Efficacy, safety and immunogenicity of HLX02 compared with reference trastuzumab in patients with recurrent or metastatic HER2-positive breast cancer: a randomized phase 3 equivalence trial

Running head: Global phase 3 equivalence study comparing HLX02 and reference trastuzumab

Authors:

Binghe Xu[1*], Qingyuan Zhang[2*], Tao Sun[3], Wei Li[4], Yue'e Teng[5], Xichun Hu[6], Igor Bondarenko[7], Hryhoriy Adamchuk[8], Liangming Zhang[9], Dmytro Trukhin[10], Shusen Wang[11], Hong Zheng[12], Zhongsheng Tong[13], Yaroslav Shparyk[14], Qingyu Wang[15] and HLX02-BC01 Investigators[#]

* Binghe Xu and Qingyuan Zhang contributed equally to this work.

[#] Investigators of HLX02-BC01 are listed in supplementary table 1.

Affiliations:

[1]Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[2]Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China

[3]Internal Medicine Oncology, Liaoning Cancer Hospital, Liaoning, China

[4]Internal Medicine Oncology, the First Hospital of Jilin University, Jilin, China

[5]Internal Medicine Oncology, the First Hospital of China Medical University, Shenyang, China

[6]Internal Medicine Oncology, Shanghai Cancer Hospital, Fudan University, Shanghai, China

[7]Chemotherapy Department, Communal Institution Dnipropetrovsk City Multifield Clinical Hospital, Dnipro, Ukraine

[8]Chemotherapy Department, Communal Institution Kryvyi Rih Oncology Dispensary of Dnipropetrovsk Regional Council, Kryvyi Rih, Ukraine

[9]Internal Medicine Oncology, Yantai Yuhuangding Hospital, Yantai, Shandong, China

[10]Daystay Care of Dispensary and Policlinic Department, Communal Institution Odesa Regional Oncological Dispensary, Odesa, Ukraine

[11]Internal Medicine Oncology, Sun Yat-Sen University, Cancer Center, Guangzhou, China

[12]Internal Medicine Oncology, West China Hospital, Sichuan University, Sichuan, China

[13]Internal Medicine Oncology, Tianjin Cancer Hospital, Tianjin, China

[14]CI of LRC Lviv Oncological Regional Treatment and Diagnostic Center, Lviv, Ukraine

[15]Shanghai Henlius Biotech, Inc., Shanghai, China

Corresponding author:

Binghe Xu,

Cancer Hospital Chinese Academy of Medical Sciences

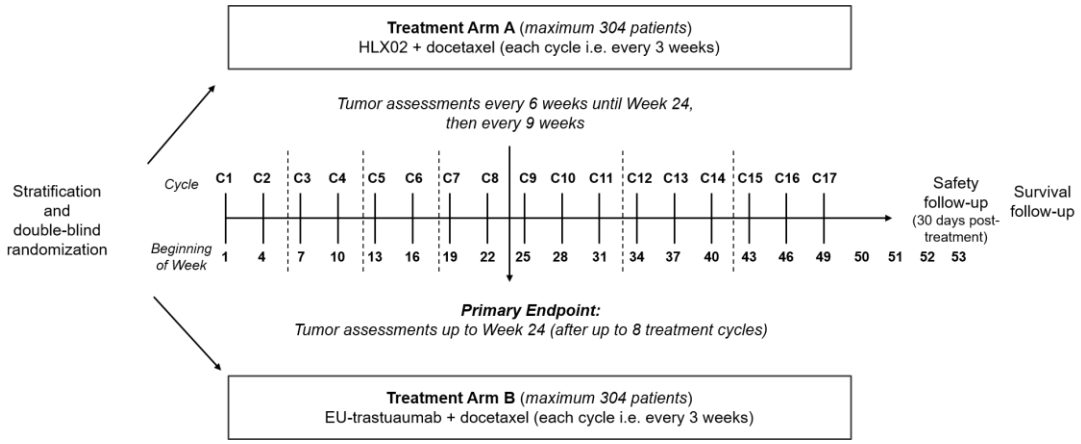
No.17, Panjiayuan Nanli, Beijing, 100021, China

Email: xubinghe@medmail.com.cn

Telephone: +86-01087788826

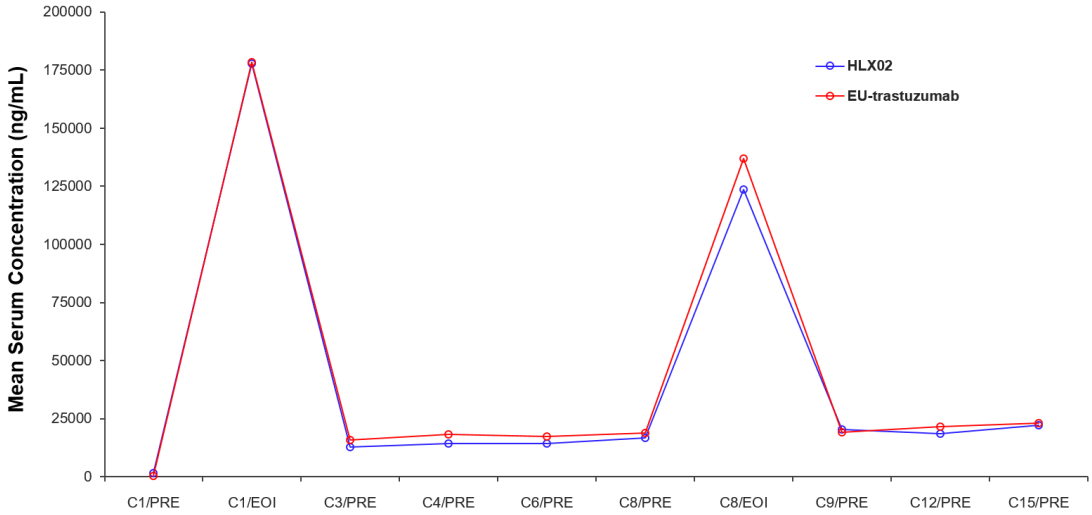
Supplementary materials

Supplementary fig. 1: Study design



C, cycle; EU-trastuzumab, European Union sourced trastuzumab.

Supplementary fig. 2: Mean (SD) drug serum concentration-time profiles for HLX02 and EU-trastuzumab treatment group—PK set



C, cycle; EOI, end of infusion; PK, pharmacokinetic; PRE, pre-dose.

Supplementary table 1: List of investigators and study sites

Principal Investigator	Study Site	Country	Number of Patients Randomized
Qingyuan Zhang	Harbin Medical University Cancer Hospital	China	45
Tao Sun	Liaoning Cancer Hospital & Institute	China	39
Wei Li	The First Hospital of Jilin University	China	36
Yuee Teng	The First Hospital of China Medical University	China	28
Xichun Hu	Fudan University Shanghai Cancer Center	China	22
Igor Bondarenko	CI Dnipropetrovsk CMCH #4 of Dnipropetrovsk RC Dept of Chemotherapy SI Dnipropetrovsk MA of MOHU	Ukraine	22
Binghe Xu	Cancer Institute and Hospital, Chinese Academy of Medical Sciences	China	20
Hryhoriy Adamchuk	CI Kryvyi Rih Oncological Dispensary of DRC	Ukraine	16
Liangming Zhang	Yantai Yuhuangding Hospital	China	15
Dmytro Trukhin	Odesa Regional Oncologic Dispensary	Ukraine	14
Shusen Wang	Sun Yat-sen University, Cancer Center	China	13
Hong Zheng	West China Hospital, Sichuan University	China	13
Zhongsheng Tong	Tianjin Medical University Cancer Institute & Hospital	China	13
Yaroslav Shparyk	CI of LRC Lviv Oncological Regional Treatment and Diagnostic Center	Ukraine	13
Xinhong Wu	Hubei Cancer Hospital	China	12
Herui Yao	Sun Yat-sen Memorial hospital, Sun Yat-sen University	China	12
Yuping Sun	Jinan Central Hospital	China	12
Huiping Li	Beijing Cancer Hospital	China	11
Yunjiang Liu	The Fourth Hospital of Hebei Medical University	China	11
Shuqun Zhang	The 2nd Hospital of Xi'An Jiaotong University	China	11
Xiaohua Zeng	Chongqing Cancer Hospital	China	11
Ihor Vynnychenko	RCI Sumy Regional Clinical Oncological Dispensary Dept of of Chemotherapy Sumy SU	Ukraine	11
Xiaojia Wang	Zhejiang Cancer Hospital	China	10
Li Sun	Xuzhou Central Hospital	China	9
Yongmei Yin	Jiangsu Province Hospital	China	9
Kunwei Shen	Ruijin Hospital, Shanghai Jiaotong Uni. School of Med.	China	9
Olexiy Kovalyov	CI Zaporizhzhia RC Onc Dispensary of ZRC Dept of Breast Pathology SI Zaporizhzhia MA of PGE of MoHU	Ukraine	9
Jian Huang	The Second Affiliated Hospital Zhejiang University School of Medicine	China	8
Chunhong Hu	The 2nd Xiangya Hospital Central South University	China	8
Anatoliy Hontsa	CI Chernivtsi RC Oncological Dispensary	Ukraine	8
Dmytro Osynskyi	Kyiv City Clinical Oncological Center	Ukraine	8
Buhai Wang	Northern Jiangsu People's Hospital	China	7
Jin Yang	First Affiliated Hospital of Xi'an Jiaotong University	China	7

Zhendong Chen	The second hospital of Anhui medical university	China	7
Vadym Prianikov	Communal Non-profit Enterprise Regional Center of Oncology	Ukraine	7
Jia Chen	Jiangsu Cancer Hospital	China	6
Xian Wang	Sir Run Run Shaw Hospital, Zhejiang University, School of Medicine	China	6
Zhou Zhu	Liuzhou General Hospital	China	6
Jianyun Nie	Yunnan Cancer Hospital	China	6
Ying Zhang	Affiliated Hospital of Guangdong Medical University	China	6
Min Yan	Henan Cancer Hospital	China	6
Iryna Sokur	CI of Kherson Reg Council Kherson Regional Oncologic Dispensary	Ukraine	6
Hryhoriy Bardakov	Community Treatment-Prevention Institution Chernihiv Regional Oncological Dispensary, Policlinic Department	Ukraine	6
Zhendong Zheng	General Hospital of Shenyang Military Region	China	5
Bangwei Cao	Beijing Friendship Hospital, Capital Medical University	China	5
Ivan Sinielnikov	Treatment-Prevention Institution Volyn Regional Oncological Dispensary	Ukraine	5
Yevhen Hotko	CCCH City Oncological Center SHEI Uzhgorod NU	Ukraine	5
Baochun Zhang	Nantong Tumor Hospital	China	4
Peng Shen	The First Affiliated Hospital,Zhejiang University	China	4
Anwen Liu	The Second Affiliated Hospital of Nanchang University	China	4
Hongsheng Li	Cancer Center of Guangzhou Medical University	China	4
Andriy Rusyn	Transcarpathian Regional Clinical Oncological Dispensary	Ukraine	4
Maria Luisa Tiambeng	Cardinal Santos Medical Center	Philippines	4
Dongyan Cai	Wuxi 4th People's Hospital	China	3
Chunsen Xu	Fujian Medical University Union Hospital	China	3
Jinghua Gao	Hebei Cangzhou Central Hospital	China	3
Wenjing Hu	The Affiliated Drum Tower Hospital of Nanjing University	China	3
Yang Zhang	The Second Hospital of Dalian Medical University	China	3
Igor Drobner	Khmelnytskyi Regional Oncological Dispensary	Ukraine	3
Oleksandr Berzoy	Community Institution Odesa Regional Clinical Hospital	Ukraine	3
Anatolii Chornobai	Poltava Reg Cl Onc Dispensary of PRC Chemotherapy Dept HSEI of Ukr UMSA	Ukraine	3
Liubov Syvak	National Institute of Cancer	Ukraine	3
Ma. Noemi Uy	Cebu Doctors University Hospital	Philippines	3
Peiguo Cao	The Third Xiangya Hospital of Central South University	China	2
Yuan Chen	Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology	China	2

Shukui Qin	Nanjing Bayi Hospital	China	2
Aimin Zang	Affiliated Hospital of Hebei University	China	2
Volodymyr Shamrai	Podilskyi Regional Oncological Center	Ukraine	2
Vanina Htun-Javier	Metro Davao Medical and Research Center, Inc.	Philippines	2
Junlan Yang	Chinese PLA General Hospital Medical School of Chinese PLA	China	1
Chunmei Bai	Peking Union Medical College Hospital	China	1
Yan Tan	Jilin Province People's Hospital	China	1
Xin Hu	Nanchong Central Hospital	China	1
Guoping Sun	The First Affiliated Hospital of Anhui Medical University	China	1
Grygorii Ursol	Treatment-Diagnostic Center of Private Enterprise of PPC Atsynus	Ukraine	1
Nataliya Banakhevych	Kyiv City Clinical Oncological Center	Ukraine	1
Fernando Gracieux	Manila Doctors Hospital	Ukraine	1
Fatima Fuerte	The Medical City	Philippines	1
Qi Luo	The First Affiliated Hospital of Xiamen University	China	0
Oleksii Kolesnik	CI Zaporizhzhia Regional Clinical Oncological Dispensary of ZRC	Ukraine	0
Anna Kryzhanivska	CI Transcarpathian Cl Onc Center Dep of Surgery#1 SHEI Ivano-Frankivsk NMU	Ukraine	0
Ying Cheng	Jilin Cancer Hospital	China	0
Guia Elena Imelda Ladrera	Lung Centre of the Philippines	Philippines	0
Tai-Chung Lam	The University of Hong Kong-Shenzhen Hospital	China	0
Jian Liu	Fujian Cancer Hospital	China	0
Rosalinda Pulido	St. Frances Cabrini Medical Centre	Philippines	0
Malgorzata Suszko-Kazarnowicz	Olsztyński Ośrodek Onkologlczny Kopernik Sp.z o.o.	Poland	0
Malgorzata Ulanska	Centrum Terapii Wspólczesnej J.M. Jasnorzewska Spólka Komandytowo-Akcyjna	Poland	0
Minghui Zhang	Chifeng Municipal Hospital	China	0

Supplementary table 2: Full inclusion and exclusion criteria

Inclusion criteria:
1. Voluntarily agreed to participate and given written informed consent
2. Male or female ≥18 years of age on day of signing the informed consent form (ICF)
3. Histologically or cytologically confirmed adenocarcinoma of the breast
4. Recurrent disease not amenable to curative surgery or radiation therapy, or metastatic disease with an indication for a taxane-containing therapy
5. Availability of formalin-fixed paraffin-embedded tissue block from the primary tumor, or a metastatic lesion, to confirm human epidermal growth factor receptor 2-positivity by the central laboratory, based on fluorescence in situ hybridization amplification ratio ≥2 or immunohistochemistry score 3+, and for hormone status (oestrogen-receptor/progesterone-receptor) determination (local or central laboratory). If not possible, a fresh biopsy was required
6. No prior systemic anticancer agent such as chemotherapy, biological or targeted agent for metastatic disease with the exception of hormonal therapy, which was stopped at least 2 weeks before randomization. Use of herbal remedies or traditional Chinese medicines for anticancer, hematologic or liver function, or anti-infective treatment was stopped at the time of the ICF signature (at least 2 weeks before randomization)
7. For patients with recurrent disease, prior neo-/adjuvant therapy containing trastuzumab and/or lapatinib had been stopped at least 12 months before the diagnosis of recurrent (local or metastatic) disease (i.e., a disease-free interval of ≥12 months). If trastuzumab/lapatinib was not used, prior neo-/adjuvant therapy with a taxane had been stopped at least 6 months before the diagnosis of recurrent (local or metastatic) disease (i.e., a disease-free interval of ≥6 months). If only other cytotoxic agents were given, they were stopped at least 4 weeks before randomization. Any hormonal therapy was stopped at the time of the ICF signature (at least 2 weeks before randomization)
8. Measurable disease (at least one measurable target lesion assessed by central imaging review; bone-only or central nervous system [CNS]-only metastases were not allowed)
9. Eastern Cooperative Oncology Group performance status of 0 to 1
10. Left ventricular ejection fraction (LVEF) within institutional range of normal at baseline (within 42 days before randomization) as determined by either echocardiogram (ECHO) or multigated acquisition scan
11. Adequate hematologic, hepatic and renal function as indicated by the following laboratory values: • Absolute neutrophil count (ANC) ≥1,500/mL without granulocyte-colony stimulating factor (G-CSF) or other medical support • Platelets ≥100,000/mL • Hemoglobin ≥9 g/dL without transfusion or other medical support within 14 days • Serum creatinine ≤1.5 × upper limit of normal (ULN) and creatinine clearance rate ≥50 mL/min, calculated according to Cockroft-Gault formula (Note: if the calculated creatinine clearance was <50 mL/min, a 24-hour creatinine clearance test might have been requested by the Principal Investigator for confirmation. Patients with a 24-hour creatinine clearance <50 mL/min were excluded) • Serum total bilirubin ≤1.5 × ULN (unless the patient had documented Gilbert's syndrome) without any medical support within 14 days • Serum aspartate aminotransferase/glutamic-oxaloacetic transaminase (AST/SGOT) or serum alanine aminotransferase/glutamate-pyruvate transaminase (ALT/SGPT) ≤2.5 × ULN (≤5 × ULN in the case of liver metastases) provided alkaline phosphatase (ALK) was ≤2.5 × ULN. In the case of bone metastasis, serum ALK was >2.5 × ULN if AST and ALT were ≤1.5 × ULN without any medical support within 14 days • International normalized ratio (INR), and activated partial prothrombin time (aPTT) or partial prothrombin time (PTT) ≤1.5 × ULN
12. Estimated life expectancy ≥3 months
13. Female patients were eligible to enter and participate in the study if they were of:-Non-childbearing potential-Childbearing potential, had a negative serum pregnancy test at Screening (within 7 days of the first investigational/comparator product administration), were not breast feeding, and used highly effective or acceptable contraceptive measures before study entry and throughout the study until 7 months after the last investigational/comparator product administration

14. Male patients with partners of childbearing potential were eligible to enter and participate in the study if they were willing to use highly effective or acceptable contraceptive measures before study entry and throughout the study until 7 months after the last investigational/comparator product administration.

Exclusion criteria:

1. Previously- or on-treated (systemic chemotherapy, biological, or targeted agent, or any other anticancer agent) metastatic breast cancer with the exception of hormonal therapy
2. Known brain metastasis or any other CNS metastasis that was either symptomatic or untreated. Central nervous system metastases that had been treated by complete resection and/or radiotherapy demonstrating stability or improvement were not an exclusion criterion provided they were stable as shown by computed tomography scan for at least 4 weeks before Screening without evidence of cerebral edema and no requirements for corticosteroids or anticonvulsants
3. Underlying medical conditions or current severe, uncontrolled systemic disease that, in the Investigator's opinion, made the administration of study drug hazardous. A major surgical procedure (defined as a procedure that required more than 3 weeks without study treatment) within 4 weeks prior to enrolment or anticipation of the need for major surgery during the course of study
4. Current uncontrolled hypertension (systolic >150 mmHg and/or diastolic >100 mmHg) or unstable angina
5. History of chronic heart failure based on any New York Heart Association criteria or left ventricular hypertrophy. Current serious cardiac arrhythmia requiring treatment (except atrial fibrillation, paroxysmal supraventricular tachycardia) or clinically significant conduction defects as seen on electrocardiogram. History of myocardial infarction within 6 months of randomization. History of LVEF declined to below 50% during or after prior trastuzumab neo-adjuvant or adjuvant therapy. Significant cardiac murmurs either on examination or ECHO
6. History of prior exposure to doxorubicin >360 mg/m² (or equivalent)
7. Use of oral, injected or implanted hormonal methods of contraception
8. Known hypersensitivity to any of the study drugs
9. Residual non-hematologic toxicity ≥ Grade 2 from prior therapy.

Supplementary table 3: Summary of major protocol deviations that excluded patients from per-protocol set by treatment group—ITT set

	HLX02 n = 324	**EU-trastuzumab n = 325**
With at least one major protocol deviation	4 (1.2)	8 (2.5)
Eligibility and Entry Criteria	4 (1.2)	6 (1.8)
Serious Adverse Event Criteria	0	2 (0.6)
Study Procedures Criteria	0	2 (0.6)
Efficacy Criteria	0	1 (0.3)
Informed Consent	0	1 (0.3)
Other Criteria	0	1 (0.3)

EU-trastuzumab, European Union-sourced trastuzumab; ITT, intention-to-treat.

Supplementary table 4: Exposure to study treatment (HLX02/EU-trastuzumab)—safety set

Characteristic	HLX02 n = 324	EU-trastuzumab n = 325
Number of cycle completed		
Mean (SD)	12.4 (5.4)	11.8 (5.4)
Median (range)	15 (1−17)	14 (1−17)
Number of cycle has completed N, n (%)		
Cycle 1	9 (2.8)	3 (0.9)
Cycle 2	20 (6.2)	21 (6.5)
Cycle 3	3 (0.9)	4 (1.2)
Cycle 4	13 (4)	20 (6.2)
Cycle 5	5 (1.5)	5 (1.5)
Cycle 6	17 (5.2)	24 (7.4)
Cycle 7	3 (0.9)	6 (1.8)
Cycle 8	19 (5.9)	21 (6.5)
Cycle 9	8 (2.5)	7 (2.2)
Cycle 10	8 (2.5)	8 (2.5)
Cycle 11	23 (7.1)	33 (10.2)
Cycle 12	5 (1.5)	7 (2.2)
Cycle 13	9 (2.8)	3 (0.9)
Cycle 14	18 (5.6)	18 (5.5)
Cycle 15	5 (1.5)	5 (1.5)
Cycle 16	4 (1.2)	2 (0.6)
Cycle 17	155 (47.8)	138 (42.5)
Total exposure duration (days)		
Mean (SD)	264.6 (114.8)	253.4 (114.3)
Median (range)	312 (21−408)	292 (21−417)
Injection times		
Mean (SD)	12.4 (5.4)	11.8 (5.4)
Median (range)	15 (1−17)	14 (1−17)
Total exposure intensity (mg/day)		
Mean (SD)	19.1 (3.8)	18.8 (3.8)
Median (range)	18.4 (12.2−33.9)	18.1 (11.1−37.1)
Relative dose intensity		
Mean (SD)	100 (0.7)	100 (1.1)
Median (range)	100 (93.3−103)	100 (88.9−110.8)
Dose reduced of IP, n (%)	0	1 (0.3)
Dose delayed of IP, n (%)	55 (17)	46 (14.2)
Dose interrupted of IP, n (%)	21 (6.5)	16 (4.9)

EU-trastuzumab, European Union-sourced trastuzumab; IP, investigational product (HLX02 or EU-trastuzumab); SD, standard deviation.

Supplementary table 5: Exposure to docetaxel—safety set

Characteristic	HLX02 n = 324	EU-trastuzumab n = 325
Number of cycle completed		
n (missing)	321 (3)	324 (1)
Mean (SD)	8.2 (3.5)	8.1 (3.5)
Median (range)	8 (1−17)	8 (1−17)
Number of cycle has completed N, n (%)		
Cycle 1	6 (1.9)	4 (1.2)
Cycle 2	20 (6.2)	21 (6.5)
Cycle 3	4 (1.2)	5 (1.5)
Cycle 4	14 (4.3)	21 (6.5)
Cycle 5	6 (1.9)	6 (1.8)
Cycle 6	25 (7.7)	28 (8.6)
Cycle 7	12 (3.7)	15 (4.6)
Cycle 8	154 (47.5)	141 (43.4)
Cycle 9	9 (2.8)	7 (2.2)
Cycle 10	17 (5.2)	14 (4.3)
Cycle 11	13 (4)	23 (7.1)
Cycle 12	6 (1.9)	6 (1.8)
Cycle 13	5 (1.5)	3 (0.9)
Cycle 14	6 (1.9)	8 (2.5)
Cycle 15	2 (0.6)	2 (0.6)
Cycle 16	1 (0.3)	2 (0.6)
Cycle 17	21 (6.5)	18 (5.5)
Total exposure duration (days)		
Mean (SD)	173.9 (74.9)	172.5 (75)
Median (range)	168 (21−407)	168 (21−380)
Injection times		
Mean (SD)	8.2 (3.5)	8.1 (3.5)
Median (range)	8 (1−17)	8 (1−17)

EU-trastuzumab, European Union-sourced trastuzumab; SD, standard deviation.

Supplementary table 6: Cardiac disorders of special interest by system organ class and preferred term—safety set

System organ class **Preferred term**	**HLX02** **n = 324** **n (%)**	**EU-trastuzumab** **n = 325** **n (%)**
Total Cardiac disorders of special interest	19	26
Cardiac disorders, n (%)	16 (4.9)	17 (5.2)
Sinus tachycardia	2 (0.6)	3 (0.9)
Left ventricular dysfunction	3 (0.9)	0 (0)
Myocardial ischaemia	2 (0.6)	1 (0.3)
Cardiac failure chronic	0 (0)	2 (0.6)
Cardiac failure congestive	0 (0)	2 (0.6)
Cardiotoxicity	1 (0.3)	1 (0.3)
Sinus arrhythmia	1 (0.3)	1 (0.3)
Systolic dysfunction	1 (0.3)	1 (0.3)
Tricuspid valve incompetence	0 (0)	2 (0.6)
Ventricular arrhythmia	1 (0.3)	1 (0.3)
Arrhythmia	0 (0)	1 (0.3)
Atrial fibrillation	1 (0.3)	0 (0)
Atrioventricular block	0 (0)	1 (0.3)
Bradycardia	0 (0)	1 (0.3)
Cardiac failure	1 (0.3)	0 (0)
Left atrial enlargement	0 (0)	1 (0.3)
Mitral valve incompetence	0 (0)	1 (0.3)
Nodal arrhythmia	1 (0.3)	0 (0)
Palpitations	0 (0)	1 (0.3)
Pericardial effusion	1 (0.3)	0 (0)
Right ventricular failure	1 (0.3)	0 (0)
Sinus bradycardia	1 (0.3)	0 (0)
Supraventricular extrasystoles	0 (0)	1 (0.3)
Tricuspid valve disease	0 (0)	1 (0.3)
Ventricular extrasystoles	0 (0)	1 (0.3)
Ventricular hypokinesia	1 (0.3)	0 (0)

EU-trastuzumab, European Union-sourced trastuzumab.

Supplementary table 7: Summary of the incidence of ADA—safety set

Visit	Parameter	HLX02 n = 324	EU-trastuzumab n = 325
Screening	Positive	6	17
	Negative	315	307
	NA	3	1
C3D1	Positive	1	1
	Negative	283	294
	NA	40	30
C6D1	Positive	0	0
	Negative	266	262
	NA	58	63
C9D1	Positive	0	0
	Negative	234	221
	NA	90	104
C12D1	Positive	0	0
	Negative	197	183
	NA	127	142
C15D1	Positive	0	0
	Negative	169	145
	NA	155	180
Follow-up	Positive	1	2
	Negative	269	263
	NA	54	60
Overall[a]	Positive	2	2
	Other	322	323

[a]A patient is considered positive if ADA positive result is observed at any visit over the course of treatment until 30 days post-last treatment.

ADA, anti-drug antibody; C, Cycle; D, day; EU-trastuzumab, European Union-sourced trastuzumab.

Supplementary table 8: Summary of the incidences of NADA in ADA positive patients at each time point—safety set

Visit	Parameter	HLX02 n = 8	EU-trastuzumab n = 18
Screening	Positive	4	6
	Negative	2	11
	Total	6	17
C3D1	Positive	1	1
	Negative	0	0
	Total	1	1
C6D1	Positive	0	0
	Negative	0	0
	Total	0	0
C9D1	Positive	0	0
	Negative	0	0
	Total	0	0
C12D1	Positive	0	0
	Negative	0	0
	Total	0	0
C15D1	Positive	0	0
	Negative	0	0
	Total	0	0
Follow-up	Positive	1	2
	Negative	0	0
	Total	1	2
Overall[a]	Positive	2	2
	Negative	6	16
	Total	8	18

[a]A patient is considered positive if NADA positive result is observed at any visit over the course of treatment until 30 days post-last treatment.

ADA, anti-drug antibody; C, cycle; D, day; EU-trastuzumab, European Union-sourced trastuzumab; NADA, neutralizing anti-drug antibody.