Abstract 63P: A Randomized, Double-blind, Phase I Study to Compare the Pharmacokinetics, Safety, Tolerability, and Immunogenicity of HLX15 and Daratumumab in Healthy Male Participants

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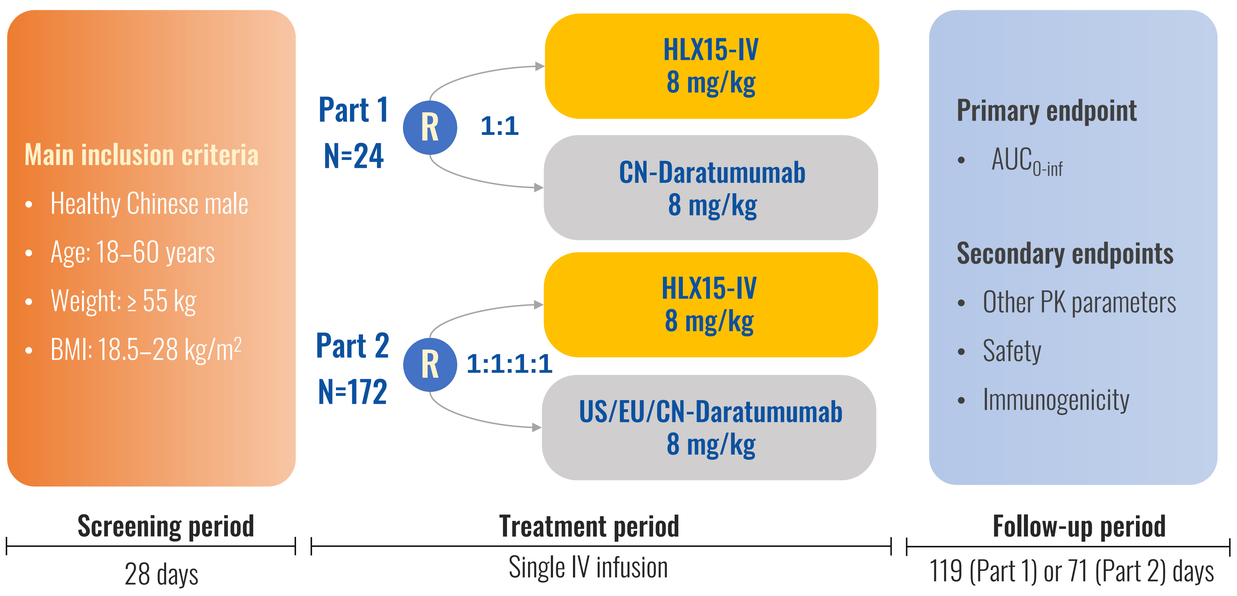
Background

- Daratumumab (anti-CD38 monoclonal antibody) has been approved for multiple myeloma. However, the discrepancy in regulatory approval across geographical regions has limited its accessibility for patients globally.
- HLX15, a proposed daratumumab biosimilar, has shown biosimilarity with reference product in preclinical studies.
- This first-in-human study aimed to evaluate the bioequivalence of intravenous injections of HLX15 (HLX15-IV) and reference daratumumab (DARZALEX®) in healthy Chinese male participants.

Methods

- This randomized, parallel-controlled, phase 1 study aimed to evaluate pharmacokinetic (PK) similarity, safety, and immunogenicity between HLX15-IV and reference daratumumab in healthy Chinese adult males (Figure 1).

Figure 1. Study design



AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; **BMI**, body mass index; **CN**, China; **EU**, the European Union; **IV**, intravenous; **PK**, pharmacokinetics; **US**, the United States;

- This phase I study consisted of two parts. Part 1 was a single-center, open-label, randomized, pilot study. Part 2 was a multicenter, randomized, double-blind, pivotal study to compare HLX15-IV with reference daratumumab.
- Healthy Chinese male participants aged 18–60 years were enrolled and randomized in a 1:1:1:1 ratio to receive a single intravenous infusion of HLX15-IV (HLX15-IV group), US-sourced daratumumab (US-dara group), European Union-sourced daratumumab (EU-dara group) or China-sourced daratumumab (CN-dara group) at 8 mg/kg.
- The primary endpoint was the area under the serum concentration-time curve from time 0 to infinity (AUC_{0-inf}).
- Secondary endpoints included other pharmacokinetic (PK) parameters, safety, and immunogenicity.

Results

Demographics

- Here we focus on the results in part 2.
- Of the 172 participants enrolled in part 2 (43 per group), 171 participants were included in the full analysis, PK concentration analysis and safety set, as one participant did not receive the study drug; 165 (HLX15-IV group, n=41; US-dara, n=42; EU-dara, n=41, CN-dara, n=41) were included in the PK parameter analysis.
- Baseline characteristics were well-balanced between treatment groups (Table 1).

Table 1. Baseline characteristic

Characteristic	HLX15-IV (N = 42)	US-Dara (N = 43)	EU-Dara (N = 43)	CN-Dara (N = 43)	Total (N = 171)
Age, year, Mean (SD)	29.6 (4.57)	28.9 (6.00)	29.1 (4.87)	29.8 (5.64)	29.4 (5.27)
Weight, kg, Mean (SD)	69.0 (8.08)	69.1 (7.56)	69.6 (7.29)	68.2 (8.57)	69.0 (7.83)
Height, cm, Mean (SD)	172.8 (6.49)	172.7 (4.44)	171.4 (6.38)	171.2 (5.89)	172.0 (5.85)
BMI, kg/m², Mean (SD)	23.1 (2.08)	23.2 (2.51)	23.6 (1.92)	23.3 (2.53)	23.3 (2.27)

BMI, body mass index; **SD**, standard deviation.

Pharmacokinetics

- The geometric mean ratios and their 90% confidence intervals for primary endpoint AUC_{0-inf} between any two groups fell within the predefined equivalence margin of 0.80–1.25 (Figure 2); Levels and changes over time in serum concentrations of HLX15-IV and reference daratumumab were also similar (Figure 3), demonstrating PK similarity.

Figure 2. Statistical comparison of PK parameters

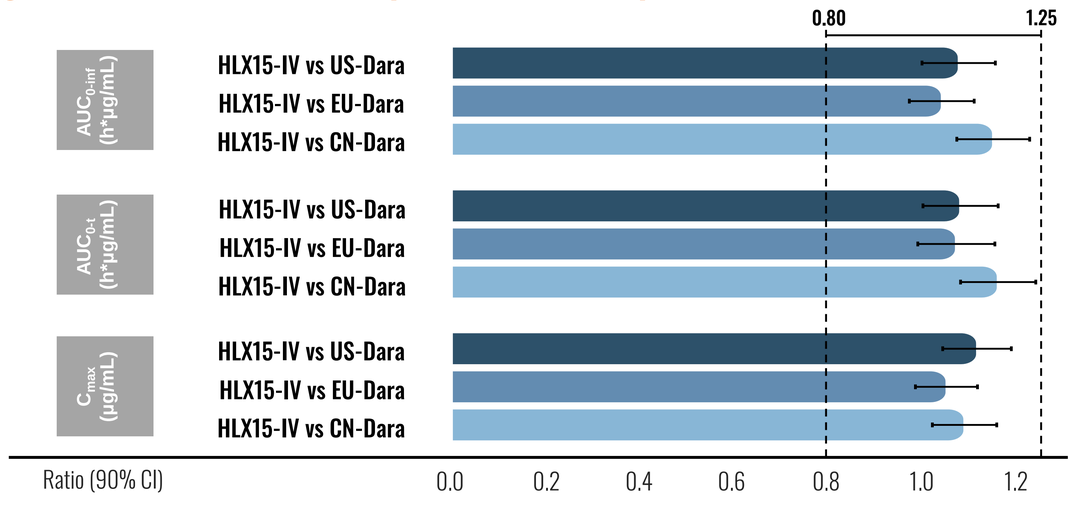
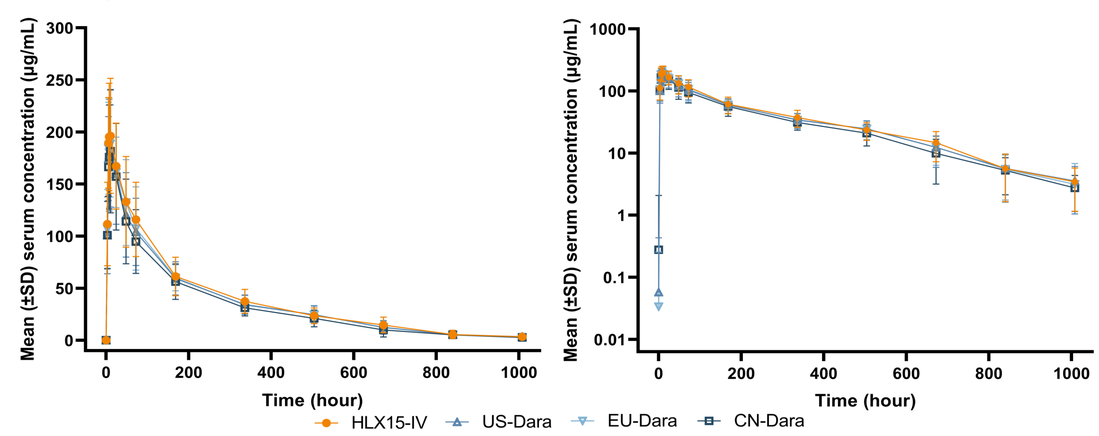


Figure 3. Mean (±SD) serum concentration-time profiles (linear and semi-logarithmic scales)



Safety and immunogenicity

- All 171 participants experienced at least one drug-related treatment-emergent adverse events (TEAEs). Seven (4.1%) participants experienced Grade 3 or 4 drug-related TEAEs. Only 1 participant (0.6%; EU-Daratumumab group) reported serious TEAEs (Grade 4), which was considered drug-related. Seven (4.1%) subjects experienced TEAEs leading to study drug discontinuation.
- No death or withdrawal due to TEAEs occurred in the study (Table 2).
- The incidence and severity of adverse events were comparable among the four treatment groups.

Table 2. Safety summary

n (%)	HLX15-IV (N = 42)	US-Dara (N = 43)	EU-Dara (N = 43)	CN-Dara (N = 43)	Total (N = 171)
Any TEAEs	42 (100)	43 (100)	43 (100)	43 (100)	171 (100)
Grade ≥ 3	3 (7.1)	0	3 (7.0)	1 (2.3)	7 (4.1)
Serious TEAEs	0	0	1 (2.3)	0	1 (0.6)
TEAEs leading to treatment discontinuation	1 (2.4)	2 (4.7)	2 (4.7)	2 (4.7)	7 (4.1)
TEAEs of special interest	35 (83.3)	40 (93.0)	38 (88.4)	38 (88.4)	151 (88.3)
TEAEs related to study drug	42 (100)	43 (100)	43 (100)	43 (100)	171 (100)
Infusion related reaction	34 (81.0)	39 (90.7)	36 (83.7)	37 (86.0)	146 (85.4)
Infections	13 (31.0)	13 (30.2)	12 (27.9)	7 (16.3)	45 (26.3)
TEAEs occurring in ≥ 25% of patients in either group					
Infusion related reaction	34 (81.0)	39 (90.7)	36 (83.7)	37 (86.0)	146 (85.4)
Neutrophil count increased	30 (71.4)	31 (72.1)	30 (69.8)	30 (69.8)	121 (70.8)
Lymphocyte count decreased	17 (40.5)	17 (39.5)	23 (53.5)	23 (53.5)	80 (46.8)
White blood cell count increased	21 (50.0)	12 (27.9)	16 (37.2)	19 (44.2)	68 (39.8)
Blood triglycerides increased	14 (33.3)	14 (32.6)	21 (48.8)	14 (32.6)	63 (36.8)
Upper respiratory tract infection	13 (31.0)	10 (23.3)	10 (23.3)	7 (16.3)	40 (23.4)
Protein urine present	8 (19.0)	11 (25.6)	7 (16.3)	6 (14.0)	32 (18.7)

- Immunogenicity results were comparable across groups. ADA incidences were 7.1% (3/42), 7% (3/43), 0, and 0 in HLX15-IV, US-dara, EU-dara, and CN-dara groups. Neutralizing antibody was not observed in any participant in the SS. Immunogenicity had no obvious effect on PK exposures and safety profiles of daratumumab.

Conclusions

PK similarity between HLX15-IV and reference daratumumab from different regions was demonstrated, along with comparable safety and immunogenicity profiles. HLX15-IV is a promising biosimilar of daratumumab that warrants further investigation.

Acknowledgement and Disclosure

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- Ci Sun, Liang Zhou, Haoyu Yu and Qingyu Wang are employees of Shanghai Henlius Biotech, Inc. All other authors declare no conflict of interest.