44P Global clinical trials validating bioequivalence with China-manufactured trastuzumab biosimilar, HLX02, and trastuzumab

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Background: HLX02 is being developed to address the current global need for high-quality yet affordable trastuzumab biosimilar (trastuzumab) for patients with breast cancer.

Methods: Following the step-wise clinical approach for the development of biosimilar, we first enrolled 12 healthy males to evaluate safety and tolerability after a single infusion of HLX02 at 2, 4, 6 and 8 mg/kg. Upon successful demonstration of safety and PK ($AUC_{0-\infty}$, C_{max}, AUC_{0-tau}) equivalence between HLX02 and reference trastuzumab in 109 healthy males received a single infusion of 6 mg/kg either HLX02, trastuzumab sourced from EU or US, we subsequently conducted a multi-national, randomized, double-blind, parallel-controlled, phase 3 study (HLX02-BC01) investigating the efficacy and safety profiles of HLX02 and trastuzumab-EU with docetaxel in adult females with HER2+ breast cancer from ~83 centers in 4 countries. The primary efficacy endpoint was best overall response rate up to week 24 (ORR_{24}), and safety endpoints included immunogenicity and incidence of adverse events.

Results: After different concentrations of HLX02 demonstrated acute and dose-dependent effect on serum concentration of 12 healthy males in a phase 1a clinical trial, a total of 109 healthy males was randomized to receive 6mg/kg of HLX02 (n = 37),trastuzumab-EU(n = 37) or trastuzumab-US(n = 35). The geometric mean ratio of the $AUC_{0-\infty}$ [90% confidence intervals] for HLX02 / trastuzumab-EU, HLX02 / trastuzumab-US and trastuzumab-US / trastuzumab-EU were 0.914 [0.858-0.973], 0.950 [0.891-1.013] and 0.962 [0.902-1.025], respectively, all within the bioequivalence margin of 0.80-1.25 (Table). No deaths, SAE or ADA-positive results were observed in any of the treatment groups. Based on these results, 653 previously-untreated females with HER2-overexpressing metastatic breast cancer in China, Poland, Ukraine and Philippines were randomized in an ongoing phase 3 pivotal study.

Table: 44P Pairwise comparison of $AUC_{0-\infty}$ between HLX02, trastuzumab-EU and trastuzumab-US

Comparison with Different Products	n	$AUC_{0-\infty}$ Geo-LSMean (μg·h/mL)	$AUC_{0-\infty}$ Ratio A/B	$AUC_{0-\infty}$ 90% CI of Ratio
HLX02 vs trastuzumab-EU	37 37	19805.4 21679.0	0.914	(0.858-0.973)
HLX02 vs trastuzumab-US	37 35	19805.4 20847.3	0.950	(0.891-1.013)
trastuzumab-US vs trastuzumab-EU	35 37	20847.3 21679.0	0.962	(0.902-1.025)

Conclusions: The three-way PK and safety equivalence of HLX02 and reference trastuzumab were demonstrated leading to the pivotal phase 3 study which has completed the enrolment in June 2018. To the best of our knowledge, the ongoing phase 3 study was the first China-manufactured trastuzumab biosimilar being investigated in a global setting.

Clinical trial identification: NCT03084237 and EudraCT-ID: 2016-000206-10.

Legal entity responsible for the study: Shanghai Henlius Biotech, Inc.

Funding: Shanghai Biotech, Inc.

Disclosure: X. Zhang, A. Luk: Employment: Shanghai Henlius Biotech, Inc. E. Liu: Employment: Henlix Biotech, Inc. W. Jiang, S. Liu: Employment: Shanghai Henlius Biotech, Inc.; Stock ownership: Shanghai Henlius, Inc. All other authors have declared no conflicts of interest.