Efficacy and safety of monoclonal antibody AK111 in the treatment of active ankylosing spondylitis: a randomised, double-blind, placebo-controlled, multicentre phase II clinical study

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Abstract

Objective

The primary objective of the study was to evaluate the efficacy and safety of the monoclonal antibody AK111 in participants with active ankylosing spondylitis (AS).

Methods

Adult participants who met the Modified New York Criteria for Ankylosing Spondylitis revised in 1984 were randomly assigned to the AK111 75 mg, 150 mg, 300 mg group or placebo group with the ratio of 1:1:1:1. Each participant received 5 subcutaneous (SC) injections of the study drug (week 0/1/4/8/12). The primary efficacy endpoint of this study was the percentage of participants who reached the Assessment of SpondyloArthritis International Society (ASAS) 20 response at week 16. The key secondary endpoint was the percentage of participants who reached the ASAS 40 response at week 16.

Results

A total of 125 participants were randomly enrolled in this study. The ASAS 20 response rates at week 16 in the AK111 75 mg, 150 mg, and 300 mg groups were 80.6%, 71.9%, and 66.7%, respectively, each of which was higher than the placebo group (37.5%). The overall response rate of ASAS 40 in the AK111 group was also better than the placebo group. The incidence rate of treatment emergent adverse events (TEAEs) after receiving AK111 75 mg, 150 mg, 300 mg, and placebo group was 93.5% (29/31), 75.0% (24/32), 73.3% (22/30), and 75.0% (24/32), respectively; the incidence of drug-related AEs was 58.1% (18/31), 50% (16/32), 50% (15/30) and 43.8% (14/32), respectively. The majority of the TEAEs were grade 1 and 2 in severity. No neutralising antibody positivity was found during the study.

Conclusion

The humanised monoclonal antibody AK111 was safe and well tolerated in treating AS and showed a good efficacy by improved ASAS 20/ASAS 40 response.

Key words

interleukin-17A, clinical study, ankylosing spondylitis, monoclonal antibody, phase II study

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Introduction

Ankylosing spondylitis primarily affects the sacroiliac joints and spine, leading to chronic inflammation in adjacent soft tissues and peripheral joints, and is characterised by inflammatory back pain, radiographic sacroiliitis, excess spinal bone formation, and a high prevalence of HLA–B27 (1). Ongoing spine inflammation leads to stiffness, and in severe cases, the vertebrae will start to fuse, which can result in restriction of spinal mobility (2). The preliminary survey on the prevalence of AS in China is around 0.3%, with a ratio of 2–4:1 for males and females, and the age of onset is 15–40 years old (3). The AS often causes severe disability and impaired quality of life in the late stage of the disease, which also causes serious psychological and economic burdens to patients and their families (4).

According to multiple international axial spondyloarthritis (axSpA) guidelines (5, 6) and literature (7), non-steroidal anti-inflammatory drugs (NSAIDs) are recommended first-line treatment drugs for AS. csDMARDs (conventional synthetic disease-modifying anti-rheumatic drugs) such as sulfasalazine, methotrexate, leflunomide, etc., have uncertain therapeutic effects on axial lesions in AS (8). In patients with active AS despite treatment with NSAIDs, biological synthetic disease-modifying anti-rheumatic drugs (bDMARDs) or Janus kinase inhibitors (JAKi) should be considered. The currently available bDMARDs include tumour necrosis factor inhibitors (TNFi) and interleukin-17 inhibitors (IL-17i) (6). However, nearly 40% of AS patients had poor response to TNFi (9) or were unable to tolerate (10).

The potential mechanisms underlying the development of AS are partially known (11-13). Immune cells (such as Th17 cells) and pro-inflammatory cytokines (such as IL-6, IL-17, and IL-1 β) play important roles in the pathogenesis of AS (14) (15), and the IL-17 signalling pathway is a crucial part of the pathogenesis of AS (16). IL-17A inhibitors have been proven to virtually improve symptoms, reduce disease activity, and improve quality of life in AS patients (17-18). Two monoclonal antibodies targeting the IL-17 have been previously approved by the Food and Drug Administration of the United States (US FDA) and National Medical Products Administration (NMPA) for the treatment of AS, namely Cosentyx (19) (Secukinumab, Novartis) and Taltz (20) (Ixekizumab, Eli Lilly).

AK111 is a humanised IgG1 monoclonal antibody targeting IL-17A, which binds to human IL-17A cytokines with specificity and high affinity. Therefore, it can prevent IL-17A binding to IL-17 receptor A (IL-17RA) expressed on T cells, natural killer cells, and antigen-presenting cells, and consequently block its mediated cellular immune response.

Material and methods

Study design

This study was designed as a randomised, parallel, double-blind, placebo-controlled, multicentre clinical study. The study consisted of 3 sequential dose-escalating (AK111 75 mg, 150 mg and 300 mg) groups and a placebo group. A total of 120 participants were planned to be enrolled in this study at the ratio of 1:1:1:1 with 30 participants in each group (n=30). Eligible participants were randomly assigned to one of the groups using the Interactive Web Response System (IWRS), following a computer-generated random allocation table created by an independent third party using the block randomisation method. Each participant received 5 SC injections of the study drug at week 0/1/4/8/12. The primary endpoint was evaluated at week 16 and the participants were followed up until the end of the study at week 20 (Fig. 1). The study was registered on China drugtrials.org (CTR20210833) and the ClinicalTrials.gov (NCT05467995). The study was designed and conducted according to the guidelines of Good Clinical Practice (GCP), the current Declaration of Helsinki, and the National Medical Product Administration (NMPA). A total of 15 research centres in China participated in this study. The protocol of this study was approved by the ethics committee of each participated centre, and all the participants signed informed consent to enrol in this study.

Participants

Eligible participants for the study were

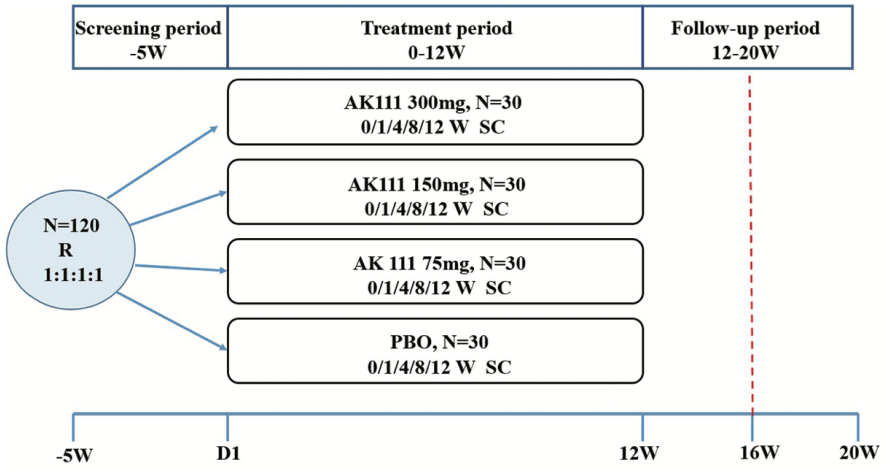

Fig. 1. Study design.
Each participant received 5 times of the study drug (0/1/4/8/12 week). The primary endpoint was assessed at week 16, and the participants were followed up until the end of the study at week 20.

men and women aged 18–75 years, confirmed with AS prior to screening. Participants were willing and able to comply with clinic visits and study-related procedures. Participants were diagnosed in according with the Modified New York Criteria for AS (1984) (21); this requires radiographic evidence of sacroiliitis. The key inclusion criteria were: i. Bath Ankylosing Spondylitis Activity Index (BASDAI) ≥4 and Spinal Pain score ≥4; ii.) ineffective or intolerable with receiving ≥1 type of non-steroidal anti-inflammatory drugs (NSAIDs); iii. previous use of DMARDs and TNF-α inhibitors with adequate washout. The key exclusion criteria include: i. participants with complete spinal rigidity; ii. participants with autoimmune diseases other than AS (such as rheumatoid arthritis, inflammatory bowel disease, etc.); iii. participants with any serious infection or chronic recurrent infectious diseases, active tuberculosis, syphilisor, viral infection, or participants with history of malignant tumours; iv. participants who previously received treatment with IL-17 inhibitors or >2 TNF inhibitors.

During the study period, participants were allowed to use NSAIDs, weak opioids, oral corticosteroids (≤10 mg of prednisone or an equivalent dose of other corticosteroids), methotrexate (≤25 mg/week), or sulfasalazine (≤3 g/day). However, stable treatment is required before randomisation and throughout the study period.

Objective and endpoints

The primary objective of this study was to evaluate the efficacy and safety of AK111 in treating AS participants. The secondary objectives of this study were to assess the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of AK111. The main efficacy endpoint of this study was the percentage of participants who reached ASAS 20 at week 16. The key secondary endpoint was the percentage of participants who reached ASAS 40 at week 16. Other secondary efficacy endpoints include the response rate of ASAS 5/6, as well as changes from baseline at each visit in BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Measurement Index (BASMI), and Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP), etc. ASAS 20 response (22) is defined as improvement of ≥20% and ≥1 unit (on a scale of 0 [least] to 10 [worst]) in at least 3 domains and no worsening of ≥20% and ≥1 unit in the remaining domain. ASAS 40 response (22) is defined as improvement of ≥40% and ≥2 units in at least 3 domains and no worsening in the remaining domain. The safety endpoints included TEAEs, serious adverse events (SAEs), and clinically significant lab test results.

Sample size determination

This study aimed to evaluate the preliminary efficacy of AK111. The sample size was primarily determined based on clinical feasibility and practical considerations. Accordingly, a sample size of 30 participants per treatment group (a total of 120 participants) was expected to detect a minimum difference of 25% in ASAS 20 response rates between each AK111 group and the placebo group, assuming a 30% response rate in the placebo group. This was calculated using a two-sided Z-test with pooled variance at a significance level of 0.05.

Efficacy analysis

The analysis of the efficacy endpoints in this study followed the principle of intention to treat (ITT), which included all randomised participants who had received at least one dose of study drug. Response rates for ASAS 20, ASAS 40, and ASAS 5/6 were calculated for each group, and their 95% confidence intervals (CIs) were estimated using the Clopper-Pearson method (23), respectively. Comparisons of response rates between each AK111 treatment group and the placebo group were performed using Fisher's exact test (24) respectively. Notably, all *p*-values presented were unadjusted for multiplicity. In addition, the differences in the response rates and their corresponding 95% CIs were estimated using the Chan-Zhang Exact method (25), respectively. Other secondary efficacy endpoints were analysed using descriptive statistics. Missing values for ASAS 20, ASAS 40, and ASAS 5/6 were conservatively imputed as non-responses, regardless of the reason for the missing data. Pre-specified subgroup analyses were conducted for the primary efficacy endpoint, ASAS 20, and the secondary endpoint, ASAS 40, based on gender, weight, previous usage of biological agents, and baseline CRP status.

Safety analysis

All safety data analysis was based on all randomised participants who have received at least one dose of study drug treatment and with at least one safety assessment (safety analysis set, SAS). Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. The number and percentage of TEAEs/

SAEs were tabulated by system organ class (SOC) and preferred term (PT) with a breakdown by treatment group. Descriptive statistical analysis was conducted on TEAE and treatment-related adverse events (TRAEs) according to different groups, and all safety data were summarised for descriptive analysis.

PK and PD analysis

Blood samples were collected from all participants for PK analysis before and 4 hours after administration (on day 1, 8, 29, 57 and 85), as well as on day 4, 15, 22, 113, 141, and the day of early discontinuation. Blood samples were collected from the first 40 participants for PD analysis on day 1, 4, 8, 29, 57, 85, 141, and the day of discontinuation. The serum concentration of AK111 was analysed by enzyme-linked immunosorbent assay (ELISA), and the lower limit of quantification for AK111 was 100 ng/mL. The AK111 was captured by the coated reagent (IL-17A) on the enzyme-linked immunosorbent assay (ELISA) plate and detected by the anti-AK111 antibody. A 4PL (Auto Estimate) weighted $1/Y^2$ fitting model was used to fit the standard curve and calculate the concentration of AK111. This method was thoroughly validated according to the guiding principles (26).

The concentration of total IL-17A in human serum was detected using electrochemical luminescence technology (ECLA), and the lower limit of quantification for total IL-17A was 4 pg/mL. A logistic (Auto Estimate) (weight $1/Y^2$) fitting model was used to fit the standard curve and calculate the concentration of IL-17A.

Immunogenicity analysis

Blood samples were collected from all participants on day 1, 29, 57, 113, 141, and the day of early discontinuation to assess the immunogenicity of AK111. Bridging electro-chemiluminescence immunoassay (ECLIA) technology based on the Meso scale discovery (MSD) platform was used for qualitative detection of anti-AK111 drug-resistant antibodies (ADA) in human serum, which including a 3-step assays for screening, confirmation, and titre determination. Samples with confirmed ADA positive had undergone analysis of neutralising antibody (NAb) activity. Qualitative detection of anti-AK111 neutralising antibodies in human serum was done using the affinity capture elution (ACE) method based on competitive ligand binding assay (CLBA) technology on the MSD platform. The analysis of immunogenicity was conducted after comprehensive methodological validation in accordance with the guiding principles (27), followed by immunogenicity sample analysis.

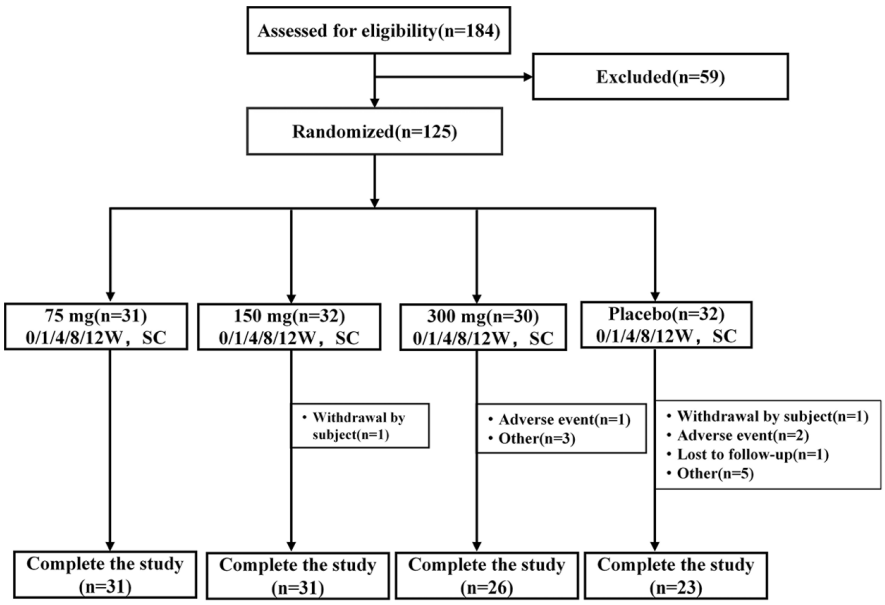

Fig. 2. Participants distribution.

Results

Participants distribution and baseline characteristics

A total of 125 participants were randomised and received at least one dose of the study drug. There were 111 (88.8%) participants who completed the study, including 31 in the 75 mg group (100%), 31 in the 150 mg group (96.9%), 26 in the 300mg group (86.7%), and 23 in the placebo group (71.9%). The main reasons for early discontinuation were participants' voluntary withdrawal of informed consent (2.4%), adverse events (1.6%), participants' loss of follow-up (0.8%), and others (6.4%, personal reasons, epidemic reasons, poor efficacy, etc.). A total of 106 (84.8%) participants completed all required treatments per protocol. The reasons for not completing the treatments included the willingness of the participants (7.2%), adverse events (1.6%), and others (6.4%, affected by the COVID-19 epidemic). The distribution of the participants is shown in Figure 2.

The clinical characteristics at baseline of participants in the AK111 treatment group and placebo group were similar. In the total population, the average age (standard deviation, SD) was 31.8 (7.2) years old, with the male proportion of 78.4%. The average weight (SD) was 68.1 (13.9) kilograms (kg). In terms of the baseline information on disease characteristics, the average course of disease was 6.5 (5.7) years, 89.6% of the participants were HLA-B27 positive, the mean CRP was 14.175 mg/L with 57.6% of the participants having elevated values compared to upper limit of normal, all participants (100%) had received ≥1 NSAIDs treatment in the past, and 39.2% of the participants had previously received TNFi treatment. At randomisation, 82.4% of the participants used NSAIDs as background treatment for AS and committed to using during the study period (Table I).

Efficacy

The response rates of ASAS 20 and ASAS 40 of participants were improved following AK111 75-300 mg. The ASAS 20 response rates of the

Table I. Baseline demographics and disease characteristics.

Parameter / statistics	AK111				Placebo	Total
	75 mg (n=31)	150 mg (n=32)	300 mg (n=30)	AK111 total (n=93)	(n=32)	(n=125)
Age (years), mean (SD)	30.9 (6.46)	33.8 (7.63)	31.2 (7.11)	32.0 (7.14)	31.0 (7.49)	31.8 (7.21)
Male, n (%)	24 (77.4)	27 (84.4)	22 (73.3)	73 (78.5)	25 (78.1)	98 (78.4)
Weight (kg), mean (SD)	66.30 (13.896)	72.86 (11.275)	67.91 (15.108)	69.08 (13.630)	65.22 (14.306)	68.09 (13.851)
Time since diagnosis of ankylosing spondylitis (years), mean (SD)	7.447 (5.7543)	7.558 (5.7473)	4.906 (4.7909)	6.665 (5.5367)	6.109 (6.0620)	6.523 (5.656)
HLA-B27 positive, n (%)	30 (96.8)	28 (87.5)	26 (86.7)	84 (90.3)	28 (87.5)	112 (89.6)
Patient global VAS score (0-100 mm scale), mean (SD)	67.2 (12.43)	65.0 (13.58)	63.3 (15.45)	65.2 (13.80)	68.8 (14.41)	66.1 (13.99)
Spinal pain VAS score (0-100 mm scale), mean (SD)	67.6 (13.58)	65.8 (15.43)	66.4 (13.83)	66.6 (14.18)	66.4 (14.74)	66.5 (14.27)
BASDAI score, mean (SD)	6.320 (1.1280)	5.904 (1.1624)	5.729 (1.1004)	5.986 (1.1460)	6.006 (1.0358)	5.991 (1.1147)
BASFI score, mean (SD)	5.168 (1.9992)	4.751 (1.7896)	4.173 (2.3417)	4.704 (2.0680)	4.864 (1.8935)	4.745 (2.0185)
CRP (mg/L), mean (SD)	17.336 (15.0064)	10.913 (9.1985)	12.921 (14.2151)	13.702 (13.1527)	15.551 (20.3451)	14.175 (15.2475)
CRP elevated at baseline, n (%)	22 (71.0)	20 (62.5)	16 (53.3)	58 (62.4)	14 (43.8)	72 (57.6)
ASDAS-CRP, mean (SD)	3.82 (0.710)	3.45 (0.648)	3.33 (0.816)	3.53 (0.746)	3.52 (0.694)	3.53 (0.730)
Previous history of NSAIDs treatment, n (%)	31 (100)	31 (96.9*)	30 (100)	92 (98.9*)	32 (100)	124 (99.2*)
Previous history of TNF inhibitor treatment, n (%)	12 (38.7)	12 (37.5)	10 (33.3)	34 (36.6)	15 (46.9)	49 (39.2)
Combined with AS system treatment at randomisation, n (%)	23 (74.2)	28 (87.5)	26 (86.7)	77 (82.8)	30 (93.8)	107 (85.6)
NSAID	23 (74.2)	27 (84.4)	24 (80.0)	74 (79.6)	29 (90.6)	103 (82.4)
Glucocorticoids	1 (3.2)	0	0	1 (1.1)	0	1 (0.8)
Immunomodulators (methotrexate or sulfasalazine)	4 (12.9)	3 (9.4)	6 (20.0)	13 (14.0)	5 (15.6)	18 (14.4)

Age (years) = (Date of signing informed consent form–date of birth+1) / 365.25. BMI: body mass index. BMI (kg/m^2) = weight (kg) / height^2 (m^2)
*One patient's NSAIDs medication record was missed in Electronic Data Capture (EDC), therefore not counted.

Table II. Efficacy endpoints of ASAS 20 and ASAS 40 at week 16.

Parameter	Statistics	AK111				Placebo
		75 mg (n=31)	150 mg (n=32)	300 mg (n=30)	AK111 total (n=93)	(n=32)
ASAS 20 response rate	N (%)	25 (80.6)	23 (71.9)	20 (66.7)	68 (73.1)	12 (37.5)
	95% CI	62.5, 92.5	53.3, 86.3	47.2, 82.7	62.9, 81.8	21.1, 56.3
Differences in response rates between groups	%	43.1	34.4	29.2	35.6	
	95% CI	16.4, 63.7	8.1, 56.3	3.0, 52.0	13.7, 53.6	
	p-value	0.0008	0.0114	0.0255	0.0005	
ASAS 40 response rate	n (%)	18 (58.1)	12 (37.5)	13 (43.3)	43 (46.2)	10 (31.3)
	95%CI	39.1, 75.5	21.1, 56.3	25.5, 62.6	35.8, 56.9	16.1, 50.0
Differences in response rates between groups	%	26.8	6.3	12.1	15.0	
	95%CI	1.2, 49.6	-17.4, 29.5	-12.7, 35.7	-5.8, 32.8	
	p-value	0.0437	0.7928	0.4314	0.1528	

n: total number of randomised patients; N: number of responders; [1] Used the Clopper Pearson method to calculate the 95% CI of response rates for each treatment group. [2] Comparisons of response rates between each AK111 treatment group and the placebo group were performed using Fisher's exact test.

AK111 75 mg group, 150 mg group, and 300 mg group at week 16 were 80.6% (25/31), 71.9% (23/32), and 66.7% (20/30), respectively, which were statistically higher than 37.5% (12/32) in the placebo group. At week 16, the response rates of ASAS 40 of the AK111 (75 mg, 150 mg, and 300 mg) groups were 58.1% (18/31), 37.5% (12/32), and 43.3% (13/30), respectively, which were higher than 31.3% (10/32) in the placebo group. There was no obvious correlation between the dosage and efficacy of the AK111 following a dose ranging from 75 mg to 300 mg (Table II).

AK111 achieved a fast onset in the treatment of active AS, with ASAS 20 response rates being 54.8% (17/31), 62.5% (20/32), and 70% (21/30) after a single dose of AK111 75-300 mg, compared to 28.1% (9/32) in the placebo group. The response rates of ASAS 40 following the first dose were 45.2% (14/31), 21.9% (7/32), and 43.3% (13/30), respectively, compared to 18.8% (6/32) in the placebo group. And with the extension of treatment time, the therapeutic effect showed a trend of further improvement. After the last ad-

Table III. Summary of TEAE incidence.

	AK111											
	75 mg (n=31)		**150 mg** (n=32)		**300 mg** (n=30)		**AK111 total** (n=93)		**Placebo** (n=32)		**Total** (n=125)	
Category	n (%)	cases	n (%)	cases	n (%)	cases	n (%)	cases	n (%)	cases	n (%)	cases
TEAE	29 (93.5)	79	24(75.0)	69	22(73.3)	72	75(80.6)	220	24(75.0)	97	99(79.2)	317
Related to study drug	18 (58.1)	37	16(50.0)	32	15(50.0)	42	49(52.7)	111	14(43.8)	48	63(50.4)	159
with CTCAE severity grade ≥ 3	2 (6.5)	4	0	0	2 (6.7)	2	4 (4.3)	6	2 (6.3)	2	6 (4.8)	8
Related to study drug	0	0	0	0	1 (3.3)	1	1 (1.1)	1	2 (6.3)	2	3 (2.4)	3
SAE	1 (3.2)	3	0	0	1 (3.3)	1	2 (2.2)	4	0	0	2 (1.6)	4
Related to study drug	0	0	0	0	0	0	0	0	0	0	0	0
TEAE leading to drug suspension	0	0	0	0	1 (3.3)	1	1 (1.1)	1	1 (3.1)	2	2 (1.6)	3
Related to study drug	0	0	0	0	1 (3.3)	1	1 (1.1)	1	1 (3.1)	2	2 (1.6)	3
TEAE leading to permanent drug discontinuation	0	0	0	0	0	0	0	0	2 (6.3)	2	2 (1.6)	2
Related to study drug	0	0	0	0	0	0	0	0	1 (3.1)	1	1 (0.8)	1
TEAE leading to withdrawal from the study	0	0	0	0	0	0	0	0	2 (6.3)	2	2 (1.6)	2
Related to study drug	0	0	0	0	0	0	0	0	1 (3.1)	1	1 (0.8)	1
TEAE leading to death	0	0	0	0	0	0	0	0	0	0	0	0
Related to study drug	0	0	0	0	0	0	0	0	0	0	0	0

Table IV. TRAE with an incidence ≥5% in the combined group of AK111.

	AK111											
	75 mg (n=31)		**150 mg** (n=32)		**300 mg** (n=30)		**AK111 total** (n=93)		**Placebo** (n=32)		**Total** (n=125)	
Preferred term	n (%)	cases	n (%)	cases	n (%)	cases	n (%)	cases	n (%)	cases	n (%)	cases
Upper respiratory tract infection	2 (6.5)	2	3 (9.4)	3	3 (10.0)	4	8 (8.6)	9	5 (15.6)	5	13 (10.4)	14
Alanine aminotransferase increased	2 (6.5)	2	2 (6.3)	4	3 (10.0)	5	7 (7.5)	11	3 (9.4)	4	10 (8.0)	15
Urinary tract infection	3 (9.7)	4	1 (3.1)	1	2 (6.7)	2	6 (6.5)	7	1 (3.1)	1	7 (5.6)	8

ministration of AK111 at week 12, the therapeutic effects were sustained until week 20.

AK111 groups also showed much better results in terms of improvements in other secondary endpoints at week 16. The response rates of ASAS 5/6 in the AK111 groups (75 mg, 150 mg, and 300 mg) were 58.1% (18/31), 53.1% (17/32), and 50% (15/30), respectively, which were higher than the response rates in the placebo group [21.9% (7/32)]. At week 16, the improvements in CRP, ASDAS-CRP and BASDAI from baseline were greater in the AK111 groups as compared to the placebo group.

Subgroup analysis showed generally consistent results in subgroups such as gender, age, weight, etc. However, within the AK111 75 mg group, the response rate of ASAS 40 was higher in participants weighing <70 kg compared to participants weighing ≥70 kg (72.2% *vs*. 38.5%). It suggested that at a lower dose (75 mg) level, high-weight individuals may experience suboptimal efficacy due to insufficient exposure. In addition, the overall efficacy of participants who had no previous use of biological agents showed a trend of better efficacy than those who had previous use of biological agents.

Safety

The incidence of TEAE and TRAE in each dose group of AK111 was similar to that in the placebo group, and there was no correlation between the incidence of TEAEs and dose level. The incidence of TEAE in the AK111 75 mg group, 150 mg group, 300 mg group, combined AK111 group, and placebo group was 93.5% (29/31), 75% (24/32), 73.3% (22/30), 80.6% (75/93), and 75.0% (24/32), respectively; the incidence of TRAE was 58.1% (18/31), 50% (16/32), 50% (15/30), 52.7% (49/93), and 43.8% (14/32), respectively (Table III). The incidence of TRAE ≥ 5% in the combined AK111 group included upper respiratory tract infections (8.6%, 8/93), alanine aminotransferase elevation (7.5%, 7/93), and urinary tract infection (6.5%, 6/93). The incidence of TRAE was higher in the placebo group compared to the treatment group, which included upper respiratory tract infections (15.6%, 5/32), and alanine aminotransferase elevation (9.4%, 3/32) (Table IV). No notable differences of TRAE ≥5% were observed among the different AK111 dose groups.

One participant in the AK111 group and 2 participants in the placebo group experienced grade 3 TRAE: (i) neutrophil count decline in the AK111 300mg group with the medication remained uninterrupted, (ii) hypotension, and (iii) plasma triglycerides elevation in the placebo group. All 3 grade 3 TRAEs recovered without clinical interventions. The remaining TRAEs were mild (grade 1) or moderate (grade 2), with the majority of them having improved or recovered.

During the study period, there were 2 participants who experienced 4 cases of SAE in the AK111 group. One participant in the 75 mg group experienced 3 SAEs, which were ureterolithiasis, hydroureter, and ureteritis (all were grade 3, possibly unrelated to study drug, all recovered), respectively. One participant in the 300 mg group experienced clavicle fracture (grade 3, not related to study drug, recovered). There was no active tuberculosis or hepatitis B during the study. There was no occurrence of tumours, severe allergic reactions, inflammatory bowel disease, or major adverse cardiovascular events (MACE).

Table V. Pharmacokinetic parameters of AK111 after single SC injection.

Dose group	n	T_{max} day	C_{max} μg/ml	AUC_{0-t} day*μg/ml
75 mg	31	6.86 (2.77-7.99)	7.99 ± 3.93	42.2 ± 24.6
150 mg	32	6.84 (2.83-7.87)	13.8 ± 6.05	68.2 ± 36.3
300 mg	30	6.90 (2.72-8.14)	34.3 ± 13.0	178 ± 71.5

T_{max} is the median value (min value-max value), C_{max} and AUC_{0-t} are arithmetic mean ± standard deviation. T_{max}: time to reach peak concentration; C_{max}: peak concentration; AUC_{0-t}: Area under the concentration time curve for the 0-168th hour.

Pharmacokinetic and pharmacodynamic

A total of 93 participants were included in the PK analysis (all randomised participants who received at least one dose of AK111 with evaluable post-treatment PK data) in this study. After subcutaneous injection of 75-300 mg AK111, the median time to reach peak serum concentration (T_{max}) was about 7 days, and the exposure of AK111 increased in a dose-dependent manner (Table V, Fig. 3).

A total of 40 participants (10 in each dose group) were included in the PD analysis. Compared with the baseline, the serum level of total IL-17A (free and AK111-bound IL-17A) rapidly increased from day 1 to day 8 following the first AK111 administration, while there was no obvious change in the serum level of total IL-17A in the placebo group over time, indicating that AK111 quickly binds to the target IL-17A post-treatment. The average percentage change of total IL-17A in the serum of each AK111 dose group from baseline reached its maximum on day 29, with 2520%, 3130%, and 4840%, respectively. From day 29 to day 141, there was a downward trend, and on day 141 after administration, the percentage change from baseline in total IL-17A of each group was about half of the maximum value compared to day 29 (Table VI, Fig. 4).

Immunogenicity

A total of 92 participants in this study were included in the immunogenicity analysis (all randomly enrolled participants who received at least one dose of AK111 and provided both a baseline sample and at least one post-treatment sample). Among the participants, the incidence of ADA positivity at baseline (before first administration) was 2.2% (2/92), and the incidence of treatment-emergent ADA positivity was 1.1% (1/92). No NAb positivity was found in the study.

Discussion

This study was a phase II clinical trial focused on exploring different doses for the treatment of AS. The primary objective was to evaluate the preliminary efficacy and safety of various dosing regimens of AK111 in treating AS. The findings will help inform dose selection for pivotal phase III clinical studies. Participants with active AS who received AK111 75–300 mg SC injection showed robust efficacy with improved ASAS 20 response. AK111 showed a rapid onset after administration, and the response rate of ASAS 20 in each dose group showed an obvious improvement in the first week. During the subsequent treatment, the efficacy continued to be improved. At week 16, the AK111 group showed superior improvement in ASAS 20 compared to the placebo group, and the efficacy had sustained for at least 8 weeks after the last administration. The efficacy of AK111 observed in the current study was similar to that observed in clinical studies of biologics in the same drug class. In one study (28) evaluating secukinumab in the Chinese AS population (known as the 'Measure 5' study), the response rates for ASAS 20 in the 150 mg dose group and the placebo group at week 16 were 58.4% and 36.6%, respectively. The therapeutic effect of AK111 75-300 mg is comparable to which of the Secukinumab 150 mg dose group. However, due to the small

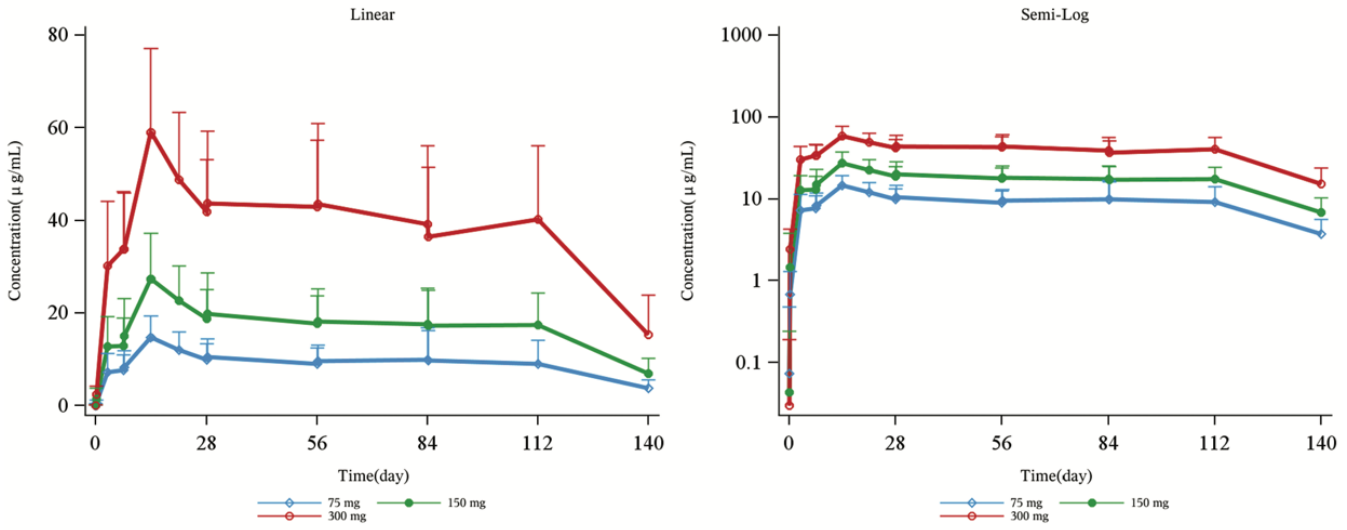

Fig. 3. Serum drug concentration *vs.* time of AK111 groups.
The x axis represents the time interval between the first administration, *i.e.* time on the x axis =study day-1.

Table VI. Percentage change in AK111 total IL-17A concentration from baseline (%).

Dose group	Parameter	Planned sampling time (day)						
		0	3	7	28	56	84	140
Placebo	n (Nmiss)	10(0)	10(0)	10(0)	8(0)	6(0)	6(0)	5(1)
	Mean	0.00	13.9	2.44	0.00	0.00	0.00	0.00
	SD	0.00	34.3	7.70	0.00	0.00	0.00	0.00
75 mg	n (Nmiss)	10(0)	10(0)	10(0)	10(0)	9(1)	10(0)	10(0)
	Mean	0.00	1040	2020	2520	1910	1680	1190
	SD	0.00	787	1810	1440	840	928	994
150 mg	n (Nmiss)	10(0)	9(0)	9(0)	9(0)	8(1)	8(1)	8(1)
	Mean	0.00	1250	2790	3130	1710	1690	1280
	SD	0.00	810	1860	1830	1070	845	615
300 mg	n (Nmiss)	10(0)	10(0)	10(0)	9(0)	9(0)	8(0)	7(0)
	Mean	0.00	2280	4070	4840	3900	4220	2590
	SD	0.00	1150	2440	2290	1960	3380	1440

Planned sampling time = study day-1. Nmiss: number of cases not included in descriptive statistics due to collection time exceed time-window. n: number of analysis cases; mean: arithmetic mean; SD: standard deviation.

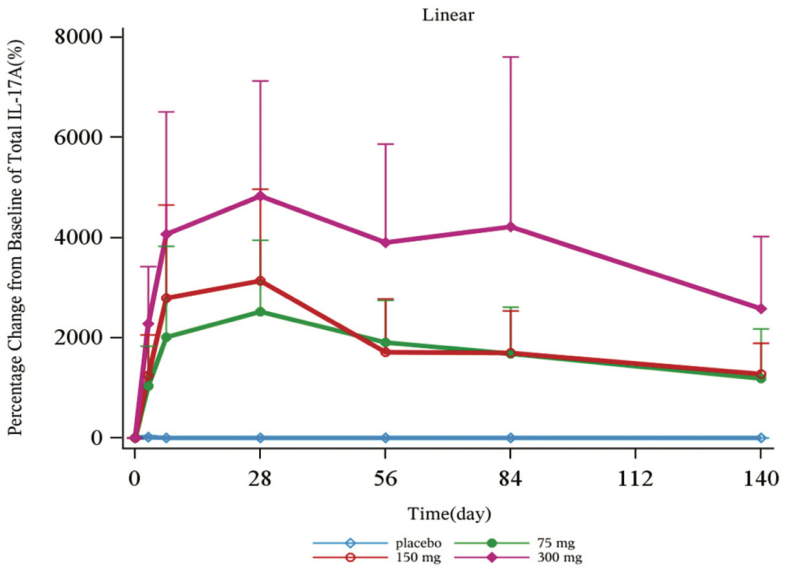

Fig. 4. Percentage change from baseline in serum total IL-17A concentration (%).
The x axis represents the time interval between the first administration, *i.e.* time on the x axis = study day-1.

sample size in this study, the dependability of results must be confirmed in further phase 3 clinical studies.

During a 20-week treatment follow-up, AK111 at doses ranging from 75 mg to 300 mg demonstrated favourable safety and tolerability in patients with AS. The incidence of TEAE and TRAE in the AK111 group was comparable to that in the placebo group, and no apparent trend was observed across dosage groups. In the treatment groups, the majority of TEAEs were mild and moderate in severity, and were resolved. Urinary tract infection resulted the only TRAE with an incidence ≥5% that was more prevalent in treatment group in comparison to placebo; all events were grade 1 and grade 2 in severity and recovered. In comparison to the safety information of other approved IL-17 inhibitors, such as secukinumab and ixekizumab) no unexpected safety signals were identified in this study.

The neutrophil count decline was reported as an occasional adverse reaction for other IL-17 inhibitors. One participant in our study experienced a grade 3 neutrophil count decline, however, it resolved spontaneously without clinical intervention and did not lead to any interruption in medication. The participant reported no concomitant infections, and the event exhibited transient and reversible characteristics, which were similar to what were reported for the products in the same drug class (19-20).

Given the crucial role of IL-17 in defending against pathogens, tumour immune surveillance, and regulating the immune system, the use of IL-17 inhibitors may pose risks such as infections, tumours, or inflammatory bowel disease in patients. In this study, the only 'grade 3' infection was a ureteral inflammation. Given that the participant had a history of ureteral stone obstruction and ureteral hydronephrosis, these were considered main causes of ureteral inflammation. No other serious infections were reported, and not active tuberculosis or active hepatitis B occurred. Throughout the study period, neither severe allergic reactions nor tumour-related AEs were observed. Inflammatory bowel disease (IBD) is known to be one of the extra-articular manifestations of AS. And IL-17 inhibitors may decrease intestinal barrier function and could potentially induce or worsen IBD. Though no case of IBD was reported throughout of the current study period, close monitoring of the risk of IBD is guaranteed in future studies. After subcutaneous injection of 75-300 mg AK111, the median time to reach peak serum concentration (T_{max}) was about 7 days, and the exposure of AK111 increased in a dose-dependent

manner. Referring to a population PK model based upon a phase Ib clinical study of AK111 in psoriasis patients in China (29), the one-compartment model of first-order absorption and first-order elimination best described the PK characteristics of AK111. The apparent systemic clearance was 0.182 L/day, and the central volume was 6.65 L. AK111 showed a slow serum clearance with an average elimination half-life ($t_{1/2}$) of 25.3 days (0.693*V/CL). The serum total IL-17A level rapidly increased from day 1 to day 8 after the first administration of AK111 in each dose group, indicating that AK111 quickly binds to the target IL-17A after entering the body, exhibiting good pharmacodynamic characteristics.

The baseline incidence of ADA positivity in the AK111 group was 2.2% (2/92), and the incidence of treatment-emergent ADA positivity after baseline was 1.1% (1/92). No neutralising antibody-positive was found, suggesting a low immunogenicity risk of AK111. AS is a chronic disease that requires long-term treatment, and ADA may attenuate efficacy and increase safety risks. Low immunogenicity contributes to an improved long-term safety, reduced the risk of secondary treatment failures, improved patient retention rates, and therefore enhanced long-term clinical outcomes.

The findings of this study demonstrated robust efficacy and safety of AK111 in patients with AS and established a foundation for dose selection for the future phase III studies. However, due to the small sample size and short duration of this phase II study, there were certain limitations. This study only evaluated the short-term efficacy of AK111 in treating AS, while the long-term efficacy requires further evaluation. Additionally, the limited sample size may affect the accuracy of the efficacy assessment. In terms of the safety, limited follow-up period and sample size may hinder the full assessment of delayed adverse events (such as tumours), events that require long-term monitoring (such as MACE), and low-incidence adverse events. The risk-benefit profile of AK 111 in treating AS warranted larger, long-term studies for further validation.

Conclusion

In summary, results from this study suggest that AK111 75–300 mg administered subcutaneously was generally safe and tolerable, and demonstrated favourable pharmacodynamics, and efficacy in participants with active ankylosing spondylitis. The exposure of AK111 increased in a linear dose-response manner, and the incidence of immunogenicity was low. These promising results warranted further verification of the efficacy and safety of AK111 in future phase III clinical studies.

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