ORIGINAL ARTICLE

Comparison of the Efficacy and Safety of Biosimilar Adalimumab Injection with Innovator Adalimumab in Subjects with Active Ankylosing Spondylitis

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Abstract

Objectives: To compare the efficacy and safety of biosimilar adalimumab injection manufactured by Enzene Biosciences Ltd. (biosimilar) with innovator adalimumab (iADA) in subjects with active ankylosing spondylitis (AS).

Methods: The prospective, multicenter, randomized, double-blind, phase 3 study involved 192 subjects with active AS recruited at 20 centers across India. The subjects who fulfilled the eligibility criteria were randomized in a ratio of 2:1 (i.e., 125 subjects in the biosimilar adalimumab arm and 67 subjects in the iADA arm). The selected subjects were randomly assigned to receive either the biosimilar or iADA at a dose of 40 mg subcutaneously every other week for a total of 12 weeks. Efficacy assessment was done based on ASAS and BASDAI response criteria. Safety assessment was based on complete physical examination, adverse event (AE) monitoring, vital signs, electrocardiogram (ECG), anti-adalimumab antibody (ADA) assessment, and laboratory tests.

Results: A total of 192 patients were randomized into two groups: biosimilar adalimumab (n = 125) and iADA (n = 67). Baseline demographics, including mean age (32.6 vs 32.4 years) and BMI (23.5 vs 23.2 kg/m^2), were comparable between groups. At 12 weeks, ASAS 20/40/70 responses were achieved by 97.5, 94.1, and 68.9% in the biosimilar group and by 98.4, 96.7, and 77% in the iADA group. A total of 44 AEs were reported in 27 subjects (14.1%), with an AE rate of 0.264 per person in the biosimilar arm and 0.16 in the iADA arm. ADA positivity rates were statistically nonsignificant between groups (p = 0.3516). Pharmacokinetic analysis confirmed bioequivalence with comparable Cmax and AUC values.

Conclusion: The ASAS 20/40/70 response rates indicated the response to biosimilar at week 12 was similar to iADA. Both drugs had comparable safety and tolerability profiles.

Trial registry name: The Clinical Trials Registry-India (CTRI), URL: http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=42640&EncHid=&userName=enzene

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Introduction

The prognosis of ankylosing spondylitis (AS), an inflammatory rheumatic disease, is variable and can result in chronic pain and serious impairment of spinal mobility, physical function, and quality of life. It primarily affects the axial skeleton and causes characteristic inflammatory back pain.[1,2] The development of biologics, and in particular the use of tumor necrosis factor (TNF) antagonists, has significantly improved the arsenal of treatments available for AS.[3,4] The first fully human, high-affinity, recombinant anti-TNF monoclonal antibody, adalimumab, binds specifically to TNF-alpha and blocks its interaction with TNF receptors, lyses surface TNF-expressing cells, and modulates biological responses that are induced or regulated by TNF.[5,6] The drug action helps in controlling the elevated levels of TNF that are found in the synovial fluid of subjects with diseases like AS. The landmark trial titled Adalimumab Trial Evaluating Long-Term Efficacy and Safety in AS (ATLAS) has demonstrated the safety and tolerability of the subcutaneous adalimumab injection in patients with active AS. The treated subjects demonstrated significant improvement in clinical signs and symptoms, physical function, and health-related quality of life.[7,8]

Adalimumab, manufactured by Abbott Laboratories in Chicago, Illinois (hereafter referred to as innovator adalimumab, iADA), gained US Food and Drug Administration (FDA) approval for the treatment of rheumatoid arthritis in 2002 and AS in 2006.[9] Several biosimilars have already been launched in India and across the globe after the expiration of the patent for the originator product in 2017.

Three circumstances that have accentuated the need for biosimilars in the field of autoimmune diseases are the rising demand for biologics as a result of their successful use in clinical trials; the approaching patent expiration for the four top-selling innovators' biologics; and the need to cut healthcare costs since biosimilars are cheaper.[10] Despite the therapeutic advantages, cost remains a major challenge for the widespread use of biologic treatments, particularly in nations like India

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where it is crucial to deliver safe and affordable medicines for its sizable, uninsured, and underprivileged population. The development of biosimilars has helped to offset the financial burden and meet the rising demand for original biologics as well as the upcoming patent expiration.[10,11]

The Central Drugs Standard Control Organization (CDSCO) recommends conducting a comparative trial for any of the approved indications of the innovator molecule. Since iADA was approved for AS, the present phase 3 trial was conducted to compare the efficacy, pharmacokinetics (PK), immunogenicity, safety, and tolerability of the biosimilar adalimumab injection manufactured by Enzene Biosciences Ltd. (biosimilar adalimumab) with iADA in subjects with active AS. The study was carried out in compliance with the Indian regulatory authority (CDSCO) guidelines for biosimilar approval in 2012.[12]

Methods

The prospective, multicenter, randomized, double-blind, phase 3 noninferiority study involved 192 subjects with active AS recruited at 20 centers across India. The inclusion criteria considered were: subjects aged between 18 and 65 years, fulfillment of the 1984 Modified New York Criteria for AS, inadequate response to or intolerance to one or more nonsteroidal anti-inflammatory drugs (NSAIDs) and on a stable dose of NSAID or methotrexate for the last 2 weeks, and active AS defined by two or more of the following criteria at both screening and baseline visits: a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of ≥4, total back pain on a visual analog scale (VAS; 0–10 cm) ≥4, and persistence of stiffness in the morning for 1 hour or longer. The interval between screening and baseline visits was 3 weeks. The recruited subjects were allowed to continue on a stable dose of NSAIDs and they remained stable throughout the study.

Patients with any of the following criteria were excluded: total spinal ankylosis (bamboo spine), history of spinal surgery or joint surgery involving joints assessed within 2 months prior to screening, intra-articular joint injection(s) or spinal or paraspinal corticosteroid injection(s) within 28 days prior to baseline, exposure to any anti-TNF (tumor necrosis factor) therapy at any time, clinically active TB and underlying conditions that may predispose to infection, and history or presence of cardiac, renal, neurologic, psychiatric, endocrinologic, metabolic, or hepatic disease (details of inclusion and exclusion criteria are listed in Supplementary Table 1). Screening for latent tuberculosis was performed by gathering detailed clinical history, chest X-ray, interferon-γ release assay, and Mantoux test. Hepatitis B, C, and HIV screening were performed by ELISA. Subjects positive for any infection were excluded.

The trial is registered with the Clinical Trial Registry-India (no. CTRI/2020/09/028070). The study was commenced after receiving written approval from the regulatory authorities and in compliance with International Council on Harmonization E6(R2) "Guideline for Good Clinical Practice" and the Declaration of Helsinki (Brazil) 2013. Ethical committee approval was obtained from all the sites. Written informed consent was obtained from all the study participants.

The primary endpoint of the study was to compare the efficacy of biosimilar adalimumab injection with iADA by Assessment of SpondyloArthritis International Society (ASAS) 20 (ASAS20) response criteria at week 6 and week 12. Secondary endpoints were to compare the PK, immunogenicity, safety, and tolerability of the biosimilar with iADA injection at week 6 and week 12.

The subjects who fulfilled the eligibility criteria were randomized in a ratio of 2:1 [i.e., 125 subjects in the biosimilar adalimumab arm (group A) and 67 subjects in the iADA arm (group B)]. Randomization was performed using the interactive web response system (IWRS) and the randomization schedule was generated using SAS® (SAS Institute Inc., USA). The selected subjects received either biosimilar adalimumab at a dose of 40 mg subcutaneously (prefilled syringe containing 40 mg adalimumab in 0.4 mL as the active ingredient) every other week for a total of 12 weeks or iADA at an equivalent dose. The principal investigator and the assessment team were blinded.

Assessments

Efficacy assessments were based on ASAS20, ASAS40, ASAS70, ASAS5/6, BASDAI50, subject's global assessment of disease activity, total back pain score, and Bath Ankylosing Spondylitis Functional Index (BASFI) score. Safety assessment was based on adverse events (AE), serious adverse events (SAE), clinical laboratory parameters, anti-adalimumab antibody (ADA), physical examination, vital signs, electrocardiogram (ECG), demographic details, and relevant medical and medication history. Immunogenicity was based on the assessment of anti-adalimumab antibodies. PK assessment was performed by comparing PK parameters, namely maximum concentration (Cmax), area under the curve from time 0 to a specific timepoint (AUC_0–t), area under the curve from time 0 to infinity (AUC_0–inf), time to maximum concentration (tmax), and half-life ($t_1/_2$).

Table 1: The number and percentage of subjects in mIIT population achieving ASAS20, ASAS40, ASAS40, ASAS5/6, and BASDAI50 at 2, 4, 6, 8, 10, and 12 weeks

mIIT population	*ASAS-20*		*ASAS-40*		*ASAS-70*		*ASAS-5/6*		*BASDAI50*	
	Biosimilar adalimumab	*iADA*	*Biosimilar adalimumab*	*iADA*	*Biosimilar adalimumab*	*iADA*	*Biosimilar adalimumab*	*iADA*	*Biosimilar adalimumab*	*iADA*
Week-2	39 (32.2%)	25 (38.5%)	5 (4.1%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	29 (24.0%)	19 (29.2%)	10 (8.3%)	4 (6.2%)
Week-4	89 (73.6%)	45 (69.2%)	33 (27.3%)	23 (35.4%)	4 (3.3%)	1 (1.5%)	75 (62.0%)	39 (60.0%)	29 (24.0%)	16 (24.6%)
Week-6	108 (89.3%)	58 (89.2%)	68 (56.2%)	40 (61.5%)	19 (15.7%)	9 (13.8%)	99 (81.8%)	54 (83.1%)	51 (42.1%)	27 (41.5%)
Week-8	114 (95.0%)	62 (95.4%)	95 (79.2%)	55 (84.6%)	38 (31.7%)	21 (32.3%)	100 (83.3%)	58(89.2%)	87 (71.9%)	46 (70.8%)
Week-10	113 (94.2%)	63 (98.4%)	107 (89.2%)	59 (92.2%)	68 (56.7%)	38 (59.4%)	106 (88.3%)	60 (93.8%)	100 (82.6%)	54 (83.1%)
Week-12	116 (97.5%)	60 (98.4%)	112 (94.1%)	59 (96.7%)	82 (68.9%)	47 (77.0%)	113 (95.0%)	58 (95.1%)	107 (88.4%)	56 (86.2%)

Sample Size and Statistical Analysis

The sample size was calculated based on the number of achievers in assessment in ASAS20 response criteria at week 12 of 58% with iADA and biosimilar in subjects with active AS.[8] Fifty-seven patients in the biosimilar group and 114 patients in the iADA group provided 80% power to detect noninferiority, with a noninferiority margin of 20% and 1-sided confidence interval of 5%. Considering a dropout rate of around 10%, a total of 192 patients (125 patients in the test group and 67 patients in the comparator group) were recruited.

The modified intention-to-treat (mITT) population comprised all randomized subjects who received at least one dose of study treatment and had at least one efficacy assessment. The per-protocol (PP) population comprised all randomized subjects who completed the study visits as per protocol without any major protocol deviations. All randomized subjects who received at least one dose of study treatment were included in the safety population. A total of 30 evaluable male subjects (i.e., 15 subjects in each treatment group) were considered for PK analysis.

The descriptive statistics for continuous variables have been presented with number (n) of nonmissing observations, mean, standard deviation, median, and minimum and maximum (range). For categorical data, the descriptive statistics have been presented with number of exposed patients and number (n) with the percentage of observations in various categories of the endpoint, where percentages have been based on the exposed patients.

Depending on the study population, data compiled up to the point of discontinuation were used for analysis. Subjects who were withdrawn prematurely from the study treatment were included in all analyses (up to the date of withdrawal), regardless of the duration of treatment. The analysis was done on observed data only; no imputation was done for missing values.

Descriptive analysis was also conducted to compare the proportion of subjects between the groups. The 95% confidence intervals (CI) for treatment differences were calculated using the Farrington-Manning method. The *p*-values for comparing biosimilar adalimumab and iADA for responders with ASAS20, ASAS40, ASAS70, ASAS5/6, and BASDAI50 from baseline to visit 3 to visit 8 were calculated using the Chi-square or Fisher's exact test. Additionally, the *p*-value was calculated for comparing the proportion between the two groups for positive subjects using the Chi-squared test or Fisher's exact test. Descriptive analyses also included graphical presentations of data wherever appropriate. Individual data listings have also been provided. Statistical analyses were performed using SAS® (SAS Institute Inc., USA).

Results

Of the 245 subjects screened for the study, 53 subjects were screen failures, and 192 subjects were randomized. Of the 192 randomized subjects, 125 were in the biosimilar adalimumab arm and 67 in the iADA arm. The corresponding mean age of the biosimilar and iADA arms was 32.6 years and 32.4 years, and the respective mean BMI noted was 23.5 and 23.2 kg/m^2. The study had 161 (83.9%) male subjects [103 (82.4%) in the biosimilar arm and 58 (86.6%) in the iADA arm] and 31 (16.1%) female subjects [22 (17.6%) in the biosimilar arm and 9 (13.4%) in the iADA arm]. The mean Bath Ankylosing Spondylitis Functional Activity Index (BASFAI) scores noted were 6.80 ± 2.41 in the biosimilar arm and 6.63 ± 2.44 in the iADA group, with a *p*-value of 0.65. Similarly, the mean BASDAI scores noted were 6.29 ± 1.48 in the biosimilar arm and 6.28 ± 1.49 in the iADA arm, with a *p*-value of 0.98, suggesting no significant difference in disease activity. The mean duration of diagnosis in the biosimilar and iADA groups was 78 months and 69 months, respectively. Forty-five (36%) and 19 (28.35%) patients were on a weekly dose of methotrexate, while the remaining patients were on different NSAIDs. Other demographic characteristics were comparable between the groups.

The mITT population included 186 (96.9%) subjects, that is, 121 (96.8%) and 65 (97%) subjects in the biosimilar adalimumab and iADA arms, respectively (6 patients who withdrew consent after the 1st dose and did not return for the 1st efficacy assessment were not considered). The PP population included 179 (93.2%) subjects, that is, 119 (95.2%) and 60 (89.6%) subjects in the biosimilar adalimumab and iADA arms, respectively. The safety population included 192 (100%) subjects, that is, 125 (100%) and 67 (100%) subjects in the biosimilar adalimumab and iADA arms, respectively. Twelve (6.3%) subjects [6 (4.8%) and 6 (9%) subjects in the biosimilar adalimumab and iADA arms, respectively] discontinued the study due to various reasons. The CONSORT diagram depicting the details of patient recruitment has been provided in Figure 1.

Efficacy

Assessment of efficacy showed that, in the mITT population, 116 (97.5%) out of 119 subjects in the biosimilar arm and 60 (98.4%) out of 61 subjects in the iADA arm achieved ASAS20 response at week 12. There was no significant difference (−0.88, 95% CI: −5.43 to 3.67) between the two treatment groups for achievement of ASAS20 response. Similarly, 112 (94.1%) out of 119 subjects in the biosimilar arm and 59 (96.7%) out of 61 subjects in the iADA arm attained ASAS40 response at week 12. Eighty-two (68.9%) out of 119 subjects in the biosimilar group and 47 (77%) out of 61 subjects in the iADA group attained ASAS70 response at week 12. One hundred thirteen (95%) out of 119 subjects in the biosimilar group and 58 (95.1%) out of 61 subjects in the iADA group reached ASAS5/6 response at week 12. There was no significant difference between the groups (−0.12, 95% CI: −6.85 to 6.60) for achievement of ASAS5/6 response. One hundred seven (88.4%) out of 119 subjects in the biosimilar group and 56 (86.2%) out of 61 subjects in the iADA arm attained BASDAI50 response at week 12. No significant difference (−1.89, 95% CI: −9.33 to 5.56) was found between the two treatment groups for achievement of BASDAI50 response. The ASAS20, ASAS40, ASAS70, ASAS5/6, and BASDAI50 achieved at weeks 2, 4, 6, 8, 10, and 12 were found to be comparable between both treatment groups (Table 1 and Fig. 2).

In the PP population, there were no significant differences between the biosimilar and iADA groups in achieving ASAS20, ASAS40, ASAS70, ASAS5/6, or BASDAI50 responses at week 12. Similar response rates were observed throughout weeks 2–12 (Supplementary Table 2).

Inflammatory Parameters

The mean values of ESR decreased from baseline (visit 2) to visit 8. The changes in mean values of ESR from baseline (visit 2) to visit 8 throughout all visits were clinically significant ($p < 0.0001$) in both arms. The difference in changes in mean values of ESR between the two treatment arms was clinically insignificant ($p = 0.8102$, 0.9842, 0.6738, 0.8164, 0.7689, 0.9183 at visits 3, 4, 5, 6, 7, and 8, respectively). The mean values of CRP also decreased from baseline (visit 2) to visit 8. The changes in mean values of CRP from baseline (visit 2) to visit 8 throughout all visits were clinically significant ($p < 0.0001$ in both arms at visits 2, 4, 5, 6, 7, and 8, and in the biosimilar arm at visit 3; $p = 0.0001$ in the iADA arm at visit 3). The difference in changes in mean values of CRP between the two

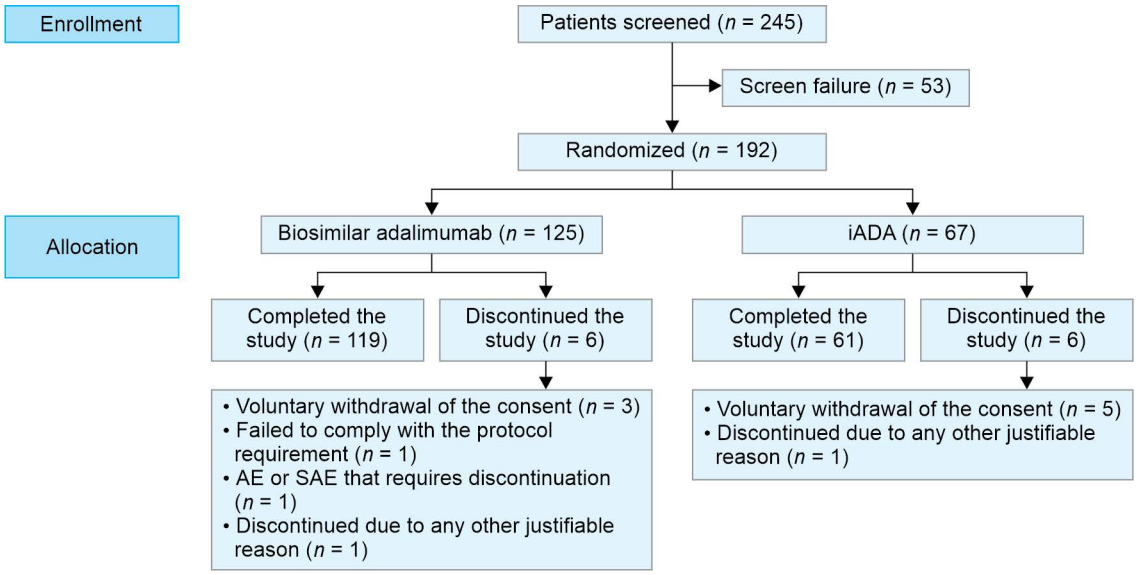


Fig. 1: CONSORT diagram depicting the details of patient recruitment

Table 2: Findings of ADA analysis noted in the biosimilar and iADA groups

Visit/weeks	*Biosimilar (N = 125)*		*iADA (N = 67)*		*p-value*
	Negative	*Positive*	*Negative*	*Positive*	
Visit 2/day 1	118 (94.40)	0 (0.00)	63 (94.03)	1 (1.49)	0.3516
Visit 5/week 6	103 (82.40)	15 (12.00)	55 (82.09)	9 (13.43)	0.8209
Visit 8/week 12	110 (88.00)	5 (4.00)	52 (77.61)	8 (11.94)	0.0637

treatment arms was clinically insignificant (p = 0.4669, 0.3122, 0.4756, 0.8647, 0.6524, and 0.9082 at visits 3, 4, 5, 6, 7, and 8, respectively).

Safety

Forty-four AEs in 27 (14.1%) subjects were reported in the entire study population (biosimilar n = 125, iADA n = 67). Out of these subjects, the AEs reported per person were 0.264 in the biosimilar arm and 0.16 in the iADA arm. There was no death reported in either treatment group, and 2 (1%) subjects had SAEs (1 each in both arms). Out of all the subjects with at least one AE, 25 (13%) subjects reported 42 nonserious AEs (14% in the biosimilar arm reported 32 AEs and 10% in the iADA arm reported 10 AEs), and 2 (1%) subjects had SAEs (1 each in both arms).

The majority of the AEs, that is, 39 AEs in 23 (12%) subjects [30 AEs in 16 (12.8%) subjects of the biosimilar arm and 9 AEs in 7 (10.4%) subjects of the iADA arm], were mild in intensity. Four AEs in 4 (2.1%) subjects [3 AEs in 3 (2.4%) subjects of the biosimilar arm and 1 AE in 1 (1.5%) subject of the iADA arm] were moderate in intensity. The proportion of patients who experienced any SAEs was comparable within each treatment group, and a majority of the events were mild to moderate in both treatment groups.

The overall safety analysis of AEs, clinical laboratory, and other safety parameters demonstrated that biosimilar adalimumab has a comparable safety profile to iADA.

Immunogenicity

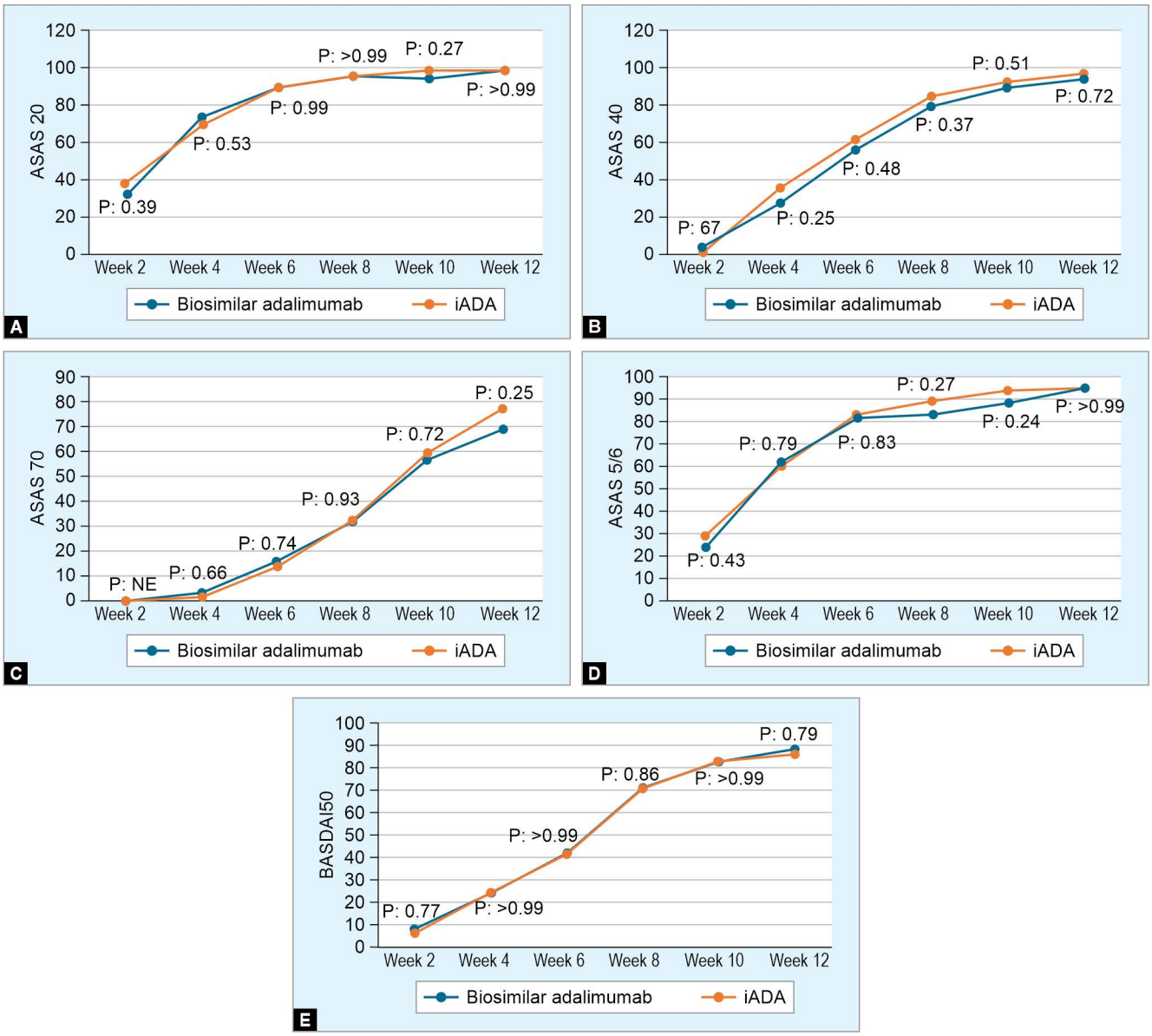
Detection of ADA at day 1 (visit 2), week 6 (visit 5), and week 12 (visit 8) was used to assess immunogenicity in all 192 participants. The analysis reported comparable immunogenicity between biosimilar and iADA. At week 12, the ADA count was negative for 110 (88%) and positive for 5 (4%) subjects in the biosimilar arm; negative for 52 (77.61%) and positive for 8 (11.94%) subjects in the iADA arm, with a statistically nonsignificant difference between the two arms. The findings of ADA analysis at day 1, week 6, and week 12 are depicted in Table 2.

Pharmacokinetics

PK analysis was performed in 30 evaluable male subjects. The analysis of Cmax, AUC0-t, AUC0-inf, Tmax, and HL_Lambda_z demonstrated a comparable PK profile between the biosimilar and iADA. Bioequivalence was confirmed, with the 90% confidence intervals (CIs) for the ratios of maximum concentration and area under the concentration–time curve falling within the standard bioequivalence limits (80–125%, Fig. 3). A summary of the pharmacokinetic parameters for the study population is provided in Supplementary Table 3.

Discussion

The current randomized, double-blind, phase III study compared the efficacy, safety, pharmacokinetics, and immunogenicity of biosimilar adalimumab injection manufactured by Enzene Biosciences Ltd. with iADA injection in subjects with active AS. Comparison of the efficacy of biosimilar adalimumab injection with iADA injection based on ASAS20, ASAS40, ASAS70, ASAS5/6, BASDAI50 response criteria, and global assessment of disease activity scores showed that the findings are similar to that demonstrated in landmark studies of adalimumab.[8,13,14] The study findings are also comparable to the results reported for other adalimumab biosimilars.[9,13–15] At 12 weeks, the ASAS20/40/70 responses were achieved by 97.5, 94.1, and 68.9% of patients who received biosimilar injection in the mITT population as compared to 98.4, 96.7, and 77% of patients who received iADA injection in the mITT population. During the same period, the ASAS20/40/70 responses were achieved by 97.5, 94.1, and 68.9% of patients



Figs 2A to E: Proportion of patients who achieved ASAS (20, 40, 70, 5/6) and BASDAI 50 at 2, 4, 6, 8, 10, and 12 weeks post-treatment in mITT population; (A) ASAS20 response in the mITT population; (B) ASAS40 response in the mITT population; (C) ASAS70 response in the mITT population; (D) ASAS5/6 response in the mITT population; (E) BASDAI50 response in the mITT population

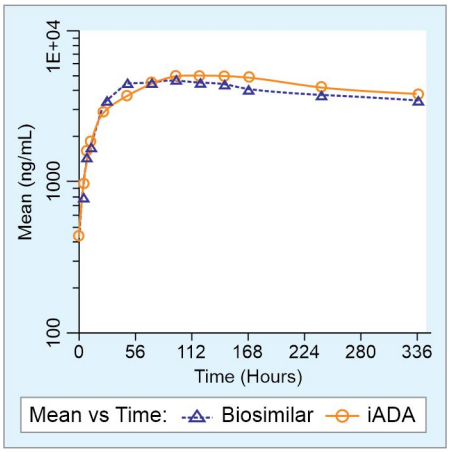


Fig. 3: Pharmacokinetics comparison between biosimilar adalimumab and iADA groups

who received biosimilar injection in the PP population as compared to 98.3, 96.7, and 76.7% of patients who received iADA injection in the PP population.

Based on the primary efficacy analysis with respect to subjects achieving ASAS20 response criteria at visit 5 (week 6) and visit 8 (week 12), it was observed that the lower limits of the 95% CI for treatment difference were within the noninferiority margin (i.e., 20% set for the study). The current study finding has demonstrated that the biosimilar adalimumab is noninferior to iADA for the treatment of AS.

The PK analysis with respect to Cmax, AUC0–t, and AUC0–inf revealed a comparable PK profile between the test and the reference drug. The present study has provided additional supporting evidence of the PK profile of biosimilars in patients with AS.

Overall, based on the safety analysis of AEs, clinical laboratory, ADA, and other safety parameters, it is demonstrated that the biosimilar has comparable safety and immunogenicity to the reference product. The majority of AEs, that is, 39 AEs in 23 subjects (30 AEs in 16 subjects of the biosimilar arm and 9 AEs in 7 subjects of the iADA arm), were mild in intensity. No action was taken with the study drug for 38 events in 24 (12.5%) subjects [30 AEs in 17 (13.6%) subjects of the biosimilar arm and 8 AEs in 7 (10.4%) subjects of the iADA]. The majority of AEs, that is, 33 AEs in 18 subjects (27 AEs in 15 subjects of the biosimilar arm and 6 AEs in 3

subjects of the iADA arm), were considered unrelated to the study drug.

The mean values of ESR and CRP demonstrated a reduction from baseline (visit 2) to visit 8. The changes in mean values of both ESR and CRP from baseline (visit 2) to visit 8, throughout all visits, were also found to be statistically significant ($p < 0.0001$) in both arms, thereby corroborating the comparable safety of the biosimilar. The difference between the groups was not significant.

The ADA analysis at visits 2, 5, and 8 revealed that the test and reference groups have comparable immunogenicity, since the *p*-values for comparison between the two treatment arms (with respect to subjects positive for ADA) at visits 2, 5, and 8 were 0.3516, 0.820, and 0.0637, respectively (statistically nonsignificant). Comparable immunogenicity with regard to the incidence of ADA, as defined by the American Association of Pharmaceutical Scientists guidelines, was also demonstrated.[16]

The present study findings showed significant variations in the percentage values of ASAS20, BASDAI50, ASAS40, and AEs when compared to the ATLAS study. Specifically, the ASAS20 response rate was 58.2% in the ATLAS study, whereas it was much higher at 98.4% in the iADA group and 97.5% in the biosimilar adalimumab group in the present study. Similar observations were made for the percentages of BASDAI50 and ASAS40 responses. In a similar open-label, single-center study conducted by Chopra et al. in Indian patients, it was demonstrated that the use of 40 mg of standard biosimilar adalimumab contributed to ASAS20 and ASAS40 response rates of 82 and 70%, respectively. This considerable difference in treatment response rates between the studies conducted in Indian settings and the ATLAS study could be attributed to differences in the ethnicity of the study population and disease characteristics, as well as potential random variations and biases.[8,17] Moreover, there are no studies with reference to originator adalimumab conducted in Indian settings.

The current randomized, double-blind, phase III study highlights the noninferiority of biosimilar adalimumab to iADA in terms of efficacy, safety, pharmacokinetics, and immunogenicity in patients with active AS. Key findings, based on ASAS20, ASAS40, ASAS70, and BASDAI50 response criteria, demonstrated comparable treatment outcomes between biosimilar adalimumab and iADA, consistent with prior studies on other biosimilars. Response rates were significantly higher in this study compared to landmark trials like ATLAS, likely due to regional population characteristics and study design. The subcutaneous administration of biosimilar adalimumab provides greater convenience than intravenous biologics, reducing hospital visits and improving patient adherence. Biosimilar adalimumab, combined with its affordability, expands access to advanced therapies in resource-constrained settings, offering a critical advantage for patients.

A review by Malhotra has evaluated the biosimilars and noninnovator biotherapeutics industry in India, highlighting critical challenges in healthcare accessibility. The study has noted that in a country like India, with a large number of economically disadvantaged and uninsured patients, the cost of biologic treatments and the growing demand for these therapies remain significant challenges. The emergence of biosimilar molecules helps to address these concerns.[11]

For physicians, the availability of additional biosimilars provides a cost-effective alternative and greater flexibility in tailoring treatments to individual patient needs in managing AS. As biosimilars become increasingly accessible, studies like this reassure physicians about their efficacy and safety, enabling evidence-based decisions for initiating or switching treatments. Such studies also empower physicians to confidently adopt biosimilars, ensuring clinical outcomes are maintained, treatment costs are reduced, and accessibility is broadened.

The multicenter study design, which corroborates the comparable efficacy, safety, and immunogenicity of both treatment arms, is a major strength of the study. Based on the results of this phase III study, Enzene Biosciences, a subsidiary of Alkem Laboratories, began marketing the biosimilar adalimumab in India after obtaining approval from the Drugs Controller General of India in 2023.[18]

However, the study has some limitations. The follow-up period was relatively short at 12 weeks, necessitating further studies to assess the long-term safety and sustained efficacy of the biosimilar. Additionally, as all 20 participating centers were located in India, the results may not be fully generalizable to diverse populations outside this region.

Conclusion

The phase III multicenter, randomized, double-blind study showed equivalent efficacy of biosimilar adalimumab and the iADA reference product, as demonstrated by the ASAS20/40/70 response rates at week 12. The biosimilar drug was well tolerated and possessed PK, safety, and immunogenicity profiles comparable to that of the reference iADA.

Ethics Approval and Consent to Participate

Since there are 20 site details, they have been shared as a supplementary file.

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The study was sponsored by Enzene Biosciences Ltd and co-sponsored by Alkem Laboratories Ltd. All principal investigators from the 20 centers, including Dr Jyoti Parida, Dr Archana Sonawale, Dr Vishnu Sharma, Dr Kaushik Basu, Dr John Mathew, Dr Chethana Dharmapalaiah, Dr Gaurav Seth, Dr Girish Kakade, Dr Neeraj Jain, Dr Reena Sharma, Dr Firdaus Fatima, Prof. Chandrashekara Srikantiah, Dr Rajeshwar Srivastav, Dr Romi Shah, Dr Bankim Desai, Dr Ajit Nalawade, Dr Vikram Haridas, Dr Uma Kumar, and Dr R Naidu, have received funding from Alkem Laboratories Ltd for conducting the study.

Competing Interests

The study was sponsored by Enzene Biosciences Ltd and co-sponsored by Alkem Laboratories Ltd. All principal investigators from the 20 centers, including Dr Jyoti Parida, Dr Archana Sonawale, Dr Vishnu Sharma, Dr Kaushik Basu, Dr John Mathew, Dr Chethana Dharmapalaiah, Dr Gaurav Seth, Dr Girish Kakade, Dr Neeraj Jain, Dr Reena Sharma, Dr Firdaus Fatima, Prof. Chandrashekara Srikantiah, Dr Rajeshwar Srivastav, Dr Romi Shah, Dr Bankim Desai, Dr Ajit Nalawade, Dr Vikram Haridas, Dr Uma Kumar, and Dr R Naidu, have received funding from Alkem Laboratories Ltd for conducting the study. Dr Roshan Pawar, Dr Amol Aiwale, Yogesh Rane, Dr Vinayak Shahavi, Dr Akhilesh Sharma, and Dattatreya Pawar are employees of Alkem Laboratories Ltd.

Availability of Data and Materials

Data can be accessed upon request to the corresponding author.

Author Contributions

All authors take full responsibility for the integrity and accuracy of all aspects of the work.

Dr Chandrashekara S helped in conceptualizing and developing the manuscript. Dr Chandrashekara S, Dr Jyoti Ranjan Parida, Dr Archana Sonawale, Dr Vishnu Sharma, Dr Kaushik Bas, Dr John Mathew, Dr Chethana Dharmapalaiah, Dr Gaurav Seth, Dr Girish Kakade, Dr Neeraj Jain, Dr Reena Sharma, Dr Firdaus Fatima, Dr Rajeshwar Nath Srivastava, Dr Romi Shah, Dr

Bankim Desai, Dr Ajit Nalawade, Dr Vikram Haridas, Dr Uma Kumar, and Dr R Naidu served as principal investigators for the clinical trial.

Dr Roshan Pawar and Dr Vinayak Shahavi helped in finalizing the protocol, closely monitoring the projects at each site, and reviewed and finalized the CSR.

Dr Amol Aiwale and Yogesh Rane conducted evaluation of each subject as per the protocol, monitored site conduct of the trial, and reviewed the CSR.

Dr Akhilesh Sharma was closely involved from the development of adalimumab to the finalization of the CSR and study reports.

Dr Dattatreya Pawar was involved in strategy and protocol development for the biosimilar adalimumab.

All authors had access to the data and reviewed the manuscript.

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Supplementary Materials

Supplementary files are available with the author. Please connect with the author for the supplementary content.

Disclaimer

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References

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369(9570):1379–1390.
2. Zhu W, He X, Cheng K, et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res 2019;7:22.
3. Mounach A, El Maghraoui A. Efficacy and safety of adalimumab in ankylosing spondylitis. Open Access Rheumatol 2014;6:83–90.
4. Sieper J, Rudwaleit M, Braun J. Adalimumab for the treatment of ankylosing spondylitis. Expert Opin Pharmacother 2007;8(6):831–838.
5. Zamora-Atenza C, Diaz-Torne C, Geli C, et al. Adalimumab regulates intracellular TNFα production in patients with rheumatoid arthritis. Arthritis Res Ther 2014;16(4):R153.
6. Schreiber S. Crohn's disease—infliximab, adalimumab and certolizumab-pegol: clinical value of anti-TNF-alpha treatment. Dtsch Med Wochenschr 2007;132(34-35):1770–1774.
7. Van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol 2006;54(7):2136–2146.
8. Van der Heijde D, Schiff MH, Sieper J, et al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Ann Rheum Dis 2009;68(6):922–929.
9. Xu H, Li Z, Wu J, et al. IBI303, a biosimilar to adalimumab, for the treatment of patients with ankylosing spondylitis in China: a randomised, double-blind, phase 3 equivalence trial. Lancet Rheumatol 2019;1(1):e35–e43.
10. Cuadrado MJ, Sciascia S, Bosch X, et al. Is it time for biosimilars in autoimmune diseases? Autoimmun Rev 2013;12(10):954–957.
11. Malhotra H. Biosimilars and non-innovator biotherapeutics in India: an overview of the current situation. Biologicals 2011;39(5):321–324.
12. Rathore A. Guidelines on similar biologics: regulatory requirements for marketing authorization in India. PDA J Pharm Sci Technol 2012;66(5):393.
13. Hennigan S, Ackermann C, Kavanaugh A. Adalimumab in ankylosing spondylitis: an evidence-based review of its place in therapy. Core Evidence 2007;2(4):295.
14. Kapoor S, Kaushik VV, Jain R, et al. Real-life tolerability and effectiveness of adalimumab biosimilar in ankylosing spondylitis: the Adalimumab Biosimilar Patient Registry Data. ACR Open Rheumatol 2019;1(8):480–484.
15. Su J, Li M, He L, et al. Evaluation of adalimumab biosimilar candidate (HS016) in Chinese patients with active ankylosing spondylitis based on a health survey: sub-analysis of a phase 3 study. Clin Rheumatol 2022;41(3):731–739.
16. Shankar G, Arkin S, Cocea L, et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J 2014;16(4):658–667.
17. Chopra A, Khadke N, Saluja M, et al. The long-term effects of short-period adalimumab biosimilar usage in ankylosing spondylitis. Cureus 2023;15(3):e36444.
18. Biosimilars of adalimumab [Internet]. [cited 2023 Jul 22]. Available from: https://gabionline.net/biosimilars/general/Biosimilars-of-adalimumab