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CHINA-MANUFACTURED ADALIMUMAB BIOSIMILAR, HLX03, DEMONSTRATED PHARMACOKINETIC EQUIVALENCE AND COMPARABLE SAFETY TO REFERENCE ADALIMUMAB

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Background: Adalimumab first launched in China in August 2010 with now more than 10 million people have its indications.^{1, 2} However, the relative high cost of the biologic drug limits the treatment accessibility and reduces the quality of life in patients living with the chronic inflammatory disease like rheumatoid arthritis and psoriasis. In accordance with the China National Medical Product Administration (NMPA) biosimilar regulatory development pathway, biosimilar products require to demonstrate similarity in pharmacokinetics (PK) and safety profile compared to its reference drug, which could further address the unmet medical needs of adalimumab. HLX03 was developed as a proposed biosimilar to adalimumab with the potential to increase affordable treatment options for access.

Objectives: The study was aiming to compare the pharmacokinetics (PK), safety and immunogenicity of the proposed adalimumab biosimilar HLX03 with reference product.

Methods: We conducted a randomised, double-blind, parallel-controlled clinical trial (NCT03357939) in China to compare the PK, safety and immunogenicity of HLX03 and China sourced adalimumab (CN-adalimumab). In this study, 211 healthy volunteers were randomised 1:1 to receive a single (40 mg) subcutaneous injection of HLX03 or CN-adalimumab. The primary PK endpoints were area under the curve (AUC) from time zero to the last quantifiable concentration (AUC_{0-∞}) and maximum observed concentration (C_{max}), secondary endpoint was AUC from time zero to infinity (AUC_{0-inf}). PK equivalence was established if the 90% confidence interval (CI) for the test-to-reference ratio fall within the 80-125% equivalence margin.

Results: Based on the analysis of 210 subjects in the per protocol population (PPS) and 211 subjects in the full analysis set (FAS), HLX03 demonstrated PK equivalence to CN-adalimumab for all primary endpoints (Table 1). The incidents of adverse events (AEs) between two treatment groups were similar, with treatment-emergent AEs (TEAEs) noted by a total of 149 (70.0%), 79 (73.8%) in HLX03 and 70 (66.0%) in CN-adalimumab group, respectively. One subject suffered non-drug-related severe AE (tuberculosis) in the HLX03 arm, and one subject occurred grade 4 AE (elevated creatine phosphokinase) in the CN-adalimumab arm. In the group of CN-adalimumab, 6 more incidents of positive anti-drug antibodies (ADA) recorded at day 7 and no further significant difference observed. Based on the established clinical PK equivalence and safety similarities, 262 patients with moderate-to-severe chronic plaque psoriasis were randomized in 21 centers at 1:1 ratio to conduct a double-blind, parallel-controlled phase 3 study (NCT03316781) to further evaluate the efficacy and safety profiles of HLX03 and reference adalimumab. The primary efficacy endpoint was the improvement rate of Psoriasis Area and Severity Index (PASI) over the baseline at week 16.

	Analysis group	Parameter	Ratio A/B	CI 90%
HLX03 vs CN-Adalimumab	PK-PPS	C _{max}	102.22	96.20, 108.61
		AUC _{0-∞}	105.72	97.07, 115.15
		AUC _{0-inf}	105.31	96.12, 115.38
	PK-FAS	C _{max}	101.95	95.96, 108.31
		AUC _{0-∞}	105.54	96.92, 114.92
		AUC _{0-inf}	108.48	98.73, 119.18

Conclusion: PK equivalence and safety similarities between HLX03 and CN-adalimumab were demonstrated which leads to a multi-center, randomised, double-blind, parallel-controlled phase 3 study to further evaluate the efficacy and safety of HLX03 as the proposed biosimilar of adalimumab in patients with moderate-to-severe plaque psoriasis.

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EFFICACY, SAFETY, AND IMMUNOGENICITY RESULTS OF THE SWITCH FROM REFERENCE ADALIMUMAB (REFADL) TO SANDOZ BIOSIMILAR ADALIMUMAB (GP2017, SDZ-ADL) FROM ADMYRA PHASE 3 STUDY IN PATIENTS WITH MODERATE-TO-SEVERE RHEUMATOID ARTHRITIS (RA)

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Background: SDZ-ADL is approved by EMA in all indications of refADL based on preclinical and clinical study results. EMA submission data included results of a Phase 3 study in patients with plaque psoriasis. ADMYRA was a Phase 3 study comparing efficacy and safety of SDZ-ADL and refADL in patients with moderate-to-severe RA with inadequate response to disease modifying anti-rheumatic drugs, including methotrexate (NCT02744755).

Objectives: The ADMYRA study was designed to compare the efficacy of SDZ-ADL and refADL over 24 weeks of treatment, and to evaluate long-term efficacy, safety, and immunogenicity of SDZ-ADL up to Week (Wk) 48. The study also investigated the effect of the switch from refADL to SDZ-ADL at Wk 24 on efficacy, safety, and immunogenicity up to Wk 48. This abstract focuses on the data after switch from refADL to SDZ-ADL.

Methods: Eligible patients were randomized 1:1 to receive 40 mg subcutaneous SDZ-ADL or refADL every other week from Wk 0–22. At Wk 24, patients in the refADL arm were switched to receive SDZ-ADL; treatment continued until Wk 46. The primary endpoint was change in Disease Activity Score-28 including high-sensitivity C-reactive protein (DAS28-CRP) from baseline at Wk 12. Secondary endpoints included mean changes in DAS28-CRP scores, the proportion of patients fulfilling EULAR responses, EULAR and Boolean remission criteria, safety, and immunogenicity. EULAR remission was defined as DAS28-CRP <2.6. Boolean remission was defined as tender joint count 28 ≤1, swollen joint count 28 ≤1, CRP ≤1 mg/dL, and patient global assessment ≤10 on a 100 mm scale.

Results: As reported previously, mean change in DAS28-CRP from baseline at Wk 12 was -2.16 for SDZ-ADL (N=140) and -2.18 for refADL (N=144).¹ Efficacy in both treatment arms was maintained throughout the study, also after the switch from refADL to SDZ-ADL at Wk 24. Mean change in DAS28-CRP from baseline at Wk 48 was -2.90 and -2.92 for refADL/switched and SDZ-ADL groups, respectively. At Wk 48, the proportion of patients with moderate/good EULAR response was 29.6/68.0% in refADL/switched group and 29.0/69.2% in SDZ-ADL group. At Wk 48, the proportion of patients in EULAR remission was 54.4 and 51.4% and in Boolean remission was 21.6 and 16.8% for refADL/switched and SDZ-ADL groups, respectively. As previously reported, safety and immunogenicity were similar in both arms before switch.¹ No new safety concerns were identified after switch. After switch, 32.5% of patients in the refADL/switched group and 36.5% of patients in the SDZ-ADL group experienced adverse events (AEs); serious AEs were reported by 3.6 and 2.5%, respectively. The proportion of patients reporting injection site reactions after switch was 1.2% in the refADL/switched group and 0.6% in the SDZ-ADL group, respectively. After switch, 26.3 and 24.0% of patients