A Phase 1 Study Comparing Pharmacokinetics, Safety, and Immunogenicity Between HLX12, a Proposed Ramucirumab Biosimilar, and Reference Ramucirumab in Healthy Chinese Males

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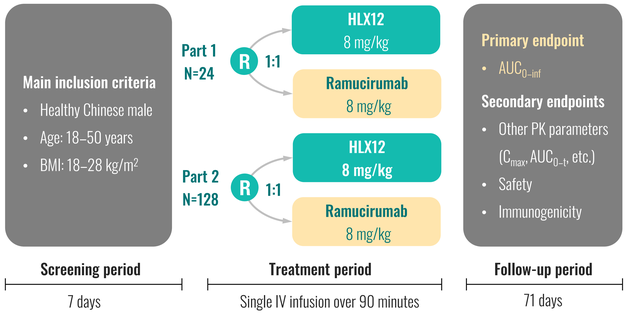
BACKGROUND

- Ramucirumab (Cyramza®), a fully human anti-VEGFR2 monoclonal antibody, has been approved in the United States and the European Union for the treatment of gastric or gastro-esophageal junction adenocarcinoma, non-small cell lung cancer, colorectal cancer, and hepatocellular carcinoma[1–2].
- According to GLOBOCAN 2020, the lung, stomach, liver, and colorectum account for >30% of the newly diagnosed cancer cases and >40% of the cancer deaths in 2020[3].
- HLX12, a proposed ramucirumab biosimilar, was demonstrated to be highly similar to reference ramucirumab in both *in vitro*, *in vivo* and toxicity studies.
- Here we report the Part 1 results collected from the phase 1 bio-equivalence study (HLX12-001, NCT03863587, HLX12 versus reference ramucirumab).

METHODS

- This randomized, parallel-controlled, phase 1 study aimed to evaluate the similarity in pharmacokinetics (PK), safety, and immunogenicity between HLX12 and reference ramucirumab in healthy Chinese adult males (Figure 1).

Figure 1. HLX12-001 study design



AUC_{0-inf}, area under the concentration-time curve from time zero to infinity: AUC_{0-t}, area under the concentration-time curve from time zero to the last quantifiable concentration: **BMI**, body mass index: C_{max}, maximum serum concentration: **IV**, intravenous: **PK**, pharmacokinetics:

- This phase 1 study was comprised of two parts. Part 1 was designed as an open-label pretrial study to provide data for sample size re-estimation in the double-blind Part 2. In Part 1, 24 eligible subjects were randomized 1:1 to receive a single intravenous infusion of 8 mg/kg HLX12 or ramucirumab. The sample size of Part 2 was estimated initially to be 128.
- The primary endpoint was the 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 (e.g., area under the concentration-time curve from time zero to the last quantifiable concentration [AUC_{0-t}] and maximum serum concentration [C_{max}]), safety, and immunogenicity.

HLX12 is comparable to reference ramucirumab in PK, safety, and immunogenicity

PK

Figure 2. Statistical comparison of PK parameters

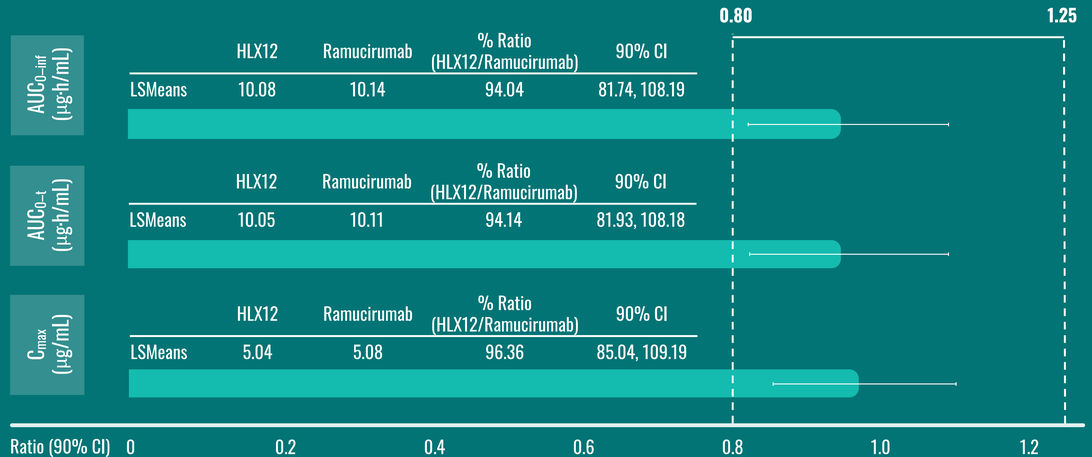
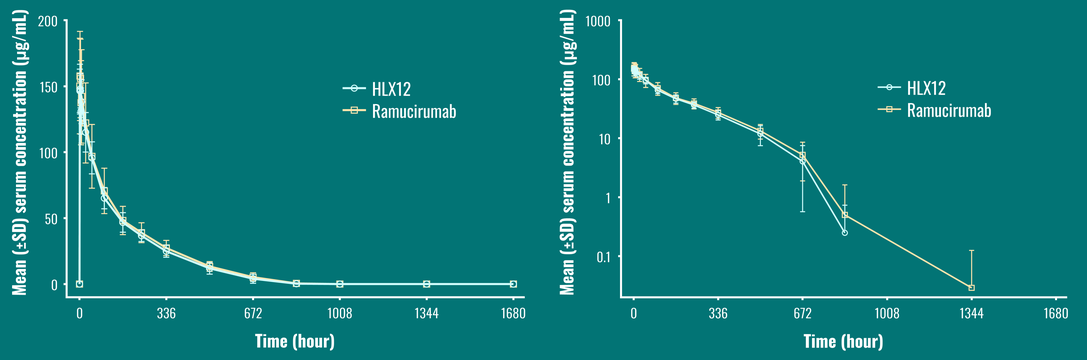


Figure 3. Mean (±SD) serum concentration-time profiles (linear and semi-logarithmic scales)



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RESULTS

Demographics

- A total of 24 subjects were enrolled in Part 1 and randomized 1:1 to receive HLX12 or reference ramucirumab. One subject from the ramucirumab group spontaneously withdrew from the study; all other subjects completed the study.
- All subjects received treatment and were included in the PK analysis set and the safety analysis set.
- Baseline characteristics were well-balanced between treatment groups (Table 1).

Table 1. Baseline characteristics

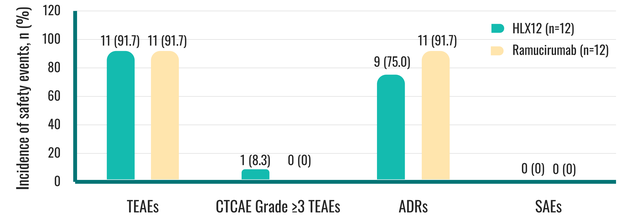
Characteristic		HLX12 (n=12)	Ramucirumab (n=12)	Overall (N=24)
Age, years	Mean (SD)	37.5 (8.3)	37.0 (8.0)	37.3 (8.0)
Weight, kg	Mean (SD)	65.5 (6.3)	64.5 (8.4)	65.0 (7.3)
Height, cm	Mean (SD)	168.3 (3.0)	167.5 (5.5)	167.9 (4.4)
BMI, kg/m²	Mean (SD)	23.1 (2.0)	22.9 (2.3)	23.0 (2.1)

BMI, body mass index: **SD**, standard deviation:

Safety

- The incidence and severity of treatment-emergent adverse events (TEAEs) were comparable between the two treatment groups (Figure 4). Most TEAEs were CTCAE Grade 1–2, except one subject from the HLX12 group experienced a Grade 3 TEAE of increased alanine aminotransferase, which recovered soon. No serious adverse events, deaths, or infusion adjustments due to TEAEs were reported.

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



ADR, adverse drug reaction: **CTCAE**, the Common Terminology Criteria for Adverse Events: **SAE**, serious adverse event: **TEAE**, treatment-emergent adverse event:

Table 2. TEAE with an incidence >10% in both treatment groups by PT, n (%)

System organ class (SOC) Preferred term (PT)	HLX12 (n=12)	Ramucirumab (n=12)	Overall (N=24)
Investigations	10 (83.3)	9 (75.0)	19 (79.2)
Alanine aminotransferase increased	7 (58.3)	6 (50.0)	13 (54.2)
Aspartate aminotransferase increased	7 (58.3)	6 (50.0)	13 (54.2)
Blood creatine phosphokinase increased	2 (16.7)	2 (16.7)	4 (16.7)

- No ADA positive results were observed in both treatment groups.

REFERENCES

1. Cyramza® Food and Drug Administration (FDA) Label
2. Cyramza® European Medicines Agency (EMA) Label
3. Sung H, *et al. CA Cancer J Clin*. **2021**;71(3):209-249.

DISCLOSURES

- This study is sponsored by Shanghai Henlius Biotech, Inc.
- X. Dong, L. Zhou, W. Kang, and J. Zhu are employees of Shanghai Henlius Biotech, Inc. All other authors declare no conflict of interest.

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