BioDrugs (2020) 34:381–393
https://doi.org/10.1007/s40259-020-00408-z

ORIGINAL RESEARCH ARTICLE

Comparison of the Efficacy and Safety of Adalimumab (Humira) and the Adalimumab Biosimilar Candidate (HS016) in Chinese Patients with Active Ankylosing Spondylitis: A Multicenter, Randomized, Double-Blind, Parallel, Phase III Clinical Trial

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Published online: 20 February 2020
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Abstract

Objective The aim of this study was to evaluate the efficacy and safety of the biosimilar candidate of adalimumab (HS016) compared with adalimumab (Humira) for the treatment of active ankylosing spondylitis.

Methods A multicenter, randomized, double-blind, parallel, positive control, phase III clinical trial was conducted at 28 locations in China. Patients with active ankylosing spondylitis were randomized in a 2:1 ratio to subcutaneously receive 40 mg of either HS016 or adalimumab every other week for 24 weeks. The primary endpoint was to achieve at least a 20% improvement (ASAS20) in patients at 24 weeks according to the Assessment of Spondyloarthritis International Society criteria. The secondary endpoint included other efficacy assessment parameters, health evaluations, safety, pharmacokinetic, and immunogenicity parameters.

Results Following the random assignment of 648 patients into HS016 ($n = 416$) and adalimumab ($n = 232$) groups, no significant difference was found in the ASAS20 response rates at 24 weeks between the HS016 (364/416, 87.5%) and adalimumab (209/232, 90.1%) treatments and the difference between the response rates (− 2.59%; 90% confidence interval [CI] − 6.77 to 1.60) was within the predefined equivalence margin (± 15%). There were also no significant differences when the secondary endpoints were compared (all $p > 0.05$). Similarly, the rates of treatment-emergent adverse events (TEAEs) were not significantly different between the two groups, with most TEAEs being mild to moderate. Only nine severe cases were found, including seven within the HS016 group, three (0.7%) of which were tuberculosis cases. Plasma concentrations of HS016 and adalimumab from weeks 12 to 14 were similar during the steady-state period and steady-state maximal concentration ($C_{max,ss}$) was equivalent for HS016 (7356.6 ng/mL) and adalimumab (7600.3 ng/mL). The accumulated proportion of patients with positive human anti-human antibodies (HAHAs) at week 24 was 326/412 (79.1%) in the HS016 group and 183/229 (79.9%) in the adalimumab group ($p > 0.05$), while the accumulated proportion of patients with positive neutralizing antibody (NAb) tests were 72/412 (17.5%) in the HS016 group and 43/229 (18.8%) in the adalimumab group ($p > 0.05$).

Conclusion HS016 resembled adalimumab in efficacy and safety over the 24-week treatment period.

Trial registration number ChiCTR1900022520.

1 Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic disease that is characterized by inflammatory changes to the sacroiliac joints and spine, resulting in progressive structural damage and reduced function and quality of life [1]. AS has also been termed radiographic axial spondyloarthritis (axSpA) and non-radiographic axSpA according to the

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40259-020-00408-z) contains supplementary material, which is available to authorized users.

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Key Points

Adalimumab is a monoclonal immunoglobulin G1-kappa isotype (IgG1-κ) antibody approved for the treatment of ankylosing spondylitis (AS).

In this multicenter, randomized, double-blind, parallel, positive control, phase III clinical trial carried out at 28 centers in China, patients with active AS received HS016 or adalimumab treatment. There were no differences between HS016 and adalimumab in terms of ASAS20 response rates, pharmacokinetic or immunogenic parameters, or treatment-emergent adverse events during the 24-week study period.

HS016 was similar to adalimumab in efficacy and safety. HS016 is a useful alternative to adalimumab for the treatment of AS.

new Assessment of SpondyloArthritis International Society (ASAS) criteria [2, 3]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment option for AS patients, followed by conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) including methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine, cyclophosphamide, auranofin, penicillamine, and thalidomide, which are generally not effective in the treatment of axial manifestations of spondyloarthritis, but csDMARDs are effective for particular cases of peripheral AS. In contrast, biological DMARDs, such as anti-tumor necrosis factor-alpha (TNFα) inhibitors and interleukin-17 antagonists, can elicit overall articular manifestation improvements, C-reactive protein (CRP) levels, and MRI-detectable inflammation in the sacroiliac joints or spine in AS patients after failed NSAID treatments [2]. Also, for patients with persistently high ongoing disease activity despite conventional treatments, anti-tumor TNFα therapy is recommended for AS patients [4].

Adalimumab is a fully human monoclonal antibody that binds to and neutralizes TNFα [5]. Adalimumab has demonstrated improvement in clinical signs and symptoms, physical function, and health-related quality of life in patients with active AS [6–10]. However, the high cost of an adalimumab regimen limits its use for AS patients on low incomes. As an alternative, adalimumab biosimilars at a lower cost have been developed and are expected to benefit more AS patients with limited incomes and also healthcare systems in general since some countries provide biologics at no cost to patients [11].

HS016 is a biosimilar candidate of adalimumab and is related to the human IgG1 antibody (approximately 148 kDa) and has virtually the same amino acid sequence as adalimumab. The results of structural stability, pharmacodynamics (PD), pharmacokinetics (PK), and safety (data not shown) in preclinical studies have verified that HS016 is indeed similar to adalimumab.

Herein, we present the results of a multicenter, randomized, double-blind, and parallel, positive control, phase III clinical trial comparing outcomes following treatment with HS016 or adalimumab for 24 weeks in patients with active AS. Our objective was to validate the equivalence of the adalimumab biosimilar candidate, HS016, to the reference, adalimumab, in terms of efficacy and safety, as well as from the results of post-treatment Health Assessment Questionnaires for spondyloarthropathies, PK assessments including drug plasma concentrations (area under the plasma drug-concentration–time curve [AUC_{τ}] and steady-state maximal concentration [$C_{max,ss}$]), and human anti-human antibody (HAHA) and neutralizing antibody (NAb) developments.

2 Patients and Methods

2.1 Study Design

A randomized, double-blind, positive control, multicenter clinical trial was conducted in 28 centers across China. This trial was designed according to the regulations of the Chinese Center for Drug Evaluation. Patients were randomly assigned to HS016 or adalimumab (Humira, Abbvie Ltd, Maidenhead, UK) groups at a ratio of 2:1. Furthermore, HS016 or adalimumab were injected subcutaneously (40 mg in 0.8 mL) once every 2 weeks for 24 weeks (Supplementary Figure 1, see electronic supplementary material [ESM]). The study was performed in accordance with Good Clinical Practice and Provisions for Drug Registration issued by the National Medical Products Administration, and the guidelines in the Declaration of Helsinki for research on humans. The study protocol and all amendments were reviewed by the independent ethics committee at each center and all patients provided written informed consent. This trial is registered with the Chinese Clinical Trial Registry (ChiCTR), number ChiCTR1900022520.

2.2 Study Population

Patients aged 18–65 years with active AS fulfilling the 1984 modified New York classification criteria [12], as well as patients who were refractory to more than one type of NSAIDs or DMARDs during standard treatment for > 4 weeks were enrolled. Inclusion criteria were a body mass index ≥ 20 kg/m^2 and ≤ 28 kg/m^2 and a bodyweight ≥ 50 kg and ≤ 85 kg, and at least one of the following: (1) a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 (range 0–10 cm); (2) a visual analog

scale (VAS) score for total back pain ≥ 4 (range 0–10 cm); and (3) morning stiffness duration ≥ 1 hour. Patients with complete spinal rigidity (fusion), those who underwent spinal or joint surgery within 24 weeks of the study, and those who received anti-TNFα agents within 12 weeks of randomization were excluded from the study. Interferon Gamma Release Assay (IGRA) tests were performed for the detection of latent tuberculosis. For details of the inclusion and exclusion criteria, see Supplementary Appendix 1 in the ESM.

2.3 Randomization and Masking

For this trial, a randomized, double-blind design was employed to ensure that researchers and patients were blinded to the trial grouping. It consisted of a stratified block randomization method with a block size of 6, which allocated the experimental and the control groups according to a 2:1 ratio. Stratification factors included age (< 40 years, ≥ 40 years) and CRP (< 28 mg/L, ≥ 28 mg/L) in addition to the center. A project random list was generated by a third-party contract research organization (CRO), which contained treatment groups and random numbers. The random table was loaded into the Central Random System (IWRS). After each test center determined that the patients met the inclusion criteria, patients were randomized through the IWRS system and a random number assigned. The IWRS provided the patient's random and drug numbers based on the randomized treatment group and the test center administered the medication to the patient based on the drug number. The IWRS system did not directly provide treatment group information.

2.4 Assessments

The primary endpoint was the proportion of patients who achieved a 20% improvement from baseline according to the Assessment of Spondyloarthritis International Society criteria (ASAS20) at week 24 [13]. The secondary endpoints were an ASAS20 response rate at week 12, ASAS40, ASAS5/6 response rates, BASDAI 50% improvement and severity of morning stiffness assessed at weeks 12 and 24. Health-evaluation endpoints included improvement in the results of the Health Assessment Questionnaire for spondyloarthropathies (HAQ-S) and Short-Form 36 Health Survey version 2 (SF-36V2) at weeks 12 and 24. Safety assessments included monitoring of vital signs, clinical laboratory abnormalities, and adverse events (AEs), serious AEs (SAEs) and treatment-emergent AEs (TEAEs). Significant AEs were defined as AEs besides SAEs that led to the use of targeted medical treatments, combined treatments, and/or termination of involvement in the trial.

The primary endpoints in the PK profile were the AUC_{τ} and $C_{max,ss}$. PK assessments also involved measuring HS016 and adalimumab plasma concentrations during the steady-state period (12–14 weeks of treatment) and other PK parameters. The PK parameters of subgroups positive and negative for HAHA and NAbs were also determined.

2.5 Immunogenicity Tests

Bridging ElectroChemiLuminescence Immunoassay assay (ECLIA) was used to detect HAHAs, which consisted of screening and immunosuppression confirmation. Screening tests were used to detect HAHA positivity and the signal-to-noise ratio (*S*/*N*) of samples was used for data analyses. When the *S*/*N* was greater than or equal the screening cut point (SCP), the samples were further tested for immunosuppression. In this confirmatory test, sufficient amounts of the drug were added to the screening positive samples (if necessary, the sample could be appropriately diluted during the confirmatory test) for signal suppression, and the sample was determined to be HAHA positive (MSD QuickPlex SQ120, Meso Scale Discovery Inc., MD, USA) if the sample showed an immune-depletion of the soluble drug. Finally, HAHA-positive samples were quantified and measured for NAbs, which was based on the principle that L-929 cells were highly sensitive to the killing and inhibition of rhTNF activity under the action of actinomycin D. If there were no NAbs (Nab negative) in the sample, then the tested drug could neutralize the killing and inhibitory effect of rhTNF on L-929 cells so that they could grow and proliferate normally. The ATP content of living cells was quantified after 20 hours of culture, and the relative luminescence units (RLU) read on a Gen5 Secure v2.04 (BioTek Instrument Inc., VT, USA) was high. If the samples tested were Nab positive, the RLU value was low.

2.6 Statistical Analysis

Based on the instructions for adalimumab and relevant clinical studies, the ASAS20 response rate in patients with active AS at week 24 after adalimumab treatment should be 51%, and the placebo group should reach 19% [7, 9]. Therefore, the ASAS20 rate at week 24 for this study was expected to be 50%, with a boundary value of 15% ([drug group − placebo group]/2, approximately 16%). To determine whether the effects of adalimumab and HS016 were equivalent (indicated by a 90% confidence interval [CI]), we followed methodology from a previous study [14] and an agreement with Center for Drug Evaluation, National Medical Products Administration (NMPA) [15]. We aimed for results within an equivalence margin of ± 15%, with a two-sided α level of 0.05 and 90% power (experimental and control groups allocated at a 2:1 ratio); the required sample sizes of 362 and 181 were calculated for the HS016 group and adalimumab group, respectively. With an assumed dropout rate of 10%, the total sample size was set at 603; 402 in the HS016 group and 201 in the adalimumab group.

All efficacy endpoints were evaluated using the full analysis set, which included all participants with analysis based on treatment. A project randomization table (including treatment groups and randomization numbers) was generated by a third-party contract research organization and loaded into the interactive web-response system. The randomized, double-blind design ensured blinding of researchers, healthcare personnel, and patients to the grouping. For the primary endpoint, the Clopper–Pearson method was used to calculate the 95% CI for the proportion of patients who achieved the ASAS20 response rate. The differences in the compliance rate between the two groups and the 90% CI were then calculated with the equivalence test. If the 90% CI fell within the range −0.15 to 0.15, it was considered to meet the equivalence standard. Predicted values generated from a mixed-effect model in repeated measurement (MMRM), and a covariance analysis model based on the last observation carried forward (LOCF), were used to fill in the missing data for VAS scores in the overall evaluation of disease activity, night back pain, total back pain, Bath Ankylosing Spondylitis Functional Index (BASFI), and morning stiffness or VAS scores related to BASDAI (last two items in BASDAI), which were used in derivative calculations of ASAS20 after treatment for 24 weeks. The Cochran–Mantel–Haenszel χ^2 test considered the center effect used to compare any differences in the primary and secondary endpoints between the two groups. Importantly, the missing-data processing method for secondary endpoints was the same as that for the primary endpoint.

Safety data were analyzed using the safety set (SS). The incidence of TEAEs, SAEs, and significant AEs was carefully documented.

PK endpoints were summarized descriptively for the PK population, and a 90% CI within the range 80–125% was considered to meet the equivalence standard. A sample size of approximately 294 patients was chosen (with a random ratio of 2:1, 196 cases in the HS016 group and 98 cases in the adalimumab group) to achieve 80% power to demonstrate equivalence between the HS016 and adalimumab groups for the AUC_{τ} and $C_{max,ss}$ values. All statistical analysis was carried out using SAS version 9.2 software (SAS, Cary, NC, USA). Notably, the scores changed before and after treatment, and each time point was compared using paired *t* tests. Independent sample *t* tests were also used to assess any differences between the two groups.

3 Results

3.1 Patient Disposition

A total of 1068 individuals were screened, of whom 419 did not meet the inclusion criteria or withdrew consent. Therefore, 649 patients were randomized, but only 648 received treatment. Of the 648 patients, 570 (87.8%) completed the trial, 362/416 (87.0%) for HS016 and 208/232 (89.7%) for adalimumab (Fig. 1). Withdrawal due to AEs occurred in the HS016 group (30 patients [7.2%]) and in the adalimumab group (13 patients [5.6%]). The PK population consisted of 297 patients (HS016, $n=188$; adalimumab, $n=109$). Medication adherence (actual dosage/planned dosage × 100) was 87.7% in the HS016 group and 90.5% in the adalimumab group for a medication adherence distribution of 80–120%, with strict compliance with treatment duration (160.41 ± 30.83 days and 162.21 ± 29.21 days for the HS016 and adalimumab treatments, respectively).

3.2 Baseline Demographics and Clinical Characteristics of Patients

Most patients in the HS016 (85.3%) and adalimumab (78.4%) groups were < 40 years old and mainly males (86.3% and 87.9%, respectively). The disease duration was 6.4 ± 5.2 and 6.5 ± 5.7 years for each group, respectively. Overall, baseline disease characteristics and health status scores were comparable between the two groups (Table 1).

3.3 Clinical Efficacy

3.3.1 ASAS20

The ASAS20 response rates at week 24 in the HS016 and adalimumab groups were 87.5% (364/416) and 90.1% (209/232), respectively (Fig. 2a). The risk difference between the two groups was −2.59% (90% CI −6.77 to 1.60, $p=0.324$), which was within the pre-specified equivalence margin (± 15%). This finding demonstrated the clinical equivalence between HS016 and adalimumab. The ASAS20 response rates at week 12 were 79.6% (95% CI 75.4–83.3) in the HS016 group and 81.0% (95% CI 75.4–85.9) in the adalimumab group (Fig. 2b), with no significant difference between the groups ($p=0.654$). The ASAS20 response rates increased with treatment duration from 46.4% (HS016) and 47.4% (adalimumab) after treatment at week 2. In the follow-up treatment, this rate continued to increase until week 12; this increasing tendency appeared to decline slightly until week 24. Overall, the proportion of ASAS20 response patients in both groups was similar at each time point examined.

3.3.2 Responses to Treatment

We evaluated the effectiveness of the treatment by assessing the response rates for ASAS40, ASAS5/6, and BASDAI improvement, severity of morning stiffness, and by using HAQ-S and SF-36V2 (physical component score [PCS] and mental component score [MCS]) (Table 2); these data were

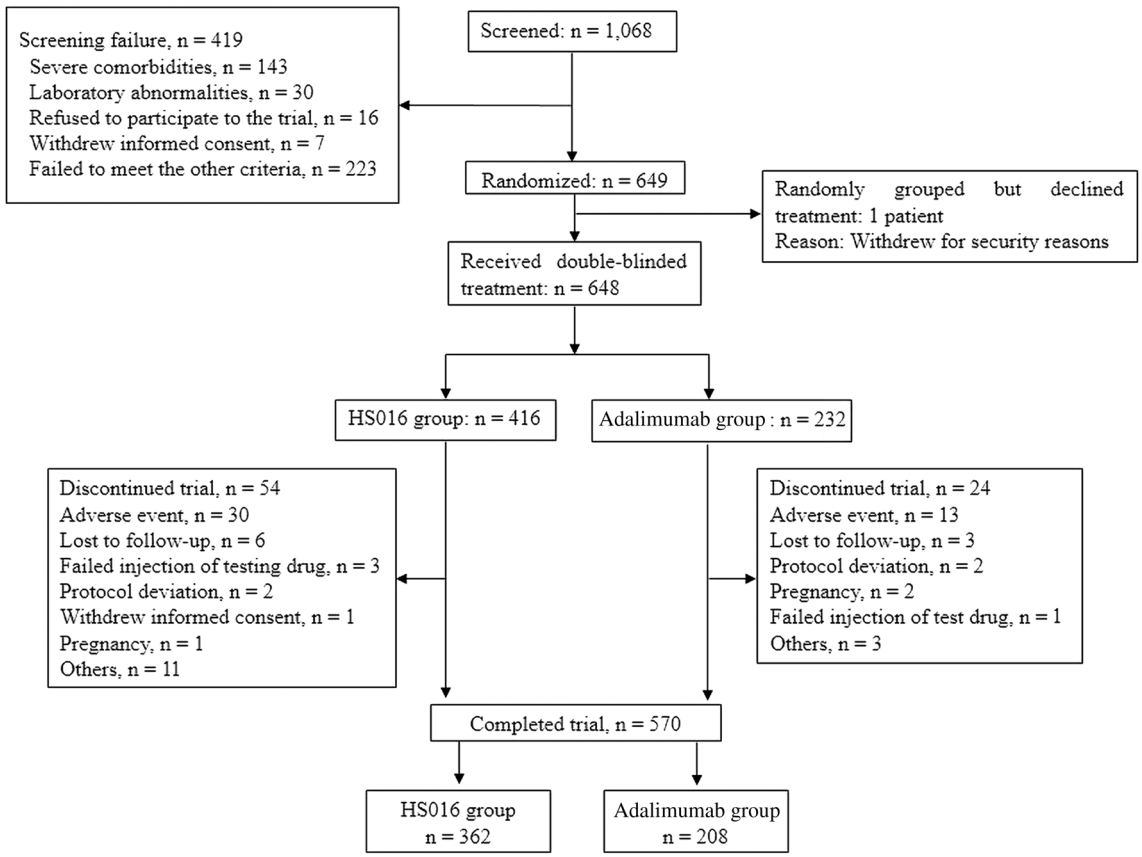

Fig. 1 Flow of patient enrolment, randomization and trial inclusion. The reasons for patient withdrawal at each stage are shown

assessed at weeks 12 and 24. However, no significant differences were found in any of the variables between the HS016 and adalimumab groups at 12 or 24 weeks for ASAS40 and ASAS5/6 responses. Similarly, the proportion of patients with a BASDAI 50% improvement at 12 and 24 weeks was not significantly different between the two groups. A difference, however, existed between the two groups regarding the severity of morning stiffness, but at weeks 12 and 24 the trend did not reach statistical significance. A similar trend was found for the mean changes in HAQ-S compared with baseline, but similarly, statistical significance was not reached at 12 or 24 weeks between the HS016 and adalimumab groups. Lastly, the PCS and MCS scores were not significantly differ between the two groups at 12 and 24 weeks (Table 2). The response rates for ASAS40 and ASDAS-CRP were not significantly different between the HS016 and adalimumab groups throughout the 24 weeks of treatment (Fig. 3).

3.4 Safety

We detected 1573 TEAEs among 352/416 (84.6%) patients in the HS016 group, and 751 TEAEs among the 200/232 (86.2%) patients in the adalimumab group (Table 3). Most TEAEs associated with the drugs in the two groups were mild to moderate (260 [67.1%] HS016-treated patients and 152 [65.5%] adalimumab-treated patients), but some were considered to be severe (7 [1.7%] patients in the HS016 group, 3 of which were cases of tuberculosis, and 2 [0.9%] patients in the adalimumab group) (Supplementary Table 1, see ESM). No significant difference was found in the incidence of TEAEs related to the experimental drugs, or of SAEs or significant AEs between the two groups. Significant AEs with a high incidence rate were related to upper respiratory infection (URI), abnormal liver function, and nasopharyngitis.

Additionally, SAEs with the highest incidence were infectious diseases, accounting for 1.4% in the HS016 group and 1.3% in the adalimumab group. No deaths occurred during the trial period. The incidence of TEAEs leading to early patient withdrawal from the trial was 5.3% in the HS016 group and 6.5% in the adalimumab group. In addition, results of routine blood biochemistry and blood electrolyte measurements, urine tests, electrocardiography, vital-sign assessments, and physical examinations of patients in the HS016 group were similar to the safety results following adalimumab treatment; namely, either normal or abnormal, with no clinical significance (data not shown).

Table 1 Baseline demographics and clinical characteristics of the study participants

Characteristic	HS016 ($n=416$)	Adalimumab ($n=232$)	p value
Age (years), mean ± SD	31.5 ± 7.8	32.1 ± 8.9	0.333
Age distribution, *n* (%)			0.026
< 40 years	355 (85.3)	182 (78.4)	
≥ 40 years	61 (14.7)	50 (21.6)	
Male, *n* (%)	359 (86.3)	204 (87.9)	0.555
Height (cm), mean ± SD	168.8 ± 7.5	168.8 ± 6.8	0.991
Weight (kg), mean ± SD	66.5 ± 9.0	66.4 ± 9.3	0.913
Body mass index (kg/m^2), mean ± SD	23.3 ± 2.4	23.3 ± 2.5	0.843
Disease duration (years), mean ± SD	6.4 ± 5.2	6.5 ± 5.7	0.929
ASDAS-CRP, mean ± SD	4.0 ± 0.8	4.0 ± 0.9	0.196
BASDAI score (0–10 cm VAS), mean ± SD	6.2 ± 1.3	6.3 ± 1.4	0.401
BASFI score (0–10 cm VAS), mean ± SD	4.6 ± 2.3	4.7 ± 2.4	0.467
BASMI (linear, 0–10 cm VAS), mean ± SD	1.3 ± 1.7	1.1 ± 1.6	0.311
Severity of morning stiffness (0–10 cm VAS), mean ± SD	6.1 ± 1.8	6.2 ± 1.9	0.565
Total back pain (0–10 cm VAS), mean ± SD	6.9 ± 1.6	7.0 ± 1.6	0.092
Nocturnal back pain (0–10 cm VAS), mean ± SD	6.7 ± 1.8	6.9 ± 1.9	0.114
Overall evaluation of disease activity (0–10 cm VAS), mean ± SD	6.8 ± 1.6	7.0 ± 1.6	0.212
HAQ-S, mean ± SD	0.6 ± 0.4	0.6 ± 0.4	0.287
SF-36V2 summary scores, mean ± SD			
Physical component	31.9 ± 7.6	30.8 ± 7.8	0.082
Mental component	39.6 ± 9.7	39.7 ± 10.4	0.816
CRP (mg/L), mean ± SD	29.7 ± 33.8	31.4 ± 31.5	0.523
ESR (mm/h), mean ± SD	29.4 ± 23.8	31.2 ± 22.4	0.331
Medication history of TNF-α inhibitors, *n* (%)	7 (1.7)	9 (3.9)	0.112
DMARDs, *n* (%)			
Methotrexate	30 (7.21)	24 (10.34)	0.167
Sulfasalazine	175 (42.07)	101 (43.53)	0.717
Smoking status, *n* (%)			0.680
Yes	119 (28.7)	63 (27.2)	
No	296 (71.3)	169 (72.8)	
Anamnesis, *n* (%)	234 (56.3)	134 (57.8)	0.741
HLA-B27 positive rate[a], *n* (%)	380/414 (91.8)	212/233 (91.0)	0.726

ASDAS Ankylosing Spondylitis Disease Activity Score, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *CRP* C-reactive protein, *DMARDs* disease-modifying antirheumatic drugs, *ESR* erythrocyte sedimentation rate, *HAQ-S* Health Assessment Questionnaire for Spondyloarthropathies, *SF-36V2* Short-Form 36 Health Survey version 2, *TNFα* tumor necrosis factor alpha, *VAS* visual analog scale

[a]HLA-B27 was detected in the randomized population

3.5 Immunogenicity

The proportion of patients who tested positive for HAHAs at each time point did not differ significantly between the two groups (Table 4). In fact, the accumulated proportion of patients with positive HAHAs at week 24 was 326 (79.1%) in the HS016 group and 183 (79.9%) in the adalimumab group. We also performed NAb tests in HAHA-positive patients and found that the accumulated proportions of patients who tested positive for NAbs at each time point were similar between the two groups. The number (proportion) of patients at week 24 was 72 (17.5%) in the HS016 group and 43 (18.8%) in the adalimumab group.

3.6 Pharmacokinetics

The PK population was 188:109, with a somewhat unbalanced proportion, and the expected number of 196 cases in the HS016 group was not achieved. We plotted the plasma concentrations of HS016 or adalimumab (following repeated subcutaneous injections of 40-mg doses) from week 12 to week 14 (Supplementary Figure 2a, see ESM). Here, we

a

	HS016 group (n = 416)	Adalimumab group (n = 232)
No. of patients achieving ASAS20 response at week 24, n (%)	364 (87.5%)	209 (90.1%)
	95% CI [83.93%, 90.52%]	95% CI [85.50%, 93.61%]
RD of ASAS20 (90% CI)	-2.59% (-6.77%, 1.60%)	
P-value	0.324	

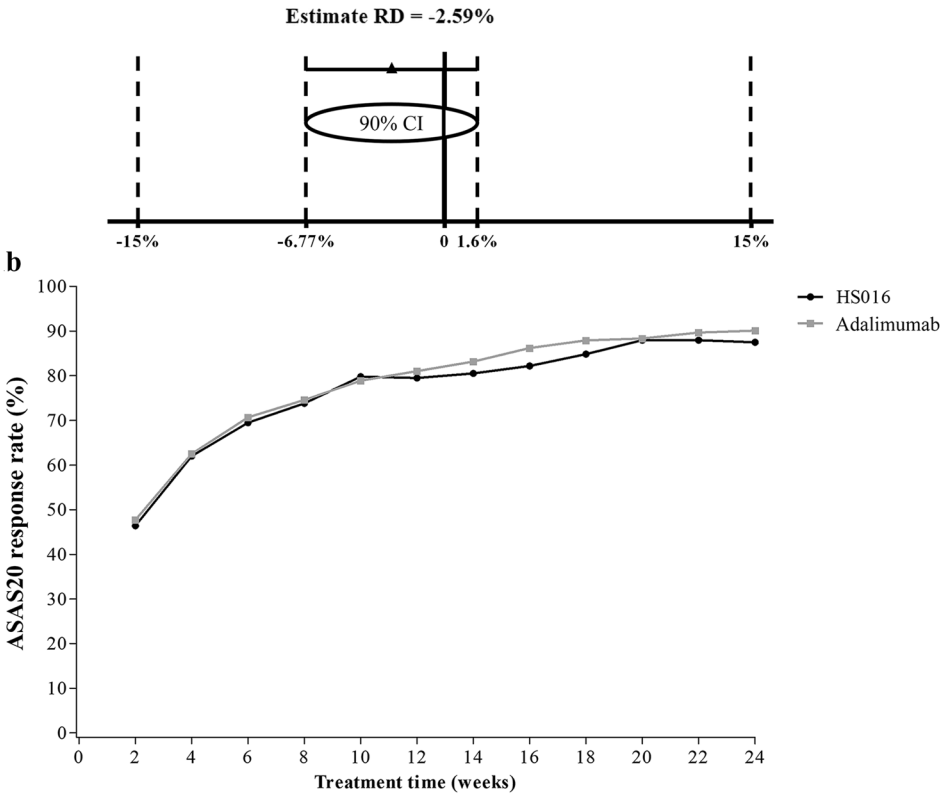

Fig. 2 ASAS20 response rates following HS016 or adalimumab treatment. **a** ASAS20 response rates at week 24. The RD 90% CI was within the pre-specified equivalence margin (±15%), demonstrating clinical equivalence between HS016 and adalimumab. **b** Changes in ASAS20 response rates throughout 24 weeks of treatment. *ASAS20* Assessment of Spondyloarthritis International Society criteria for a 20% improvement, *CI* confidence interval, *RD* ratio difference

found that HS016 and adalimumab plasma concentrations were similar during the steady-state period. Notably, the steady state $C_{max,ss}$ was equivalent for HS016 (7356.6 ng/mL) and adalimumab (7600.3 ng/mL) (90% CI 82–116%), while the AUC_{τ} (1,903,819.4 h·ng/mL and 1,993,029.9 h·ng/mL) were not equivalent in the overall PK population (90% CI 78–121%) (Supplementary Figure 2b, see ESM). The AUC_{τ} and $C_{max,ss}$ (as well as average concentration at steady state [$C_{av,ss}$], minimum concentration at steady state [$C_{min,ss}$], and half-life [$t_{½}$]) values in the HAHA-positive population were approximately half the values found in the HAHA-negative population, with no significant differences between the HS016 and adalimumab groups (Supplementary Table 2, see ESM). Clearance rates in the HAHA-positive population were nearly twice those found in the HAHA-negative population. However, the clearance rates in the NAb-positive population in both groups were higher than those in the NAb-negative population, whereas the AUC_{τ} and $C_{max,ss}$ in the NAb-positive population were approximately one-third of those in the NAb-negative population. Although the generation of HAHA increased the clearance rate in both groups, AUC_{τ}, $C_{max,ss}$, and other PK parameters were similar between the HS016 and adalimumab groups.

3.7 Correlations Between Anti-drug antibody (ADA) Titer, HAHA, NAb and ASAS20 Response Rates, Primary Pharmacokinetic Parameters and TEAEs

In order to find clinical responses according to the HAHA status, we analyzed the relationships between ADA titer and PK parameters, TEAEs, and the ASAS20 response rate at week 24. In the overall HAHA-positive patients, there were no significant differences between the HS016 and adalimumab groups regarding all included items, and also

Table 2 Comparisons of the effectiveness of treatment with HS016 and adalimumab at weeks 12 and 24

	HS016 group ($n=416$)	Adalimumab group ($n=232$)	p value
Week 12			
ASAS40, *n* (%)	244 (58.7)	143 (61.6)	0.350
ASAS5/6, *n* (%)	239 (57. 5)	136 (58.6)	0.860
BASDAI improvement > 50%, *n* (%)	257 (61.8)	142 (61.2)	0.960
Severity of morning stiffness (0–10 cm VAS), mean ± SD	2.7 ± 2.1	2.5 ± 1.8	0.371
HAQ-S, mean ± SD	0.3 ± 0.3	0.3 ± 0.3	0.636
SF-36V2 summary scores, mean ± SD			
Physical component	39.5 ± 8.7	39.5 ± 8.7	0.995
Mental component	43.1 ± 10.4	42.9 ± 9.9	0.861
Week 24			
ASAS40, *n* (%)	296 (71.2)	175 (75.4)	0.176
ASAS5/6, *n* (%)	262 (63.0)	156 (67.2)	0.375
BASDAI improvement > 50%, *n* (%)	318 (76.4)	182 (78.5)	0.517
Severity of morning stiffness (0–10 cm VAS), mean ± SD	2.1 ± 2.0	2.0 ± 1.7	0.662
HAQ-S, mean ± SD	0.3 ± 0.3	0.3 ± 0.3	0.459
SF-36V2 summary scores, mean ± SD			
Physical component	40.7 ± 8.8	40.0 ± 8.5	0.324
Mental component	43.8 ± 10.4	43.7 ± 10.0	0.871

ASAS Assessment of Spondyloarthritis International Society, *ASAS40* 40% improvement from baseline according to ASAS criteria, *ASAS5/6* improvement in at least five of six domains, according to ASAS criteria, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *HAQ-S* Health Assessment Questionnaire for Spondyloarthropathies, *SF-36V2* Short-Form 36 Health Survey version 2, *VAS* visual analog scale

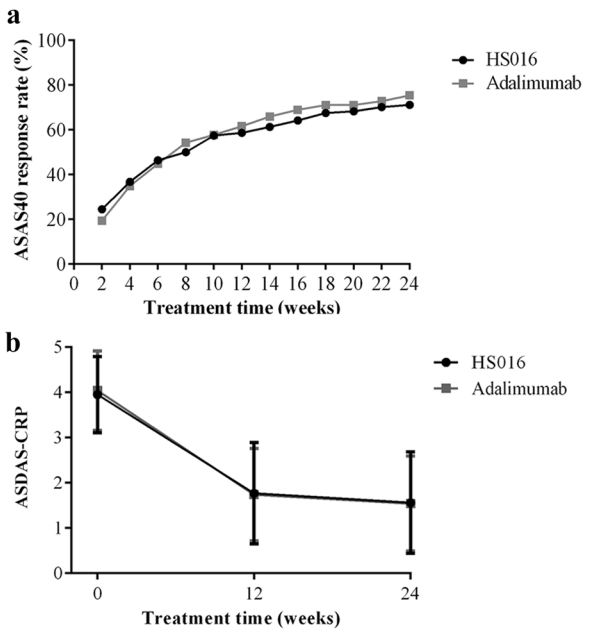

Fig. 3 ASAS40 response rate (**a**) and ASDAS-CRP (**b**) throughout 24 weeks of treatments. *ASAS40* 40% improvement from baseline according to Assessment of Spondyloarthritis International Society criteria, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *CRP* C-reactive protein

whether they had a high or low ADA titer. However, the PK parameters AUC_{τ} and $C_{max,ss}$ were significantly lower within the HS016 and adalimumab groups when their intragroup ADA titers were high. In HAHA-negative patients, the ASAS20 response rate at week 24 was significantly higher in the adalimumab group compared with the HS016 group, whereas PK parameters and TEAEs were not significantly different in the two groups. However, there was no difference in clinical response, PK parameters, and TEAEs in the NAb-positive adalimumab and HS016 groups (Table 5).

4 Discussion

During the last few decades, the introduction of anti-TNFα medication has revolutionized the treatment of patients with AS [16], and adalimumab has been proven to be effective in reducing spinal and sacroiliac joint inflammation in various trials [6–10], but the development of biologic agents has contributed to an increase in healthcare costs. However, biosimilars of drugs that are no longer under patent protection have been rapidly developed [17] as they offer alternatives with greater affordability for patients and healthcare systems [11, 18]. It has been estimated that biosimilars might reduce healthcare-related costs by US$54 billion from 2017 to 2026 in the US alone

Table 3 Comparison of the incidence of AEs following treatment with HS016 and adalimumab

	HS016 group ($n=416$)		Adalimumab group ($n=232$)		p value
	Events (n)	Number of patients, n (%)	Events (n)	Number of patients, n (%)	
Total TEAEs	1573	352 (84.6)	751	200 (86.2)	0.645
TEAEs related to drugs	783	267 (64.2)	400	154 (66.4)	0.607
URI	135	94 (22.6)	63	48 (20.7)	
Abnormal liver function	79	60 (14.4)	23	19 (8.2)	
TEAEs not related to drugs	790	267 (64.2)	351	139 (60.0)	0.310
TEAEs leading to dropout	23	22 (5.3)	17	15 (6.5)	0.600
SAEs	25	18 (4.3)	6	6 (2.6)	0.288
Significant AEs	475	229 (55.1)	219	114 (49.1)	0.163
URI	125	90 (21.6)	46	41 (17.7)	
Abnormal liver function	53	41 (9.9)	17	13 (5.6)	
Nasopharyngitis	22	18 (4.3)	16	12 (5.2)	

AEs adverse events, *SAEs* serious AEs, *URI* upper respiratory infection, *TEAEs* treatment-emergent AEs

Table 4 Positive test results for HAHAs and NAbs at different time points

Time point	HAHAs			NAbs		
	HS016 group ($n=412$) n (%)	Adalimumab group ($n=229$) n (%)	p value	HS016 group ($n=412$) n (%)	Adalimumab group ($n=229$) n (%)	p value
Week 2	120 (29.1)	75 (32.8)	0.339	10 (2.4)	11 (4.8)	0.105
Week 4	160 (38.8)	99 (43.2)	0.277	24 (5.8)	16 (7.0)	0.560
Week 8	219 (53.2)	124 (54.2)	0.809	35 (8.5)	24 (10.5)	0.405
Week 12	283 (68.7)	154 (67.3)	0.708	48 (11.7)	31 (13.5)	0.486
Week 18	315 (76.5)	172 (75.1)	0.702	65 (15.8)	39(17.0)	0.680
Week 24	326 (79.1)	183 (79.9)	0.814	72 (17.5)	43 (18.8)	0.682

HAHAs human anti-human antibodies, *NAbs* neutralizing antibodies

[19]. Studies that aimed to introduce biosimilars for anti-TNFα medications included switching from an originator treatment to a biosimilar [20–22] and direct comparisons of the originator and biosimilar [14, 23]. An expert consensus has been published with five overarching principles and eight consensus recommendations for the use of biosimilars for the treatment of rheumatological diseases, which is based on a systematic literature review including abstracts and annual meetings of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) [24]. This study compared the efficacy and safety of the novel adalimumab biosimilar candidate, HS016, and adalimumab treatments for Chinese AS patients. We found no significant differences in efficacy and safety between the drugs. Similarly, the HAQ-S and SF-36 scores did not differ significantly between the treatment groups, suggesting similar quality-of-life improvements. ASAS20 response rates after one treatment dose (week 12) were 79.6% for HS016 and 81.0% for adalimumab and were without significant difference. The ASAS20 values were somewhat higher in the present trial compared with similar previous adalimumab AS treatment studies at 58.2% [9] and 67.2% [7]. The high response rate in our study might be attributed to the low proportion of patients previously treated with biological agents (Table 1). Compared with previous data in AS patients, the positive rate of HAHAs and NAbs was significantly higher in this study population, which might be attributed to the improved antibody detection method (Bridging-ECLIA) used in the present study. In addition, due to the cost in clinical practice, AS patients may first choose small molecule therapeutic drugs with acceptable efficacy, and few of the randomized patients had received TNFα inhibitors for AS treatment before, which might have had an influence on HAHA and NAb-positive rates. However, the comparison of effects of ADA titers and NAb-positive cases on ASAS20 response rates, primary PK parameters, and TEAEs showed that there was no significant difference

Table 5 Influence of different HAHA status (low titer *vs* high titer) and NAb-positive on ASAS20 response rates, primary PK parameters and TEAEs

	ASAS20 response rate at week 24, *n* (%)		AUC_{τ} (GM, CV%)		$C_{max,ss}$ (GM, CV%)		TEAEs, *n* (%)	
	HS016	Adalimumab	HS016	Adalimumab	HS016	Adalimumab	HS016	Adalimumab
HAHA-positive	283/326 (86.8%)	160/183 (87.4%)	*N* = 151 1,650,007.3 (188.2%)	*N* = 90 1,779,395.0 (135.3%)	*N* = 151 6513.6 (42.8%)	*N* = 90 6903.7 (36.1%)	274/326 (84.1%)	160/183 (87.4%)
p value	0.827		0.625		0.627		0.362	
Low titer	153/176 (86.9%)	90/100 (90.0%)	*N* = 77 2,944,589.8 (36.1%)	*N* = 50 2,636,522.1 (28.6%)	*N* = 77 10,244.3 (16.1%)	*N* = 50 9428.9 (13.1%)	147/176 (83.5%)	87/100 (87.0%)
p value	0.358		0.064		0.183		0.489	
High titer	130/150 (86.7%)	70/83 (84.3%)	*N* = 74 903,128.2 (296.27%)	*N* = 40 1,088,487.8 (231.46%)	*N* = 74 4066.2 (52.1%)	*N* = 40 4675.8 (47.4%)	127/150 (84.7%)	73/83 (88.0%)
p value	0.533		0.516		0.519		0.560	
p value (low titer vs high titer)	0.944	0.250	< 0.001	< 0.001	< 0.001	< 0.001	0.779	0.847
HAHA-negative	77/86 (89.5%)	46/46 (100.0%)	*N* = 37 3,413,687.1 (33.9%)	*N* = 19 1,978,850.0 (33.9%)	*N* = 37 12,088.7 (14.1%)	*N* = 19 12,983.6 (15.1%)	75/86 (87.2%)	40/46 (87.0%)
p value	0.022		0.991		0.927		1.00	
NAb-positive	62/72 (86.1)	37/43 (86.1)	*N* = 37 522,740.9 (102.6%)	*N* = 22 741,845.3 (76.4%)	*N* = 37 2789.1 (88.2%)	*N* = 22 3680.9 (76.4%)	64/72 (88.9%)	36/43 (83.7%)
p value	0.081		0.479		0.461		0.568	

Low titer: below or equal to the median titer; high titer: above the median titer, where the median titer value at 24 weeks is 20

ASAS20 20% improvement from baseline according to the Assessment of Spondyloarthritis International Society criteria, AUC_{τ} area under the plasma drug-concentration–time curve, $C_{max,ss}$ steady-state maximal concentration, *CV%* coefficient of variance, *GM* geometric mean, *HAHA* human anti-human antibodies, *NAb* neutralizing antibodies, *PK* pharmacokinetic, *TEAEs* treatment-emergent AEs

between the adalimumab and HS016 groups, although the ADA titer volume showed effects in the intra group comparisons.

Similar to other TNFα inhibitors [9], we found that HS016 was generally well tolerated by patients with AS. In fact, most TEAEs were mild or moderate in severity and the incidence of SAEs was low, with 4.3% in the HS016 group and 2.6% in the adalimumab group. The rate of TEAEs and SAEs did not significantly differ between the two groups.

$C_{max,ss}$ was equivalent for HS016 and adalimumab (90% CI 82–116%), thereby satisfying the criteria set for the PK equivalence of HS016 versus adalimumab. However, the 90% CI for the AUC_{τ} was 78–121%, but almost within the predefined margins of 80–125%, which may be related to the larger geometric CV% in both groups (165.92% in the HS016 group and 124.99% in the adalimumab group). The geometric means of AUC_{τ} and $C_{max,ss}$ in the HAHA-negative subset of patients were higher than those in the overall PK population (Supplementary Table 2, Supplementary Figure 2, see ESM), which correlated with the results obtained with another biosimilar anti-TNFα drug (infliximab) for AS treatment [25].

Nocebo refers to effects complementary to placebo and have been proposed to be the causes of withdrawal of treatment due to adverse events in placebo-arm participants treated for rheumatic and musculoskeletal diseases (RMDs). In addition, lower biosimilar retention rates than in previous RCTs have been attributed to nocebo effects after transition from bio-originator to biosimilar therapeutics [26]. However, since in the present study the patients were blinded to their treatment drugs, a direct nocebo effect caused by awareness of treatment with a biosimilar could be excluded.

Limitations of the present study were the relative short treatment duration of 24 weeks, which did not capture long-term effects of the medications, and the short follow-up times, in addition to a generalization limitation and a lack of MRI as well as peripheral arthritis, enthesitis, uveitis, and other data.

5 Conclusions

An equivalent biosimilar (HS016) to the reference drug, adalimumab, was successfully assessed through an analysis of efficacy, safety, and immunogenicity. Based on our findings, HS016 should be considered as an affordable alternative for the treatment of Chinese patients with AS.

Compliance with Ethical Standards

Funding This work was supported by the Chinese National Key Technology R&D Program, Ministry of Science and Technology (Grant number: 2017YFC0907601); Medicine and Health Technology Innovation Project, Chinese Academy of Medical Sciences (Grant number: 2019-I2M-2-008) and ZHEJIANG HISUN PHARMACEUTICAL CO., LTD. Open access publication of this article was funded by Haisun BioRay Bio-pharmaceutical., Ltd.

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the Peking Union Medical College Hospital and Chinese Academy of Medical Sciences (no. 001402) and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed written consent was obtained from all individual participants included in the study.

Author contributions ML and XZ contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors. The first draft of the manuscript was written by JS and LH; all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript submitted to the journal.

Data availability The datasets generated during and/or analyzed in the current study are available from the corresponding author on reasonable request.

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