

A Randomized Phase 1 Study Evaluating the Pharmacokinetic Equivalence of Proposed Biosimilar HLX14 and Denosumab in Healthy Chinese Volunteers

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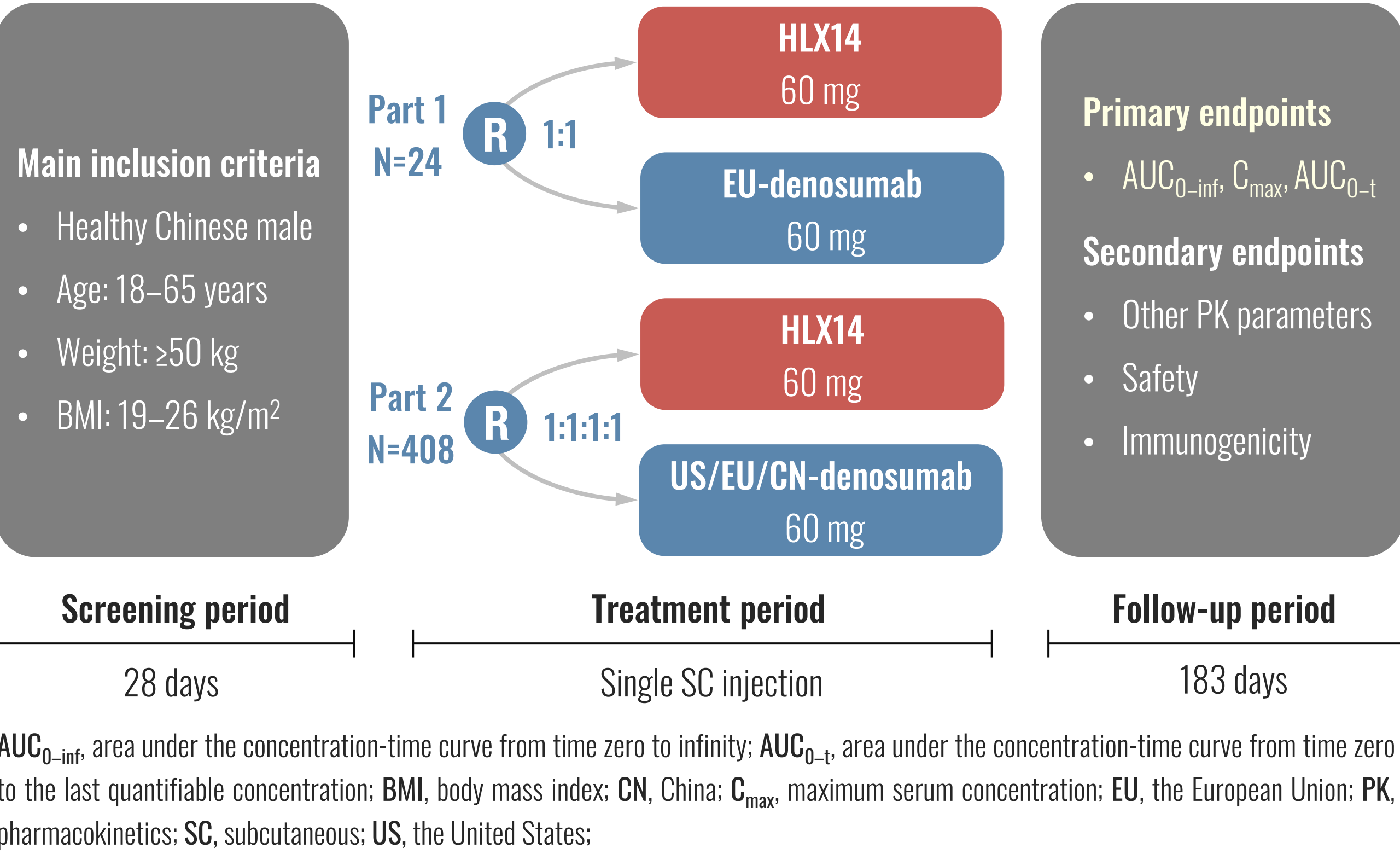
BACKGROUND

- In the United States (US), osteoporosis prevalence among adults aged ≥50 years was 19.6% in women and 4.4% in men¹. In China, this prevalence was as high as 32.1% in postmenopausal women and 6.9% in men ≥50 years².
- Denosumab is the first approved IgG2 monoclonal antibody targeting RANKL. In 2010, denosumab (Prolia®, 60 mg/mL) was approved in the US and the European Union (EU) for the treatment of postmenopausal women with osteoporosis at high risk for fracture^{3–4}.
- HLX14, a proposed denosumab biosimilar, was demonstrated to be highly similar to reference denosumab in preclinical studies.
- Here we report the Part 1 results from the phase 1 bioequivalence study (HLX14-001, NCT04534582, HLX14 versus reference denosumab).

METHODS

- This randomized, parallel-controlled, phase 1 study aimed to evaluate the similarity in pharmacokinetics (PK), safety, and immunogenicity between HLX14 and reference denosumab in healthy Chinese adult males (Figure 1).

Figure 1. HLX14-001 study design



- Part 1 was an open-label pilot study in which 24 eligible subjects were randomized 1:1 to receive a single subcutaneous injection of 60 mg HLX14 or EU-approved denosumab. Part 2 was a double-blind phase 1 study in which 408 eligible subjects are planned to be enrolled and randomized 1:1:1 to receive a single dose of 60 mg HLX14, US-, EU-, or China (CN)-denosumab.
- The primary endpoints were area under the concentration-time curve from time zero to infinity (AUC_{0–inf}), area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{0–t}), and maximum serum concentration (C_{max}). PK bioequivalence was established if 90% confidence interval (CI) of the geometric mean ratio of AUC_{0–inf}, AUC_{0–t}, and C_{max} fell within the range of 80%–125%.
- Secondary endpoints included other PK parameters, safety, and immunogenicity (anti-drug antibody [ADA] and neutralizing antibody [NAb]).

HLX14 is comparable to reference denosumab in PK, safety, and immunogenicity

PK

Figure 2. Statistical comparison of PK parameters

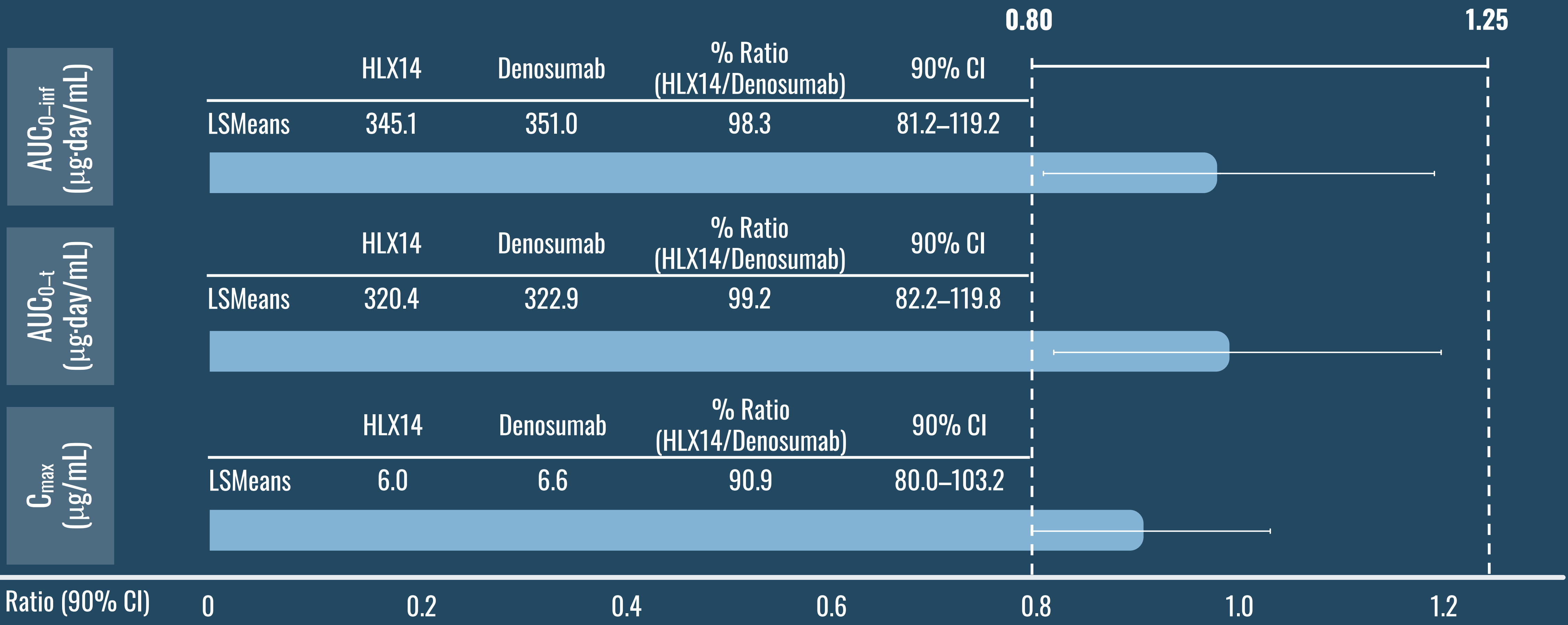
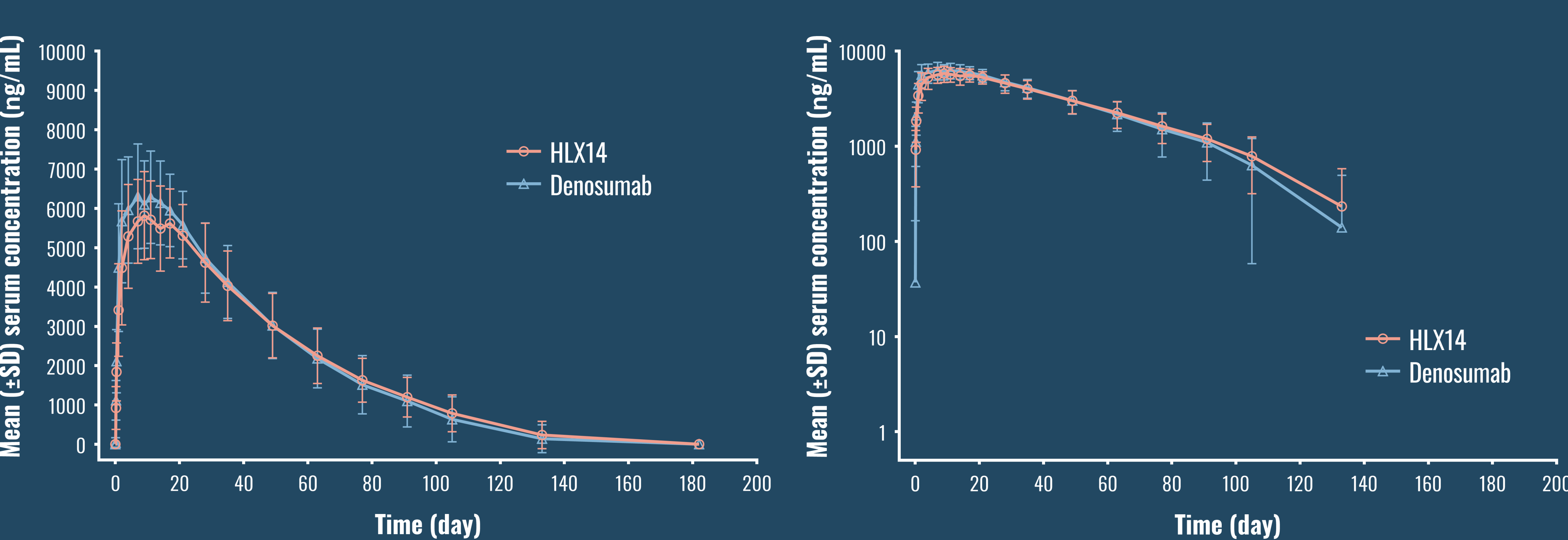


Figure 3. Mean (±SD) serum concentration-time profiles (linear and semi-logarithmic scales)



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RESULTS

Demographics

- 24 eligible subjects were enrolled in Part 1 and randomized 1:1 to receive HLX14 or reference denosumab.
- All subjects received study 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

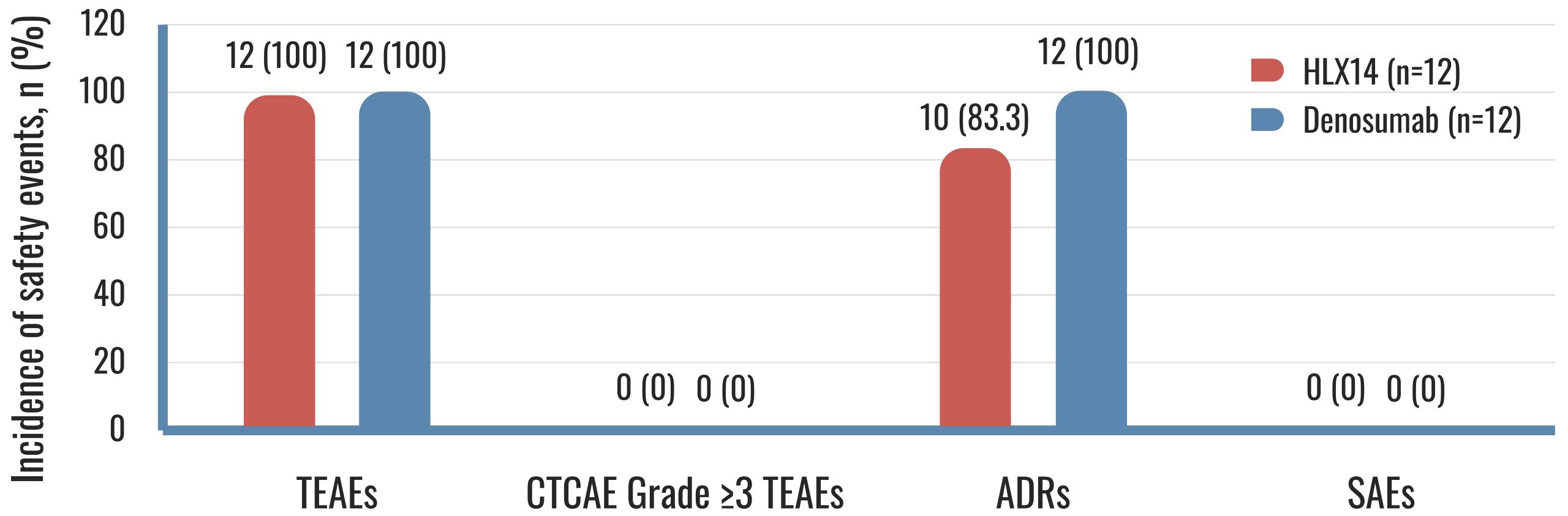
Characteristic		HLX14 (n=12)	Denosumab (n=12)	Overall (N=24)
Age, years	Mean (SD)	31.1 (7.8)	28.9 (8.0)	30.0 (7.8)
Weight, kg	Mean (SD)	64.1 (4.5)	64.8 (6.5)	64.5 (5.5)
Height, cm	Mean (SD)	169.5 (3.9)	171.9 (6.8)	170.7 (5.6)
BMI, kg/m ²	Mean (SD)	22.3 (1.5)	21.9 (1.5)	22.1 (1.5)

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). All of the TEAEs are CTCAE Grade 1–2. No serious TEAEs or TEAEs of special interest (AESI) were reported. No death or withdrawal due to TEAEs occurred in the study.

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 >15% in both treatment groups by PT, n (%)

System organ class (SOC) Preferred term (PT)	HLX14 (n=12)	Denosumab (n=12)	Overall (N=24)
Investigations	10 (83.3)	12 (100.0)	22 (91.7)
Blood phosphorus decreased	3 (25.0)	7 (58.3)	10 (41.7)
Blood cholesterol increased	5 (41.7)	2 (16.7)	7 (29.2)
Aspartate aminotransferase increased	2 (16.7)	3 (25.0)	5 (20.8)
Blood calcium decreased	3 (25.0)	2 (16.7)	5 (20.8)
Blood triglycerides increased	2 (16.7)	2 (16.7)	4 (16.7)
Infections and infestations	5 (41.7)	4 (33.3)	9 (37.5)
Upper respiratory tract infection	4 (33.3)	3 (25.0)	7 (29.2)

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

REFERENCES

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- Wang L, et al. *JAMA Netw Open*. **2021**;4(8):e2121106.
- Prolia® Food and Drug Administration (FDA) Label
- Prolia® European Medicines Agency (EMA) Label

DISCLOSURES

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

ACKNOWLEDGEMENTS

- The authors would like to acknowledge the participants and their families, investigators and staff at all study sites, as well as the members of the Independent Data Monitoring Committee.