A Randomized Phase 1 Study to Compare the Pharmacokinetics, Safety, Tolerability and Immunogenicity Between HLX02, Reference US- and EU-Approved Trastuzumab in Healthy Chinese Male Volunteers

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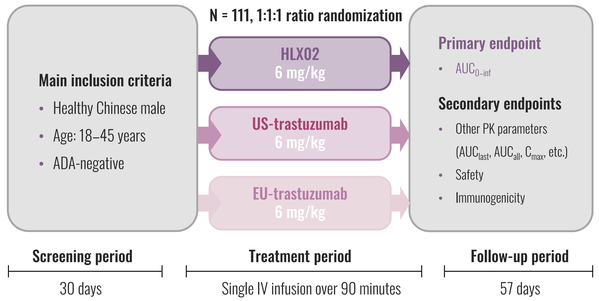
BACKGROUND

- Breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases (11.7%) occurred in 2020 worldwide[1].
- Trastuzumab (Herceptin®), an anti-HER2 humanized monoclonal antibody, has been approved by FDA for the treatment of HER2+ breast cancer and metastatic gastric or gastroesophageal junction adenocarcinoma[2].
- **HLX02, a trastuzumab biosimilar, has been demonstrated to be highly similar to the China (CN) and the European Union (EU)-approved trastuzumab based on the phase 1 (NCT02581748) and phase 3 (NCT03084237) clinical studies[3,4]. In 2020, HLX02 (CN: Han-Qu-You®; EU: Zercepac®) was approved both in China and the EU[5,6].**
- Here we report the results of a phase 1 study (HLX02-HV02, NCT04670796) comparing HLX02 to the United States (US) and EU-approved trastuzumab.

METHODS

- This randomized, double-blind, three-arm phase 1 study aimed to compare pharmacokinetics (PK), safety and immunogenicity between HLX02, US- and EU-approved trastuzumab (Figure 1).

Figure 1. HLX02-HV02 study design



ADA, anti-drug antibody; **AUC_{0-inf}**, area under the concentration-time curve from time zero to infinity; **AUC_{all}**, area under the concentration-time curve from time zero to the last concentration (whether quantifiable or not); **AUC_{last}**, area under the concentration-time curve from time zero to the last quantifiable concentration; **C_{max}**, maximum serum concentration; **EU**, the European Union; **IV**, intravenous; **PK**, pharmacokinetics; **US**, the United States;

- Eligible subjects were randomized 1:1:1 to receive a single dose of 6 mg/kg HLX02, US- or EU-trastuzumab by intravenous infusion.
- The primary endpoint was area under the concentration-time curve from time zero to infinity (AUC_{0-inf}). PK bioequivalence was established if 90% confidence interval (CI) of the geometric mean ratio of AUC_{0-inf} fell within the range of 0.80–1.25.
- Secondary endpoints included other PK parameters, safety and immunogenicity (ADA).

HLX02 is comparable with US-trastuzumab and EU-trastuzumab in PK, safety and immunogenicity

PK

Figure 2. Statistical comparison of PK parameters

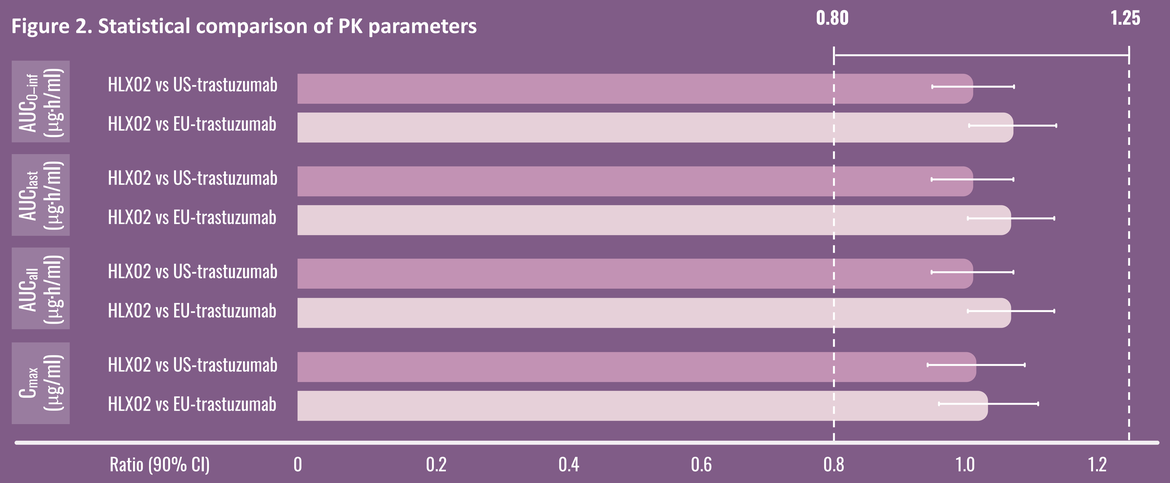
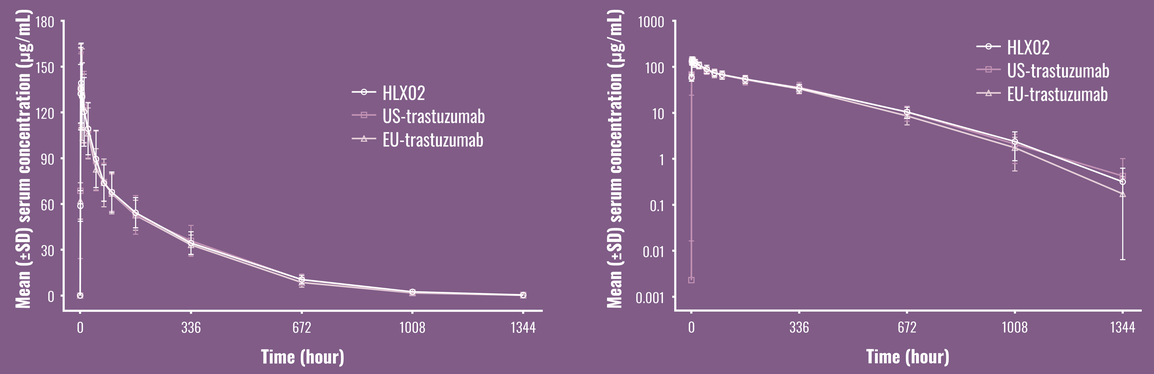


Figure 3. Mean (±SD) serum concentration-time profiles (linear and semi-logarithmic scales)



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RESULTS

Demographics

- 111 eligible subjects were enrolled and randomized 1:1:1 to receive one of three study drugs: HLX02, US-trastuzumab or EU-trastuzumab.
- A total of 111 patients treated with the study drugs were included in the PK analysis set and the safety analysis set.
- Baseline characteristics were well-balanced among treatment groups (Table 1).

Table 1. Baseline characteristics

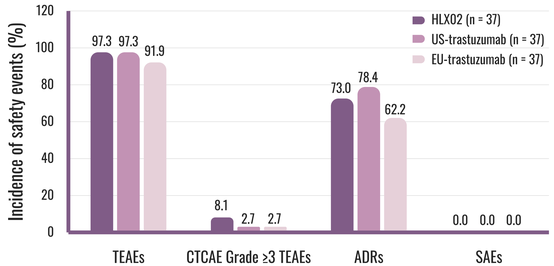
Characteristic		HLX02 (n = 37)	US-trastuzumab (n = 37)	EU-trastuzumab (n = 37)	Total (N = 111)
Age, years	Mean (SD)	26.8 (4.9)	27.8 (5.2)	28.5 (5.6)	27.7 (5.2)
Weight, kg	Mean (SD)	66.7 (6.5)	66.4 (7.9)	65.3 (7.3)	66.1 (7.2)
Height, cm	Mean (SD)	170.5 (5.0)	172.7 (5.2)	169.3 (5.9)	170.8 (5.5)
BMI, kg/m^2	Mean (SD)	22.9 (2.2)	22.2 (2.1)	22.8 (2.4)	22.7 (2.2)

BMI, body mass index; **EU**, the European Union; **SD**, standard deviation; **US**, the United States;

Safety

- The incidence and severity of adverse events (AEs) were comparable among the treatment groups. Most of treatment-emergent adverse events (TEAEs) were CTCAE Grade 1–2. No serious adverse events (SAEs) or deaths were reported, and no subjects discontinued the study due to TEAEs (Figure 4).
- In all eligible subjects, the most frequently reported TEAEs by preferred term (PT) were white blood cell count increased (59.5%), neutrophil count increased (32.4%), blood triglycerides increased (26.1%), and blood uric acid increased (25.2%).

Figure 4. Incidence of safety events in each treatment group, %



ADR, adverse drug reaction; **CTCAE**, the Common Terminology Criteria for Adverse Events; **EU**, the European Union; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event; **US**, the United States;

- The ADA positive rate were low and comparable among the treatment groups: HLX02 (1/37), US-trastuzumab (2/37), and EU-trastuzumab (1/37). No neutralizing antibody (NAb) positive results were observed.

REFERENCES

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5. Han-Qu-You® National Medical Products Adminidtration (NMPA) Approval
6. Zercepac® European Medicines Agency (EMA) Label

DISCLOSURES

- This study is sponsored by Shanghai Henlius Biotech, Inc.
- G. Sun, L. Zhou, Q. Wang and J. Zhu are employees of Shanghai Henlius Biotech, Inc. All other authors declare no conflict of interest.

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