated glycans (w/o high mannoses) and sum of high mannoses. The difference in N-glycosylation resulted in an expected difference in FcγRIIIa-V, FcγRIIIa-F and FcγRIIIb binding and in ADCC activity. It is generally known that ADCC activity is not primary mechanism of action for pertuzumab, but it might have a role in certain indications even though the role still remains somewhat unclear. In this case, as the commercial HLX11 batches will have generally higher ADCC activity than the EU-Perjeta, the difference may be considered a factor that may impact clinical safety and efficacy. Thus, it is important to control the afucosylated glycan levels with sufficiently tight active substance release criteria to ensure similarity between HLX11 and EU-Perjeta in the future commercial batches.

To establish a stringent control for afucosylation levels, a correlation study between afucosylation and ADCC activity has been performed using a NK cell line-based assay. The study indicates a linear correlation between ADCC activity and Afuc% level for up to 6%. Furthermore, the results indicate that when Afuc% level is controlled within 2.8-5.6%, the corresponding ADCC activity are within 75% - 125%. The Applicant initially proposed an active substance release specification for total afucosylated glycans with acceptance criteria of 2.0-5.6%. It is essential to ensure that the ADCC activity of future HLX11 batches does not fall below the ADCC activity observed in EU-Perjeta batches. The tightened minimum afucosylation value seen in EU-Perjeta (2.2%) is considered clinically justified and is thus acceptable.

The analytical biosimilarity study showed in general good comparability between the proposed biosimilar and its RMP.

Non-clinical

See Quality

Clinical

PD/PK

Overall, the PD/PK/Immunogenicity data support biosimilarity between HLX-11 and EU-Perjeta.

Efficacy

The efficacy analysis conducted in study HLX11-BC301 does support clinical comparability between HLX11 and Perjeta. The primary endpoint (tpCR rate assessed by IRC) was falling within the pre-defined equivalence margin of [-13%, 13%].

Overall, the provided efficacy data support the biosimilarity between HLX11 and EU-Perjeta given the observed difference in the tpCR rate and its clinical relevance.

Safety

A sufficiently large number of patients was treated with HLX11 and the reference medicinal product Perjeta. Based on the provided safety data of the two clinical studies, no unexpected safety concerns were detected. The observed safety findings correspond to the known safety profile of the reference

product Perjeta. Overall, the submitted safety data are considered supportive for demonstration of biosimilarity.

Immunogenicity

In study HLX11-BC301 the immunogenicity profile of HLX11 is similar to that of EU-Perjeta in terms of ADA/NAb incidence, ADA titres and time of appearance. No apparent correlation of antibody development with PK, clinical response or adverse events has been observed.

9.5. Extrapolation of safety and efficacy

Poherdy was developed as biosimilar to Perjeta, the active substance, pertuzumab, being the same. The mechanism of action is identical across all indications approved for Perjeta. Thus, extrapolation to all indications might be possible.

The clinical data were derived from male Chinese healthy volunteers and female subjects with early stage or locally advanced, HER2-positive and HR-negative breast cancer. These are regarded sensitive populations in terms of evaluating biosimilarity of Poherdy (HLX11) and the reference product EU-Perjeta.

According to scientific literature cited by the applicant, the efficacy and safety profile of Perjeta has been consistent across studies conducted in both metastatic and early stage breast cancer. Therapeutic equivalence of HLX11 and EU-Perjeta could be considered as demonstrated by study HLX11-BC301, which yielded similar results in the primary endpoint, tpCR rate after surgery, as assessed by the IRC. Similar efficacy was supported by sensitivity analyses, supplementary analyses in the PPS, subgroups analyses and the currently available results for the secondary efficacy endpoints. The extrapolation is further supported by the fact that the known PK, PD, safety and immunogenicity profile of pertuzumab as summarized in the product information for EU-Perjeta is comparable across the approved indications and patient populations.

Published literature on the reference product Perjeta referred by the Applicant have suggested no PK differences based on age, gender, race (Japanese or non-Japanese) or disease status (neoadjuvant of adjuvant vs. metastatic setting). Furthermore, in general, monoclonal antibodies (mAbs) are metabolized through proteolytic catabolism and do not interact with transporters, therefore, ethnic differences in metabolism and elimination are not expected to affect the PK of mAbs. PK results from the studies HLX11-001 and HLX11-BC301 support biosimilarity between HLX11 and EU-Perjeta.

The safety database is considered sufficient in terms of number of subjects and duration of treatment for adequate comparison between HLX11 and Perjeta. Similar incidence of TEAEs was seen in study HLX11-001 across study groups. In study HLX11-BC301, no relevant differences between treatment arms were seen in either nature, incidence or severity of AEs, AESI, SAEs or deaths. Even though some data from study HLX11-BC301 are pending, the large amount of efficacy and safety data currently available support similar efficacy and safety of HLX-11 and EU-Perjeta. In studies on Perjeta, low risk for immunogenic potential or immunogenicity-related AEs were observed in patients with either early-stage or metastatic breast cancer. In the Phase 1 study, the incidence of ADA was higher for HLX-11 than Perjeta (62,5 vs 37,5% ADA positive). However, no difference was seen in this study in the incidence of NAb. No difference in the frequency of ADA or NAb levels was observed in the longer and larger Phase 3 study. Furthermore, immunogenicity had no obvious effect on PK, efficacy or safety in either clinical study, therefore, the difference in ADA incidence in the Phase 1 study does not affect extrapolation of efficacy and safety.

Based on the above, the safety and efficacy profile of HLX11 (Poherdy) as assessed in the enriched (HR-negative) HER2+ early breast cancer indication can be extrapolated to all indications applied for.

9.6. Additional considerations

None.